ExtraVascular Implantable Cardioverter Defibrillator (EV ICD) Pivotal Study

NCT04060680

Clinical Investigation Plan, 02-JUL-2019

Medtronic

Clinical Investigation Plan

Clinical Investigation Plan/Study Title	ExtraVascular Implantable Cardioverter Defibrillator (EV ICD) Pivotal Study
Clinical Investigation Plan Identifier	MDT16028
Study Product Name	EV ICD System
Sponsor/Local Sponsor	**Sponsor:** Medtronic, Inc. 8200 Coral Sea Street NE Mounds View, MN USA 55112 +1-800-328-2518 **Local Sponsors:** **Australia** Medtronic Australasia Pty Ltd 2 Alma Road Macquarie Park NSW, 2113 Australia +61 2 9857 9000 **Canada** Medtronic of Canada, Ltd. 99 Hereford Street Brampton Ontario, L6Y 0R3 Canada +1-905-460-3800 **Europe, Middle East, Africa** Medtronic, Bakken Research Center B.V. Endepolsdomein 5 6229 GW Maastricht The Netherlands +31-43-35-66-566 **Hong Kong** Medtronic Hong Kong Medical Ltd. 1104-11, 11/F, Tower 1, The Gateway, Harbour City, Kowloon Hong Kong SAR, China +852-2919-1300

	Japan Medtronic Japan Co., Ltd. 1-2-70 Konan, Minato-ku, Tokyo Japan 108-0075 Shinagawa Season Terrace 22F Phone: (+81) 3-6774-4611 Fax: (+81) 3-6774-4605 **New Zealand** Medtronic New Zealand Limited Level 3, Building 5 666 Great South Road Penrose Auckland 1051 New Zealand +64 9 634-1049
Document Version	1.0, 02-JUL-2019
Lead Principal Investigator/Coordinating Investigator	Dr. Paul Friedman Mayo Clinic Rochester [redacted]

Table of Contents

1. Contact Information and Glossary

1.1. Steering Committee

The Steering Committee (SC) is responsible for the scientific content of the study and provides input for its execution. The SC will also serve as the sponsor's Medical Experts for the trial. The members and contact details of the SC will be provided under separate cover.

1.2. Sponsor Contact Information

Medtronic contact information is provided below. This information is subject to change during the course of the clinical study. Periodic updates to study contact information will be sent to the sites as needed. Other sponsor contact information, such as name and address of local monitors, etc. will be provided under a separate cover to the sites as needed.

Table 1: Study sponsor contact information

Study sponsor and contacts	
Program Manager Sarah Willey, Program Manager Direct Phone: +1 763 526 2813 Email: sarah.a.willey@medtronic.com	*Worldwide Clinical Study Leader* Jo Krueger, Prin. Clinical Research Specialist Direct Phone: +1 612 271 2848 Email: jo.krueger@medtronic.com
Australia and New Zealand Samuel Liang, Sr. Clinical Research Specialist Direct Phone: +61-2 9857 9391 Email: samuel.liang@medtronic.com	*Canada* Aarthi Kamath, Sr. Clinical Research Specialist Direct Phone: +1 905 460 3722 Email: aarthi.kamath@medtronic.com
Europe, Middle East, and Africa (EMEA) Katrien Vandersteegen, Sr. Clinical Research Specialist Direct Phone: +31 433566728 Email: katrien.vandersteegen@medtronic.com	*Hong Kong* Tina Ling, Clinical Research Specialist Direct Phone: +85 229191300 Email: tina.ling@medtronic.com
Japan Naohiro Masumoto, PhD, Pr. Clinical Research Specialist Direct Phone: +81 367760056 Email: naohiro.masumoto@medtronic.com	*United States of America (US)* Diedre Ribbens, Sr. Clinical Research Specialist Direct Phone: +1 763 526 3075 Email: diedre.j.ribbens@medtronic.com

Monitoring contacts	
US/Canada	*EMEA/Asia Pacific/Hong Kong/Japan*
Taryn Randall, Sr. Clinical Monitoring Manager Direct Phone: +1 763 250 0785 Email: taryn.randall@medtronic.com	Anja Hesse, Monitoring Portfolio Specialist CRHF Direct Phone: +49 1702266577 Email: anja.hesse@medtronic.com

1.3. CROs and Core Labs

No core labs will be used in this study. At the time of finalization of this clinical investigation plan (CIP), there is only one contract research organization (CRO) planned:

Cognizant Technology Solutions
500 Frank W. Burr Blvd.
Teaneck, NJ 07666
United States of America
Direct Phone: +1 201 801 0233
Direct Fax: +1 201 801 0243

Duties performed:

- Development of study electronic case report forms, edit checks, and study management reports
- Review of electronic case report forms and management of discrepancies.

1.4. Glossary

Term	Definition
AE	Adverse Event
ADE	Adverse Device Effect
ALARA	As Low as Reasonably Achievable
ANZ	Australia and New Zealand
AP	Anterior-Posterior
ATP	Antitachycardia Pacing
BMI	Body Mass Index
"can"	Used to indicate that something is possible, for example, that an organization or individual is able to do something
CEC	Clinical Events Committee
CIP	Clinical Investigation Plan
CMS	Centers for Medicare & Medicaid Services
CFR	(US) Code of Federal Regulations
DD	Device Deficiency
DMC	Data Monitoring Committee
EC	Ethics Committee
ECG	Electrocardiogram
Ethics Committee	Term that will be used collectively in reference to an Institutional Review Board (IRB)/Medical Ethics Committee (MEC)/Human Research Ethics Committee (HREC)/Research Ethics Board (REB)/Head of Medical Institution (HOMI) unless otherwise stated
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
EGM	Electrogram
EMEA	Europe, Middle East, and Africa
EP	Electrophysiologist/Electrophysiology
ERC	Episode Review Committee
EV ICD	Extravascular Implantable Cardioverter Defibrillator
FDA	(US) Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act
FPAS	Florida Patient Acceptance Survey
GCP	Good Clinical Practice
HCU	Health Care Utilization
HIPAA	Health Insurance Portability and Accountability Act of 1996
HOMI	Head of Medical Institution
IB	Investigator's Brochure
IC	Informed Consent
ICD	Implantable Cardioverter Defibrillator
ICF	Informed Consent Form
ID	Identification
IFU	Instructions for Use

Term	Definition
IRB	Institutional Review Board
ISF	Investigator Site File
LA	Left Atrium
LAT	Lateral
LV	Left Ventricular
LVEF	Left Ventricular Ejection Fraction
LVEDD	Left Ventricular End Diastolic Diameter
“may”	Used to indicate that something is permitted
MedDRA	Medical Dictionary for Regulatory Activities
NHMRC	The National Health and Medical Research Council
NOAC	Novel Oral Anticoagulant
PA	Posterior-Anterior
PHD	Pre-Hospital Discharge
OPC	Objective Performance Criterion
SAE	Serious Adverse Event
SADE	Serious Adverse Device Effect
SC	Steering Committee
SDN	Software Distribution Network
“shall”	Indicates a requirement
“should”	Indicates a recommendation
SF-12	Short Form, 12-question (Quality of Life Survey)
SSI	Significant Safety Issue
SSVA	Sustained Shockable Ventricular Arrhythmia
TEE	Transesophageal Echocardiogram
TV	Transvenous
US	United States of America
USM	Urgent Safety Measure
UADE	Unanticipated Adverse Device Effect
USADE	Unanticipated Serious Adverse Device Effect
VF	Ventricular Fibrillation
VT	Ventricular Tachycardia
Zone 1	Tunnelling and deployment of the lead in the substernal space
Zone 2	Tunnelling of the lead from the sternum to the device pocket

2. Synopsis

Title	Extravascular Implantable Cardioverter Defibrillator (EV ICD) Pivotal Study
Clinical Study Type	Prospective, multi-center, single-arm, non-randomized, pre-market clinical study
Product Name and Status	Investigational System Components: • Medtronic Model DVEX3E4 EV ICD • Medtronic Model EV2401 EV ICD Lead Investigational Accessory Components: • Medtronic Model EAZ101 Sternal Tunneling Tool • Medtronic Model EAZ201 Transverse Tunneling Tool • Oscor SafeSheath® II, model number SSCL9 introducer (market-released in US) • EV ICD SW041 Programmer Software Version 8.1 (or greater) • MyCareLink Patient Monitor Model 24952 (may become available during the course of the study) Market Released Components: • Medtronic 2090 CareLink Programmer with analyzer (or CareLink Encore 29901 Programmer)
Sponsor	Medtronic, Inc. 8200 Coral Sea Street NE Mounds View, MN 55112 United States of America +1 800 328 2518
Local Sponsor	**Local Sponsors:** **Australia** Medtronic Australasia Pty Ltd 2 Alma Road Macquarie Park NSW, 2113

	Australia +61 2 9857 9000 **Canada** Medtronic of Canada, Ltd. 99 Hereford Street Brampton Ontario, L6Y 0R3 Canada +1 905 460 3800 **Europe, Middle East, Africa** Medtronic, Bakken Research Center B.V. Endepolsdomein 5 6229 GW Maastricht Netherlands +31 433566566 **Hong Kong** Medtronic Hong Kong Medical Ltd. 1104-11, 11/F, Tower 1, The Gateway, Harbour City, Kowloon Hong Kong SAR, China +852 29191300 **Japan** Medtronic Japan Co., Ltd. 1-2-70 Konan, Minato-ku, Tokyo Japan 108-0075 Shinagawa Season Terrace 22F Phone: +81 3 6774 4611 **New Zealand** Medtronic New Zealand Limited Level 3, Building 5 666 Great South Road Penrose Auckland 1051 New Zealand +64 9 634 1049
Indication under investigation	The Medtronic EV ICD System (defibrillator and lead) is indicated for the automated treatment of patients who have

	experienced, or are at significant risk of developing, life-threatening ventricular tachyarrhythmias.
Investigation Purpose	The main purpose of the EV ICD Pivotal study is to demonstrate safety and efficacy of the EV ICD System.
Primary Objective(s)	Primary Safety Objective: Demonstrate the freedom from major complications related to the EV ICD System and/or procedure at 6 months post-implant exceeds 79% Objective Performance Criterion (OPC). The endpoint is defined as a subject's first occurrence of a major complication related to the EV ICD System and/or procedure, as determined by an independent Clinical Events Committee (CEC), that occurs on or prior to 6 months (182 days) post-implant. Primary Efficacy Objective: Demonstrate the EV ICD defibrillation testing success rate at implant is greater than 88% OPC. The endpoint, defibrillation testing success, is defined as: • Single SSVA conversion at 20J, or • Conversion of two successive episodes of SSVA at 30J in final system configuration.
Ancillary Objective(s)	• Characterize appropriate and inappropriate shocks • Characterize electrical performance (pacing capture thresholds, pacing impedance, sensing amplitudes) over time • Characterize extracardiac pacing sensation • Characterize asystole pacing • Summarize ATP performance with spontaneous arrhythmias • Summarize adverse events • Characterize the EV ICD defibrillation testing success rate at 6 months post-implant.
Sample Size	Up to 400 enrollments at up to 60 sites worldwide, to allow at least 292 subjects to, in the case of the safety objective, undergo an implant attempt of the EV ICD System, and in the

	case of the efficacy objective, complete the pre-specified defibrillation testing protocol. Maximum number of subjects enrolled at each site will be capped at 35, which is approximately 10% of the total number of subjects enrolled.
Inclusion/Exclusion Criteria	<u>Inclusion Criteria</u> 1. Patient has a Class I or IIa indication for implantation of an ICD according to the ACC/AHA/HRS Guidelines[i], or ESC guidelines[ii]. 2. Patient is at least 18 years of age and meets age requirements per local law. 3. Patient is geographically stable and willing and able to complete the study procedures and visits for the duration of the follow-up. <u>Exclusion Criteria</u> 1. Patient is unwilling or unable to personally provide Informed Consent. 2. Patient has indications for bradycardia pacing [iii] or Cardiac Resynchronization Therapy (CRT) [iv] (Class I, IIa, or IIb indication). 3. Patient with an existing pacemaker, ICD, or CRT device implant or leads. 4. Patients with these medical interventions are excluded from participation in the study: • Prior sternotomy

i Al-Khatib SM, Stevenson WG, Ackerman MJ, Bryant WJ, Callans DJ, Curtis AB, Deal BJ, Dickfeld T, Field ME, Fonarow GC, Gillis AM, Hlatky MA, Granger CB, Hammill SC, Joglar JA, Kay GN, Matlock DD, Myerburg RJ, Page RL. 2017 AHA/ACC/HRS guideline for management of patients with ventricular arrhythmias.
ii Priori SG, Blomstrom-Lundqvist C, Mazzanti A, Blom N, Borggrefe M, Camm J, Elliot PM, Fitzsimons D, Hatala R, Hindricks G, Kirchhof P, Kjeldsen K, Kuck KH, Hernandez-Madrid A, Nikolaou N, Norekval TM, Spaulding C, Van Veldhuisen DJ. 2015 ESC guidelines for the management of patients with ventricular arrhythmias and the prevention of sudden cardiac death. European Heart Journal 2015 36:41 (2793-2867). https://doi.org/10.1093/eurheartj/ehv316
iii 2015 HRS/EHRA/APHRS/SOLAECE expert consensus statement on optimal implantable cardioverter-defibrillator programming and testing).
iv ACC/AHA/HRS guidelines for Cardiac Resynchronization Therapy

	• Any prior medical condition or procedure that leads to adhesions in the anterior mediastinal space (i.e., prior mediastinal instrumentation, mediastinitis) • Prior abdominal surgery in the epigastric region • Planned sternotomy • Prior chest radiotherapy Or any other prior/planned medical intervention not listed that precludes their participation in the opinion of the Investigator. 5. Patient has previous pericarditis that: • Was chronic and recurrent, or • Resulted in pericardial effusion [v], or • Resulted in pericardial thickening or calcification. [vi] 6. Patients with these medical conditions or anatomies are excluded from participation in the study: • Hiatal hernia that distorts mediastinal anatomy • Marked sternal abnormality (e.g., pectus excavatum) • Decompensated heart failure • COPD with oxygen dependence • Gross hepatosplenomegaly Or any other known medical condition or anatomy type not listed that precludes their participation in the opinion of the Investigator. 7. Patients with a medical condition that precludes them from undergoing defibrillation testing: • Severe aortic stenosis • Intracardiac LA or LV thrombus • Severe proximal three-vessel or left main coronary artery disease without revascularization • Hemodynamic instability • Unstable angina

v As documented on echo or MRI
vi As documented on CT scan or MRI

	• Recent stroke or transient ischemic attack (within the last 6 months) • Known inadequate external defibrillation • LVEF <20% • LVEDD >70 mm Or any other known medical condition not listed that precludes their participation in the opinion of the Investigator. 8. Patient with any evidence of active infection or undergoing treatment for an infection. 9. Patient is contraindicated from temporary suspension of oral/systemic anticoagulation 10. Patient with current implantation of neurostimulator or any other chronically implanted device that delivers current in the body. 11. Patient meets ACC/AHA/HRS or ESC clinical guideline Class III criteria for an ICD (e.g., life expectancy of less than 12 months). 12. Patient is enrolled or planning to enroll in a concurrent clinical study that may confound the results of this study, without documented pre-approval from a Medtronic study manager. 13. Patient with any exclusion criteria as required by local law (e.g., age or other). 14. Pregnant women or breastfeeding women, or women of child bearing potential and who are not on a reliable form of birth regulation method or abstinence. [vii]
Study Procedures and Assessments	Subjects indicated for single-chamber ICD therapy will be recruited and implanted with the Medtronic EV ICD System. Once enrolled, a subject will be assessed at the following visits: • Baseline

vii if required by local law, women of child-bearing potential must undergo a pregnancy test within seven days prior to EV ICD Pivotal Study procedures

- Implant
- Pre-Hospital Discharge (PHD)
- 2 Weeks (2WK)
- 3 Months (3M)
- 6 Months (6M)
- Long-term: Every 6 months thereafter until study closure (12, 18, 24… Months)
- Unscheduled (as they occur)
- System Modifications (as they occur)
- Exit

Study procedures are outlined in the table below.

Study procedure	Baseline	Implant	PHD	2WK	3M	6M	Long Term	Unscheduled	Sys Mod	Exit
Informed Consent	X									
Inclusion/Exclusion Assessment	X									
Physical Exam, Demographics, Cardiovascular Medical History, Surgical History	X									
SF-12 quality of life survey	X					X				
Florida Patient Acceptance Survey (FPAS)[1]						X				
System and procedure information		X							X	
Pre-procedure Transesophageal Echocardiogram (TEE)[2]		X[2]								
CT-Scan or MRI	X[3]									
Fluoroscopy recordings during tunneling procedure		X							X[6]	
Fluoroscopy (AP and Lateral cine) of final ICD generator and lead position		X							X[6]	
Sensing, Impedance, & Pacing tests		X	X	X	X	X	X	X[5]	X[6]	
Defibrillation testing		X				X[4]			X[6]	
Chest Radiographs (PA/Lateral)	X		X			X				
Echocardiographic data within the last 6 months	X									
Save-to-media files		X	X	X	X	X	X	X	X	X
Medications (for subjects implanted with any device)	X	X	X	X	X	X	X	X	X	X

Adverse Events[7] (including AEs with fatal outcome), Device Deficiencies, HCUs, Study Deviations, and Other cardiac imaging	As they occur

1 Only for subjects who complete their ICF in English.
2 Required for subjects presenting in persistent atrial fibrillation to confirm the absence of LA or LV thrombus.
3 Taken within the last year. Recommended for first 3 subjects at minimum, for each implanter. If collected/reviewed, send CT-scan and/or MRI to Medtronic.
4 Only for subjects participating in chronic defibrillation testing, see CIP Addendum for 6-Month Defibrillation Testing.
5 Optional. If electrical testing conducted, print the Testing Reports to PDR or paper and send a copy of the reports to Medtronic.
6 System modification where a subject leaves the procedure with an EV ICD System.
7 Recommended to collect incision photographs if an infection related to the EV ICD System is suspected.

Safety Assessments	All Adverse Events that occur from the time of enrollment through study exit will be collected and reported to Medtronic and regulatory agencies (per local requirement) during the study. Additionally, any device deficiency related to the EV ICD System or accessory will be collected.
Statistics	The efficacy primary objective will be evaluated using a binomial confidence interval compared against a pre-specified threshold. To evaluate the safety primary objective, the 95% confidence interval for the 6-month system/procedure major complication-free rate will be generated and compared against a pre-specified threshold. A Kaplan-Meier survival curve will also be generated to provide incidence of EV ICD System/procedure-related major complications over time. Descriptive statistics will be used to summarize remaining endpoints. For some endpoints such as pacing testing, multiple measurements per subject will be assessed and compared.

3. Introduction

3.1. Background

Today, implantable cardioverter defibrillator (ICD) therapy is the treatment of choice for patients who are at risk for sudden cardiac death due to life-threatening ventricular arrhythmias. Traditional ICD systems with transvenous leads are considered standard of care for primary or secondary prevention of tachyarrhythmic death. However, these systems have limitations. Short- and long-term complications arising from ICD systems with transvenous leads, such as infection, pneumothorax, venous thrombosis, lead dislodgement, lead malfunction, and lead perforation, have persisted for decades as impediments to ICD usage[1,2,3,4,5]. As a result, there is demand for novel ICD systems that circumvent the potential disadvantages of transvenous ICD systems by preserving the heart and vasculature[6,7].

Non-transvenous ICD systems may represent a means of providing life-saving therapy to patients in whom it is not possible or desired to enter the venous system or heart chambers; for example, patients with anatomical anomalies, high infection risk, limited vascular access, or juvenile patients where the venous anatomy is preferably avoided[8,9,10,11].

Currently, there are non-transvenous subcutaneous and epicardial leads that are used with standard ICDs. Cameron Health developed the SQ-RX SubQ ICD system, which was market released in 2009. Boston Scientific acquired the Cameron Health device, and market released their Emblem Subcutaneous (SubQ) ICD system in 2015. During clinical studies for both of these devices, patients were implanted with a non-transvenous ICD system and a subcutaneous lead. Perioperative results from the S-ICD post approval study indicate acceptable short-term complication rates[12], and first year post-implant results from the EFFORTLESS study confirm the safety demonstrated in the IDE S-ICD trial, and indicate performance rates for S-ICD complications, inappropriate shocks, and conversion efficacy similar to those observed in transvenous systems[13].

Medtronic has developed an extravascular ICD system which uses a substernal lead rather than a transvenous or a subcutaneous lead. The EV ICD System has similar capabilities to a single-chamber transvenous system while avoiding leads in the heart or vasculature. Compared to current market-released non-transvenous subcutaneous ICDs, the EV ICD System includes a smaller device that uses less defibrillation energy which may result in longer battery life and has the additional capabilities to deliver pacing therapies such as ATP and backup asystole pacing from a single device.

Previously published case studies indicate defibrillation from non-endocardial locations is possible and shock energies similar to those of transvenous devices can successfully defibrillate if the defibrillation coil is placed in an epicardial or mediastinal location[8,9,10,14,15,16,17,18,19,20]. The EV ICD System is of similar size and energy outputs as current transvenous systems (e.g., approximately 33cc and 40 Joules).

The first human experience of acute and chronic defibrillation lead placement in the substernal extra-cardiac space was reported by Tung et al. in 2007 using a minimally invasive approach via the manubrium[10]. In three patients (two patients having ipsilateral venous occlusion and one patient wishing to avoid additional transvenous hardware placement), either a Medtronic Model 6996SQ or Model 6937 coil was tunneled to the substernal extra-cardiac space anterior to the right ventricle (RV). All implants were successful without complication. Ventricular Fibrillation (VF) was induced with T-wave shock. In each patient, the safety margin was determined to be at least 10 Joules (J) by two successful VF terminations.

Later, Guenther et al. reported the results of failed subcutaneous defibrillation lead implantation in one human patient for whom defibrillation threshold testing (DFT) at 65 Joules and 80 Joules failed to terminate VF six times[17]. As a result of failed subcutaneous DFT, the lead was instead positioned substernally using an 11-French peel-away insertion sheath and the tunneling tool of the manufacturer. After making a small incision at the xiphoid process, fluoroscopy and “direct bone contact” were used to guide lead placement. Substernal DFT was successful and substernal sensing quality was acceptable. There were no complications, including no damage to the pericardium. The patient reported no chronic pain and there were no other findings at follow-up of four weeks. Guenther et al. concluded that “substernal lead positioning is easy to achieve” and provides an effective means of extravascular lead implantation[17].

In order to develop and evaluate a newly designed system for the substernal space, Medtronic completed pre-clinical research evaluations of substernal defibrillation, pacing, and sensing, and subsequently initiated three acute human clinical research feasibility studies with combined 121 implants to explore the potential development of a future chronic implantable extravascular defibrillation system with a lead implanted in the substernal space. Both pre-clinical and clinical data are described in further detail within the Investigator’s Brochure.

The first human clinical feasibility study, Acute Substernal Defibrillation (ASD), showed substernal defibrillation is feasible with energy available in current transvenous ICDs, with defibrillation successful in 13 of 14 subjects (93%) at 35J (95% CI: 74.7% - 99.8%). One failure was associated with high and lateral shock coil placement[21]. The second human clinical feasibility study, Substernal Pacing Acute Clinical Evaluation (SPACE), in which 26 subjects underwent pacing evaluation, showed that pacing is possible in nearly all patients from the extravascular substernal location[22]. The third human clinical feasibility study, Acute Extravascular Defibrillation, Pacing and Electrogram (ASD2), was designed to further assess study pacing thresholds and defibrillation efficacy via substernal therapy delivery in a larger cohort as well as collect additional data, mainly multi-vector substernal electrograms during induced VF/VT and intrinsic rhythms directly from an investigational lead placed in the substernal space. The substernal lead was implanted in 79 patients, with a median implantation time of 12.0 ± 9.0 min. Ventricular pacing was successful in at least 1 vector in 76 of 78 patients (97.4%), and 72 of 78 (92.3%) patients had capture in ≥1 vector with no extracardiac stimulation. A 30-J shock successfully terminated

104 of 128 episodes (81.3%) of ventricular fibrillation in 69 patients. The ASD2 study demonstrated the ability to pace, sense, and defibrillate using a lead designed specifically for the substernal space[23].

Acute feasibility data from 121 patients provided assurance to initiate a pilot study with first-in-human chronic device implant of the EV ICD System. The main benefits of conducting a pilot study included (1) facilitating optimization of device settings, (2) providing additional recommendations and best practices during the implant procedure, and (3) providing an avenue for more robust data collection leading up to a pivotal trial. A pilot study was initiated to allow for characterization of the EV ICD System in a limited number of subjects before launching into this large-scale, global, pivotal study.

The EV ICD Pilot Study is a prospective, non-randomized, chronic first-in-human study conducted in four sites in Australia and New Zealand. In this pilot study, 21 patients underwent the EV ICD implant procedure. Patients were evaluated at implant, two weeks, four to six weeks, and three months after device implant, and continue to be followed. Study investigators characterized the safety of the system and implant procedure, defibrillation effectiveness, and sensing and pacing. At the time of implant, defibrillation testing was completed on 20 patients. The system successfully terminated induced ventricular arrhythmias in 18 patients (90.0%), which is consistent with prior clinical studies of existing ICDs[24,25]. Pacing capture was achieved in more than 95% of study patients. One patient experienced ventricular tachycardia outside the hospital setting, which was successfully detected and treated by the EV ICD system. This first-in-human chronic study demonstrated that the EV ICD system can be implanted with no major complications, and can sense, pace and defibrillate the heart[26].

In summary, the acute feasibility and pilot studies contributed to the advancement of the EV ICD program, including refinement of the device, algorithm and implant procedure.

3.2. Purpose

The purpose of the clinical study is to demonstrate the safety and efficacy of the EV ICD System: a complete single-chamber extravascular ICD system with the lead implanted substernally.

4. Objectives and/or Endpoints

4.1. Objectives

4.1.1. Primary Objectives

The first primary objective is to demonstrate the freedom from major complications related to the EV ICD System and/or procedure at 6 months post-implant exceeds 79% Objective Performance Criterion (OPC). The endpoint is defined as a subject's first occurrence of a major complication related to the EV

ICD System and/or procedure, as determined by an independent Clinical Events Committee (CEC), that occurs on or prior to 6 months (182 days) post-implant.

For an adverse event to meet the endpoint, the event must have occurred within 182 days (inclusive) of the EV ICD System implant and be adjudicated by the CEC as being a major complication related (causal relationship) to the EV ICD System and/or procedure. Major complications are those complications resulting in:

- Death
- Permanent loss of defibrillation function (specifically shock) due to mechanical or electrical dysfunction of the device
- Hospitalization
- Prolongation of an existing hospitalization by at least 48 hours
- System revision (reposition, replacement, explant)

The second primary objective is to demonstrate the defibrillation efficacy at implant of the EV ICD System exceeds 88% (OPC). The endpoint, defibrillation testing success, is defined as:

- Single sustained shockable ventricular arrhythmia (SSVA) conversion at 20J, or
- Conversion of two consecutive episodes of SSVA at 30J in final system configuration.

Notes:

- In one of the two consecutive SSVA episodes, up to two 30J shocks are permitted.
- To achieve final system configuration, changing the position of the ICD generator and/or the lead, or changing shock polarity is permitted.
- Subjects can return for testing on another day if testing is not fully completed on the day of implant.
- If SSVA cannot be induced, the EV ICD System must be removed (refer to section 8.5.8).
- For more information on the rationale behind these objectives, refer to section 12.

4.1.2. Ancillary Objectives

- Characterize appropriate and inappropriate shocks
- Characterize electrical performance (pacing capture thresholds, pacing impedance, sensing amplitudes) over time
- Characterize extracardiac pacing sensation
- Characterize asystole pacing
- Summarize ATP performance with spontaneous arrhythmias
- Summarize adverse events
- Characterize the EV ICD defibrillation testing success rate at 6 months post-implant.

5. Study Design

The EV ICD Pivotal Study is a prospective, multi-center, single-arm, non-randomized, pre-market clinical study. Enrollment will include up to 400 subjects at up to 60 sites worldwide.

Participating geographies are expected to include but are not limited to: ANZ (Australia and New Zealand), Canada, EMEA (Europe, Middle East, and Africa), Hong Kong, Japan, and the United States.

Participating sites that enroll faster than others will be allowed to do so to maintain an adequate enrollment rate. However, to ensure a reasonable distribution of experience and minimize site bias in study results, the maximum number of subjects enrolled at each site will be capped at 35 (approximately 10% of total enrollments).

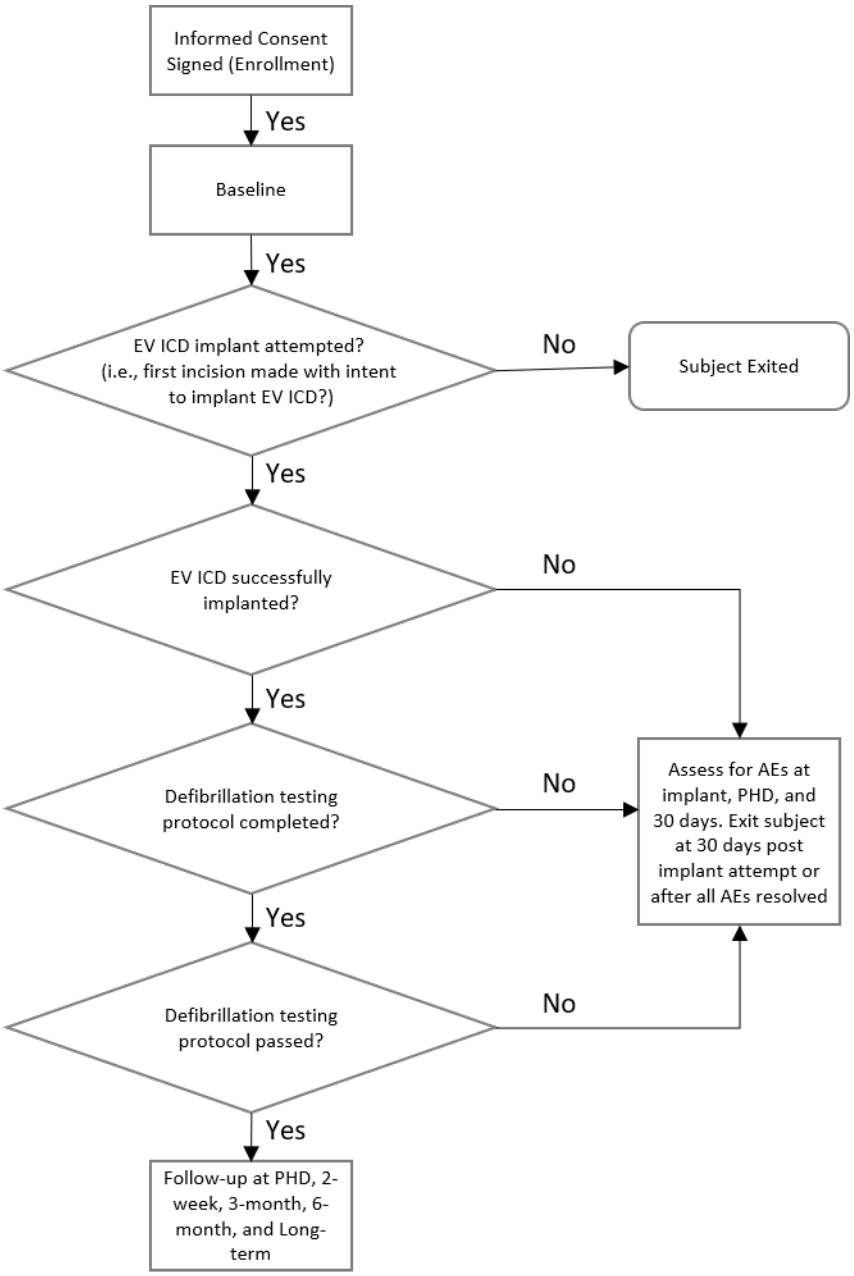


Figure 1: Overview of the EV ICD Pivotal Study

5.1. Duration

The expected study duration is approximately 3 years from the study's first enrollment. The enrollment period is expected to take approximately 15 months. Individual subjects may be participating in the study for a period of minimum 2 to approximately 3.5 years. The duration of individual subject participation will vary based on timing of site activation, timing of enrollment and enrollment rate. Subjects will undergo assessments at Baseline, Pre-Hospital Discharge, 2 Weeks, 3 Months, 6 Months, and every 6 months thereafter until official study closure. Official study closure is defined as when Medtronic and/or applicable regulatory authority agency or governing body requirements have been satisfied per the CIP and/or by a decision by Medtronic or regulatory authority to stop or close the study. Official study closure is expected to occur after the EV ICD System is approved by the FDA, anticipated in 2022.

5.2. Rationale

The main purpose of the EV ICD Pivotal Study is to demonstrate safety and efficacy of the EV ICD System.

Prior to this study, three acute human feasibility studies were performed:

- The ASD study demonstrated that substernal defibrillation is feasible with energy available in current transvenous (TV)-ICDs[21]
- The SPACE study demonstrated that pacing is possible in nearly all patients with detection comparable to TV-ICD[22]
- The ASD2 study demonstrated that pacing, sensing, and defibrillation is feasible with a lead designed specifically for the substernal space[23]

EV ICD device features were designed and developed using data collected from these studies and supplemented with animal and bench evaluations.

In addition to the acute feasibility studies, the EV ICD Pilot study was initiated to allow for chronic characterization of the EV ICD System in a limited number of subjects before launching into a large-scale, global, pivotal study. At this time, the EV ICD Pilot study long-term follow-up is ongoing, and will continue through the duration of the EV ICD Pivotal Study in order to continue collecting long-term follow-up data.

5.3. Minimization of Bias

Selection of subjects, treatment of subjects, and evaluation of study data are potential sources of bias. Methods incorporated in the study design to minimize potential bias include (but are not limited to):

- Subject demographics and comorbidities will be collected at baseline to later assess possible characteristics that may influence endpoints
- Data collection requirements and study procedures will be standardized across all geographies
- To ensure a reasonable distribution of data among sites, the maximum number of enrollments per site will be 35 subjects. Additionally, sites will be encouraged to enroll at least 3 subjects.
- A statistical analysis plan will be developed prior to analyzing data which will document all pre-specified analyses and analysis methods
- All study clinicians will be trained on and required to follow the CIP
- All study clinicians and Medtronic personnel will be trained on their respective aspects of the study using standardized training materials
- An independent Clinical Events Committee (CEC) will be utilized to regularly review and adjudicate reported adverse events
- An Episode Review Committee (ERC) containing independent reviewers will be utilized to review and adjudicate device-treated episodes to determine appropriateness of therapy (shocks and ATP) delivered to subjects
- An independent Data Monitoring Committee (DMC) will be utilized to review accumulating data and interim analyses, help safeguard the interests of study subjects, and monitor the overall conduct of the study
- All sites will use the same version of the CIP and standardized case report forms when possible
- All study investigators will be required to meet 21 CFR Part 54, Financial Disclosure by Clinical Investigators
- Monitoring visits will be conducted to verify adherence to the CIP and source data.

In summary, potential sources of bias that may be encountered in this clinical study have been considered and minimized by careful study design.

6. Product Description

6.1. General

The EV ICD System consists of market-released and investigational components.

Table 2: EV ICD System Components

Model Number	Component	Investigational or Commercially Available at study start
System Components		
DVEX3E4	Extravascular Implantable Cardioverter Defibrillator (EV ICD)	Investigational in all geographies
EV2401	Extravascular quadripolar lead with shaped passive fixation	Investigational in all geographies
Accessory Components		
EAZ101	Sternal Tunneling Tool	Investigational in all geographies
EAZ201	Transverse Tunneling Tool	Investigational in all geographies
SSCL9	Oscor SafeSheath® II Hemostatic Tear-away Introducer System with Infusion Side Port	Investigational in all geographies
SW041	Medtronic EV ICD SW041 Programmer Software Version 8.1 or greater	Investigational in all geographies
2090 *or* 29901	Medtronic CareLink Programmer with analyzer *or* Medtronic CareLink Encore Programmer	Commercially available in all geographies Investigational EV ICD SW041 software is downloaded onto programmer, and programmer is subsequently labeled as containing investigational software
24952	Medtronic MyCareLink Patient Monitor (may become available during the course of the study)	Commercially available in all geographies, but investigational when used with EV ICD

The CIP permits up to 400 enrollments to allow at least 292 subjects undergoing system implant and defibrillation testing to be included in the study. Under the assumption that one system is used per subject, as well as a 15% increase to account for system revisions, dropped product, etc., it is expected that up to approximately 460 of the following investigational devices may be used during the trial: EV ICD, lead, sternal tunneling tool, transverse tunneling tool, introducer, and MyCareLink monitor. Each site (up to 60 sites) will have access to at least one programmer with software.

6.1.1. EV ICD (Model DVEX3E4)

The Medtronic Model DVEX3E4 is an investigational single-chamber, MR-conditional, extravascular implantable cardioverter defibrillator (EV ICD). It consists of a titanium generator and a connector port housing made from polyurethane and silicone rubber. This multiprogrammable cardiac device monitors and regulates the subject's heart rate. It provides asystole detection and therapy (Pause Prevention), ventricular tachyarrhythmia detection and therapy including ATP, and post-shock pacing. The EV ICD also provides diagnostic and monitoring features to assist with system evaluation and patient care.

Figure 2: The Medtronic EV ICD Model DVEX3E4

The DVEX3E4 EV ICD contains an EV4 connector, which is compatible with an EV4-LLHH quadripolar lead.

6.1.2. EV ICD Lead (Model EV2401)

The Medtronic Model EV2401 extravascular lead is an investigational, pre-shaped, MR-conditional lead with passive fixation, designed for sensing, cardioversion, defibrillation and pacing therapies. The lead is 8.7 Fr and available in both 52 cm or 63 cm lengths. The body of the lead is made from polyurethane, with ring electrodes made from titanium nitride coated platinum iridium, and coil electrodes from platinum iridium and tantalum. The lead has two ring electrodes and two coil electrodes: Ring 2 (proximal ring), Coil 2 (proximal coil), Ring 1 (distal ring), Coil 1 (distal coil). The configuration of these electrodes is shown in Figure 3. The lead has the ability to pace and sense between the ring and coil electrodes. In addition, the Coil 1 and Coil 2 electrodes deliver cardioversion and defibrillation therapy.

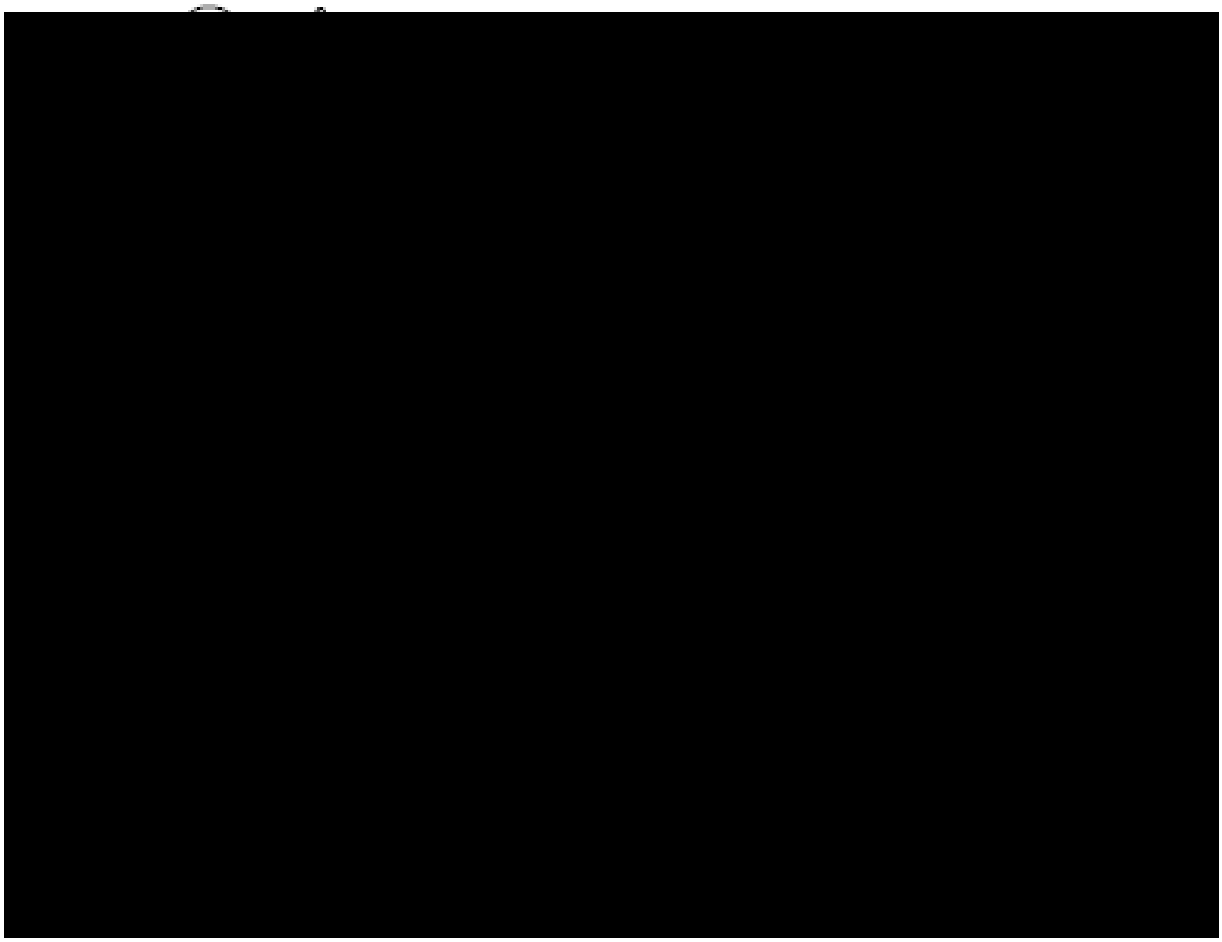


Figure 3: The EV2401 lead

The proximal end of the lead features an EV4-LLHH quadripolar connector, which is compatible with an EV4 connector on an EV ICD.

6.1.3. Sternal Tunneling tool (Model EAZ101)

The Medtronic Model EAZ101 sternal tunneling tool is an investigational tool designed to deliver an introducer and an extravascular lead into the anterior mediastinum during implant of an extravascular implantable device system. This is referred to as Zone 1 in Table 5: Outline of the proposed implant procedure steps.

The sternal tunneling tool, shown in Figure 4 below, consists of the following components:

- Handle
- [redacted] tunneling rod that delivers a [redacted] introducer to the anterior mediastinum. The tunneling rod is malleable to accommodate patient anatomy
- External guide that remains above the skin and indicates the distance and direction of the tunneling rod. The external guide is hinged and removable to accommodate physician preference and patient anatomy
- Thumb tab used to raise and lower the external guide

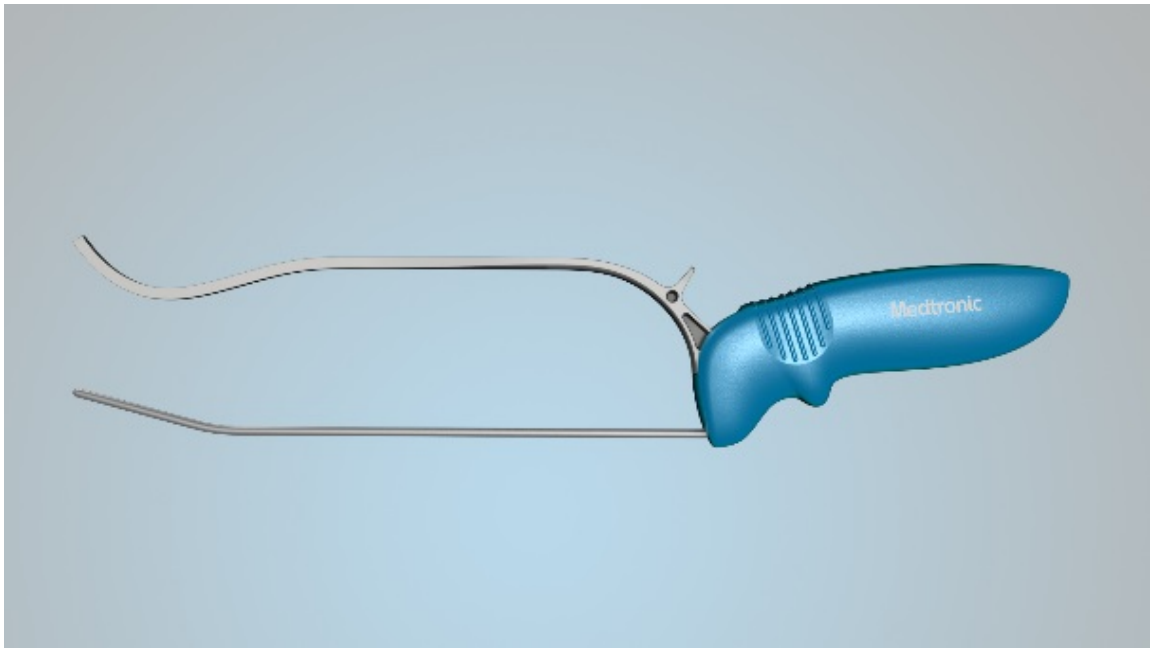


Figure 4: EAZ101 sternal tunneling tool

[redacted] The Oscor SafeSheath® II (Model SSCL9) introducer (section 6.1.5) is to be used with the sternal tunneling tool.

6.1.4. Transverse Tunneling tool (Model EAZ201)

The Medtronic Model EAZ201 transverse tunneling tool, shown in Figure 5, is an investigational tool designed to deliver the proximal portion of an extravascular lead to the device pocket during implant of an extravascular implantable device system. This is referred to as Zone 2 in Table 5: Outline of the proposed implant procedure steps.

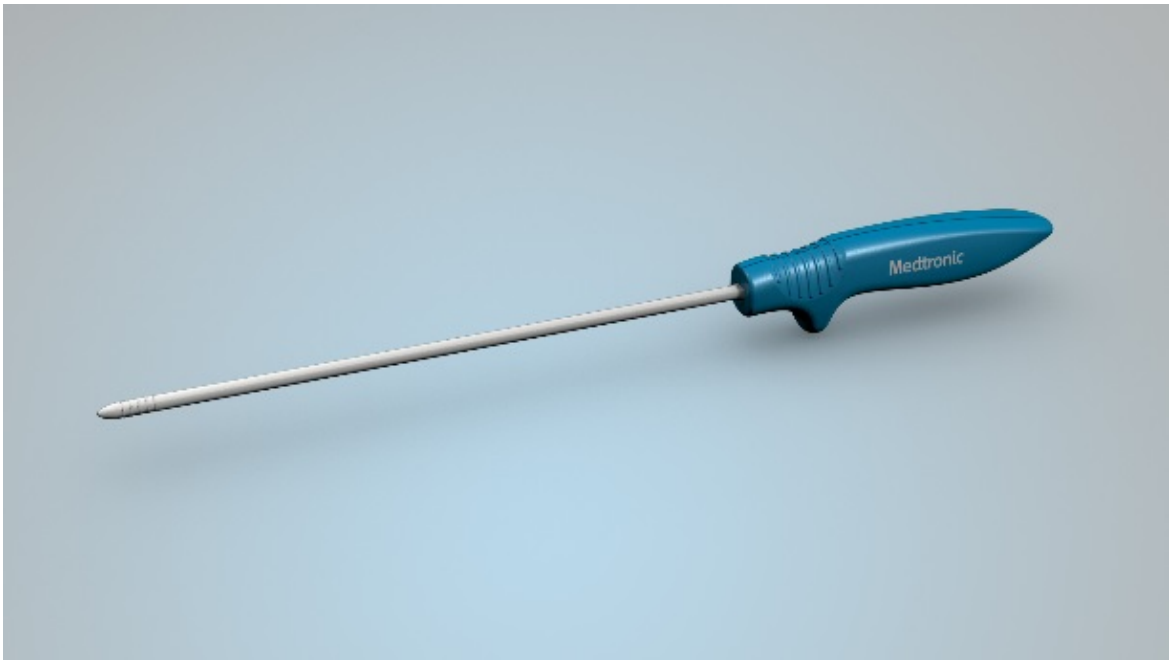


Figure 5: EAZ201 transverse tunneling tool

[redacted]

If additional tunneling tools are used to tunnel the lead subcutaneously, this shall be discussed with Medtronic clinical study personnel prior to use and the tools used will be documented. Use of additional tools will be considered a study deviation.

6.1.5. Oscor SafeSheath® II Model SSCL9

The Oscor (Palm Harbor, FL) SafeSheath® II Model SSCL9 introducer is a hemostatic tear-away introducer. [redacted] A 10cc plastic syringe will be packaged with the introducer sheath. The introducer sheath and hemostatic valve are indicated for the introduction of various types of pacing leads and catheters. The infusion side port is used to inject or aspirate through the sheath.

In this study, the SSCL9 introducer is used over the tunneling rod of the EAZ101 sternal tunneling tool to create a tunnel and facilitate insertion of the EV2401 extravascular lead into the mediastinum with a saline-filled syringe connected to the infusion sideport.

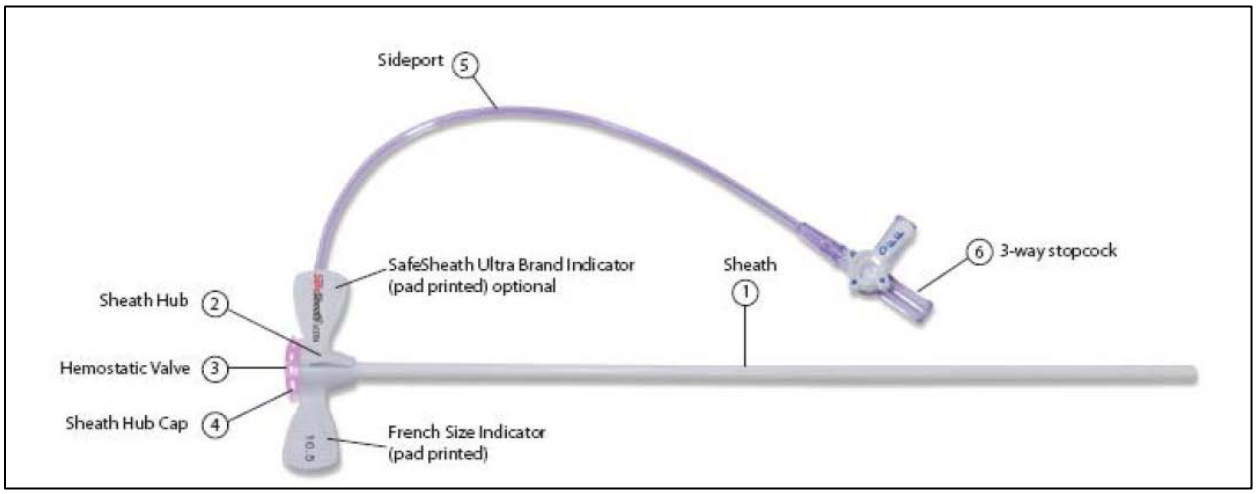


Figure 6: The Oscor SafeSheath® II Model SSCL9

The Oscor SafeSheath® II Model SSCL9 introducer is considered investigational in all geographies but may become commercially available during the course of the study.

6.1.6. EV ICD Programmer Software (Model SW041), Medtronic CareLink 2090 Programmer with Analyzer and Medtronic CareLink Encore 29901 Programmer

The investigational Medtronic Model SW041 programmer software, Version 8.1 (or greater) runs on the commercially available Medtronic CareLink 2090 Programmer or the commercially available Medtronic CareLink Encore 29901 Programmer, both with Conexus telemetry, and communicates with an implanted EV ICD Model DVEX3E4. Following software download, the Medtronic Programmer 2090 or 29901 will be labeled per local requirements to indicate that it contains investigational software.

Within its intended use, the programmer and programmer software will be used to provide a user interface with which the user can interrogate the device, control induction, shocking, sensing and pacing features and their parameters, and display diagnostic information. At implant, the 2090 analyzer (which is part of the 2090 programmer) will be used to test the lead electrical signals before the device is implanted.

6.1.7. MyCareLink Patient Monitor (Model 24952)

The commercially available Model 24952 MyCareLink Patient Monitor may be made available to subjects during this study when CareLink is made available for use with EV ICD. The MyCareLink Patient

Monitor communicates with an implanted EV ICD Model DVEX3E4 device to transmit data about device episodes to the subject's clinic using the CareLink network. In this study, the CareLink monitor will be used within its intended use, but will be considered investigational when used with EV ICD until the firmware is approved for use with the EV ICD system.

6.2. Manufacturer

All of the EV ICD System and accessory components are manufactured by Medtronic, with the exception of the SSCL9 introducer sheath, manufactured by Oscor, Inc.

Manufacturer Name	Manufacturer Address
Medtronic	710 Medtronic Parkway Minneapolis, MN 55432 USA www.medtronic.com +1 763 514 4000

6.3. Packaging

For investigational products, the device labeling and clinical manuals will be translated into the local language. The Clinical Manuals or Instructions for Use (IFU) will accompany each investigational component. Investigational products will be clearly labeled, e.g., "Exclusively for clinical investigations" and with the study identifier "Protocol #: MDT16028" per local requirements. In some geographies, the IFUs may be delivered via an alternate format (e.g., CD-ROM format, USB, or electronic format) if allowed within local requirements.

The investigational Medtronic Model SW041 programmer software application may be installed onto the Medtronic CareLink 2090 or Medtronic CareLink Encore 29901 programmers using USB drives with SW041 or Software Distribution Network (SDN) (if available); media packaging requirements are not applicable for distribution via the SDN. USB drives containing SW041, will be clearly labeled with identifier, version, and marked as "Exclusively for clinical investigations".

When investigational Medtronic Model SW041 software is installed on the 2090 or 29901 Medtronic Programmers, the Medtronic Programmers will be labeled to indicate they contain investigational software per local requirements.

Packaging and labeling for all other market approved system components can be found with each package insert. Manuals for market approved Medtronic devices can be found on http://manuals.medtronic.com. For CE marked devices and market devices in Japan, the labeling is in the appropriate local language.

The labeling for all components may include but is not limited to the following:

- Device Name
- Model number
- Serial or Lot number, as applicable
- Date of manufacture
- Expiration date

6.4. Intended Population

The Medtronic EV ICD System is indicated for the automated treatment of patients who have experienced, or are at significant risk of developing, life-threatening ventricular tachyarrhythmias. The intended population to receive the EV ICD System includes patients who are indicated for implantation of a single chamber ICD according to current ACC/AHA/HRS or ESC guidelines, and who do not have a bradycardia pacing or cardiac resynchronization therapy indication.

6.5. Equipment

Sites are responsible for maintaining and calibrating site equipment used in the course of this study (e.g., radiograph machine and fluoroscope) as applicable in accordance with established site practice and local regulation. Records shall be kept and available to be provided during monitoring visits and upon request by the Sponsor or regulatory agency.

6.6. Product Use

Instructions for installation and use for the components of the EV ICD System and accessories are located in the accompanying IFU for each component. Additionally, trained and experienced Medtronic personnel will provide support at implant.

6.7. Product Training Requirements

The EV ICD implant procedure is to be performed by an investigator who has received training on all aspects of the implant procedure, including but not limited to:

- Access into the anterior mediastinum,
- Substernal tunneling (Zone 1),
- Lead anchoring technique
- Transverse tunneling to the device pocket (Zone 2),
- Device pocket creation, and
- Implant device testing

All implant training will be documented in the Investigator Site File (ISF).

During the implant procedure, the investigator will be placing the lead utilizing a tunneling procedure. It is imperative that methods are utilized to ensure safe access to the anterior mediastinum via a sub-xiphoid approach. As cardiothoracic surgeons routinely perform midline sternotomy procedures, Medtronic intends to use a team approach during the EV ICD implant to ensure the knowledge and skills are transferred to a non-surgical physician specialty (EP/Cardiologist). A Cardiac Surgeon/Cardiothoracic Surgeon trained on relevant components of the study procedure will attend, at minimum, the first five implant procedures attempted by each implanting physician to partner on safe blunt dissection technique for tunneling into the anterior mediastinum and support the implant procedure. The Cardiac Surgeon/Cardiothoracic Surgeon can also add context to specific subject anatomy. It is required that the Cardiac Surgeon/Cardiothoracic Surgeon will also provide emergency support during all clinical study implant procedures.

For sites that participated in the EV ICD Pilot study, implanting physicians with previous proctored implant procedures from the EV ICD Pilot study may be counted towards the requirement for the Cardiac Surgeon/Cardiothoracic Surgeon to attend the first five EV ICD Pivotal Study implant procedures.

If the implanting physician is also trained and currently performing activities similar to a cardiothoracic surgeon, there may be instances where a separate CT surgeon is not required. If this occurs, this shall be discussed ahead of time with the Medtronic clinical study team, and Medtronic approval must be documented prior to the procedure taking place.

6.8. Product Receipt, Tracking, and Accountability

The EV ICD System components (EV ICD, lead) and accessory components (sternal tunneling tool, transverse tunneling tool, SafeSheath introducer, software, and MyCareLink Patient Monitor), will be considered investigational in geographies in which the product is not available commercially and will be labeled for exclusive use in clinical investigations. Investigational system components will be distributed to a site only when Medtronic has received all required documentation (not limited to, Ethics Committee or Competent Authority approval, a signed Clinical Trial Agreement, and documentation of training) and has notified the site of site readiness.

Distribution of the investigational product to study sites will be managed by Medtronic and investigational products may only be ordered by Medtronic personnel. Sites with these clinically labeled EV ICD System components will track disposition upon receipt or return of the components, as well as upon implant or explant of the components.

Product accountability will be documented on the Device Accountability electronic Case Report Form (eCRF), which will be maintained in the Electronic Data Capture (EDC) system.

This eCRF will track, at a minimum, the following information:

- Date of receipt

- Identification of the investigational components, if applicable (Lot or serial number or unique code)
- Expiration date, if applicable
- Date used or installed
- Subject identification (ID) Number, if applicable
- Date and reason for return or disposal, if applicable
- Name of person responsible for receipt, return or destruction/disposal, if applicable
- Uninstallation or explant date of the investigational components and software, if applicable

Medtronic will perform internal final study product reconciliation per the applicable study-specific document or per local requirements, to ensure all study product has been accounted for either by physical return to Medtronic or documented disposal at the site or vendor (including method of disposal). Periodic reconciliation of investigational product will be performed to ensure traceability.

6.9. Product Storage

All investigational products must be stored in accordance with their labelling in a secure location at the site with access limited only to authorized personnel. It is the responsibility of the investigator to correctly handle, store, and track the investigational products. If allowed per local regulations, the programmer installed with the investigational software may be used for commercial use as the software can only communicate with investigational EV ICD devices.

6.10. Product Return

All explanted, open but unused and potentially defective products (device, leads, tools, etc.) should be returned to Medtronic for analysis whenever possible and when permissible by local laws and regulations. If the products are explanted but not returned, a justification is required to be reported on the appropriate eCRF(s) (note that this is not considered a study deviation). The Device Accountability eCRF must be updated in the event of an explant. Local Medtronic field personnel or representative can be contacted to receive a Return Mailer Kit. All unused investigational products must be returned to Medtronic upon study closure at the site.

The SW041 software may remain installed on specific 2090 programmers for the purposes of providing support for subject's EV ICD System after the study is closed. If SW041 software is no longer required (e.g., replaced by updated market-released software), the SW041 software will be removed from the 2090 or 29901 programmers manually.

7. Selection of Subjects

7.1. Study Population

The study population will consist of subjects who have class I or IIa indication for implantation of a single chamber Implantable Cardioverter Defibrillator (ICD) according to current ACC/AHA/HRS or ESC guidelines, and who do not have a bradycardia pacing or cardiac resynchronization therapy indication.

7.2. Subject Enrollment

Patients will be screened to ensure they meet all the inclusion and none of the exclusion criteria.

Subjects are considered enrolled in the study upon signing the Informed Consent Form. Informed Consent must be obtained prior to performing any study-related procedures.

7.3. Inclusion Criteria

	Inclusion Criteria	Rationale
1.	Patient has a Class I or IIa indication for implantation of an ICD according to the ACC/AHA/HRS Guidelines[viii], or ESC guidelines[ix].	Study will be evaluated in the standard patient population that is indicated for the device under evaluation.
2.	Patient is at least 18 years of age and meets age requirements per local law.	Ensure age is appropriate to provide Informed Consent.
3.	Patient is geographically stable and willing and able to complete the study procedures and visits for the duration of the follow-up.	Ensure ascertainment of data required for clinical evaluation.

viii Al-Khatib SM, Stevenson WG, Ackerman MJ, Bryant WJ, Callans DJ, Curtis AB, Deal BJ, Dickfeld T, Field ME, Fonarow GC, Gillis AM, Hlatky MA, Granger CB, Hammill SC, Joglar JA, Kay GN, Matlock DD, Myerburg RJ, Page RL. 2017 AHA/ACC/HRS guideline for management of patients with ventricular arrhythmias.

ix Priori SG, Blomstrom-Lundqvist C, Mazzanti A, Blom N, Borggrefe M, Camm J, Elliot PM, Fitzsimons D, Hatala R, Hindricks G, Kirchhof P, Kjeldsen K, Kuck KH, Hernandez-Madrid A, Nikolaou N, Norekval TM, Spaulding C, Van Veldhuisen DJ. 2015 ESC guidelines for the management of patients with ventricular arrhythmias and the prevention of sudden cardiac death. European Heart Journal 2015 36:41 (2793-2867). https://doi.org/10.1093/eurheartj/ehv316

7.4. Exclusion Criteria

	Exclusion Criteria	Rationale
1.	Patient is unwilling or unable to personally provide Informed Consent.	Not allowing legally authorized representatives.
2.	Patient has indications for bradycardia pacing [x] or Cardiac Resynchronization Therapy (CRT) [xi] (Class I, IIa, or IIb indication).	First generation of system does not include chronic bradycardia pacing support and does not include a left ventricular lead.
3.	Patients with an existing pacemaker, ICD, or CRT device or leads.	Avoid possible confounding factors (e.g., complications due to changeout procedure). Subjects who have recently had a system removal may be considered if the physician feels procedure complications and/or infections are resolved.
4.	Patients with these medical interventions are excluded from participation in the study: • Prior sternotomy • Any prior medical condition or procedure that leads to adhesions in the anterior mediastinal space (i.e., prior mediastinal instrumentation, mediastinitis) • Prior abdominal surgery in the epigastric region • Planned sternotomy • Prior chest radiotherapy Or any other prior/planned medical intervention not listed that precludes their participation in the opinion of the Investigator.	Avoid possible surgical risks during the tunneling procedure due to fibrosis or scarring in the mediastinal tissue.
5.	Patient has previous pericarditis that: • Was chronic and recurrent, or • Resulted in pericardial effusion [xii], or • Resulted in pericardial thickening or calcification. [xiii]	Avoid possible surgical risks related to the tunneling procedure arising from clinically significant pericarditis.

x 2015 HRS/EHRA/APHRS/SOLAECE expert consensus statement on optimal implantable cardioverter-defibrillator programming and testing).
xi ACC/AHA/HRS guidelines for Cardiac Resynchronization Therapy
xii As documented on echo or MRI
xiii As documented on CT scan or MRI

	Exclusion Criteria	Rationale
6.	Patients with these medical conditions or anatomies are excluded from participation in the study: • Hiatal hernia that distorts mediastinal anatomy • Marked sternal abnormality (e.g., pectus excavatum) • Decompensated heart failure • COPD with oxygen dependence • Gross hepatosplenomegaly Or any other known medical condition or anatomy type not listed that precludes their participation in the opinion of the Investigator.	Excluded due to anatomical abnormalities that increase procedure risk, increased risk of infection, or risk of potential comorbidities that impact evaluation of the system during a clinical study.
7.	Patients with a medical condition that precludes them from undergoing defibrillation testing: • Severe aortic stenosis • Current Intracardiac LA or LV thrombus • Severe proximal three-vessel or left main coronary artery disease without revascularization • Hemodynamic instability • Unstable angina • Recent stroke or transient ischemic attack (within the last 6 months) • Known inadequate external defibrillation • LVEF < 20% • LVEDD >70 mm Or any other known medical condition not listed that precludes their participation in the opinion of the Investigator.	Exclude patients who may be more vulnerable to potential increased risk during the evaluation of the clinical study defibrillation protocol.
8.	Patient with any evidence of active infection or undergoing treatment for an infection.	Standard exclusion criterion for device implant, emphasized due to importance.
9.	Patient is contraindicated from temporary suspension of oral/systemic anticoagulation	To reduce risk of bleeding/hematoma intraprocedurally or in the event that an urgent sternotomy/thoracotomy is required
10.	Patient with current implantation of neurostimulator or any other chronically implanted device that delivers current in the body.	For the purposes of clinical data collection and interpretation it is preferable to avoid any possible electrical interference with the EV ICD System.

	Exclusion Criteria	Rationale
11.	Patient meets ACC/AHA/HRS or ESC clinical guideline Class III criteria for an ICD (e.g., life expectancy of less than 12 months).	Standard exclusion criterion to ensure study cohort is expected to survive to the time of endpoint evaluation and to ensure the study only includes patients with current clinical indications for an ICD.
12.	Patient is enrolled or planning to enroll in a concurrent clinical study that may confound the results of this study, without documented pre-approval from a Medtronic study manager.	Standard exclusion criterion to avoid confounding procedural requirements due to multiple experimental studies.
13.	Patient with any exclusion criteria as required by local law (e.g., age or other).	Standard exclusion criterion to comply with any additional local requirements which may apply.
14.	Pregnant women or breastfeeding women, or women of child bearing potential and who are not on a reliable form of birth regulation method or abstinence. [xiv]	Pregnant women are excluded to avoid harm to the fetus caused by fluoroscopy requirements.

8. Study Procedures

The following criteria were considered when selecting sites for the EV ICD Pivotal Study:

- Investigator/site is qualified by training, education, and relevant experience appropriate to the use of the product and associated procedures
- Investigator/site expects to have adequate time and resources to conduct the study throughout the duration of the study
- Investigator/site has access to an adequate number of eligible subjects
- Ability to comply with applicable Ethics Committee and regulatory requirements
- Investigator is not debarred, disqualified, or working under sanctions in applicable regions
- Site has demonstrated experience working (well) with Medtronic clinical research in the last 3 years
- Site can support timely data entry (e.g., coordinator)
- Site has the ability to do full (90°) lateral fluoroscopy (biplane preferred), anesthesia, and the ability to treat AEs that require surgical intervention in the location where they plan to perform the procedure

xiv If required by local law, women of child-bearing potential must undergo a pregnancy test within seven days prior to EV ICD Pivotal Study procedures

- Investigator(s) is willing and able to attend hands on implant training as outlined in section 6.7 (1-2 implanting investigators per site)
- Site has a robust emergency protocol - site can react to need for major cardiac surgery within 10 minutes

Medtronic contracts with participating institutions/investigators through a Clinical Trial Agreement that defines the scope and responsibilities and associated compensation related to carrying out the obligations under a clinical study sponsored by Medtronic.

During the activation process (prior to subject enrollment), Medtronic will train site personnel on, but not limited to, the current version of the CIP, relevant standards and regulations, Informed Consent process, data collection and reporting tools. In addition, site personnel must be delegated by the Principal Investigator to perform study-related activities. If new members join the site team, required documentation will be obtained and they will receive training on the applicable clinical investigation requirements relevant to their role before contributing to the clinical investigation. Medtronic will provide each study site with written documentation of study site/investigator readiness. In order to receive written documentation of study site/investigator readiness, the following documentation must be available:

- Regulatory authority approval
- Ethics Committee approval and voting list
- Signed Clinical Trial Agreement
- Current CVs for investigators and authorized designees, signed and dated
- Confirmation of receipt of IB, if available
- Financial disclosure for investigators

Prior to performing study-related procedures, all sites must have Ethics Committee and associated regulatory authority approval if applicable (e.g., Competent Authority approval) as well as documentation from Medtronic of site readiness.

8.1. Schedule of Events

Visit schedule and data collection requirements are summarized below in Table 3.

Table 3: EV ICD Pivotal Study schedule of events

Study procedure	Baseline	Implant	PHD	2 Weeks	3 Months	6 Months	Long-Term (12, 18, 24…months)	Unsched.	Sys. Mod.	Exit
Informed Consent	X									
Inclusion/Exclusion Assessment	X									
Physical Exam, Demographics, Cardiovascular Medical History, Surgical History	X									
SF-12 quality of life survey	X					X				
Florida Patient Acceptance Survey (FPAS)[1]						X				
System and procedure information		X							X	
Pre-procedure Transesophageal Echocardiogram (TEE)[2]		X[2]								
CT or MRI scan	X[3]									
Fluoroscopy recordings during tunneling procedure		X							X[6]	
Fluoroscopy (AP and Lateral cine) of final ICD generator and lead position		X							X[6]	
Sensing, Impedance & Pacing Tests		X	X	X	X	X	X	X[5]	X[6]	
Defibrillation Testing		X				Subset[4]			X[6]	
Chest Radiographs – (PA/Lateral)	X		X			X				
Echocardiographic data within the last 6 months	X									
Save-to-media files		X	X	X	X	X	X	X	X	X
Medications (for subjects implanted with any device)	X	X	X	X	X	X	X	X	X	X
Adverse Events[7] (including AEs with fatal outcome), Device Deficiencies, HCUs, Study Deviations, and Other Cardiac Imaging	As they occur									

1 Only for subjects who complete their ICF in English.

2 Required for subjects presenting in persistent atrial fibrillation to confirm the absence of LA or LV thrombus.

3 Taken within the last year. Recommended for first 3 subjects at minimum, for each implanter. If collected/reviewed, send CT-scan and/or MRI to Medtronic.

4 Only for subjects participating in chronic defibrillation testing, see CIP Addendum for 6-Month Defibrillation Testing.

5 Optional. If electrical testing conducted, print the Testing Reports to PDF or paper and send a copy of the reports to Medtronic

6 System modification where a subject leaves the procedure with an EV ICD System.

7 Recommended to collect incision photographs if an infection related to the EV ICD System is suspected.

8.2. Medications

Medication details will be collected via electronic case report forms (eCRFs) on a rolling basis throughout the study. Document all oral and intravenous medications prescribed to the subject at the time of the Baseline visit on the eCRFs and continue to document medication changes (when medications are stopped or started) throughout the subject's participation in the study. In addition, medications administered or adjusted to treat a reported adverse event shall be reported. If the subject is not implanted or attempted to be implanted, medication collection is not required.

8.2.1. Prior and Concomitant Medications

There are no restrictions regarding prior or concomitant medications, with the exception of oral/systemic anticoagulants per study exclusion criteria (section 7.4).

8.3. Subject Consent

Informed Consent (IC) is defined as a legally effective documented confirmation of a subject's voluntary agreement to participate in a particular clinical study. This confirmation occurs after information has been given to the subject on all aspects of the clinical study that are relevant to the subject's decision to participate (ISO 14155:2011). This process includes obtaining an Informed Consent Form (ICF) and an Authorization to Use and Disclose Personal Health Information/Research Authorization/other privacy language as required by law. The ICF and Authorization to Use and Disclose Personal Health Information/Research Authorization/other privacy language as required by law shall be approved by Medtronic and each study site's Ethics Committee (EC) prior to enrolling subjects. These shall be signed and personally dated by the subject and the Principal Investigator or authorized designee as required.

Subjects of centers that agree with and obtain approval from their EC and associated regulatory authority, if applicable, will be invited to participate in the optional 6-month defibrillation testing. Subjects are free to decline this testing with no penalty.

An ICF, either part of the initial ICF or a stand-alone document, will be provided to potential participants, outlining the procedure, potential risks, and benefits. Subjects will be considered enrolled for the 6-month defibrillation testing at the time they sign the ICF.

The document(s) must be controlled (i.e., versioned and dated) to ensure it is clear which version(s) was/were approved by Medtronic and the EC. Any adaptation of the previously approved ICF must be reviewed and approved by Medtronic and the EC prior to being used to consent or re-consent a study subject.

The investigator must notify the subject of any significant new findings about the study that become available during the course of the study which are pertinent to the safety and well-being of the subject, as this could impact a subject's willingness to participate in the study. If relevant, subjects must be requested to confirm their continued participation in writing.

Prior to initiation of any study-specific procedures, IC must be obtained from the subject. Subjects in the US will be required to sign a HIPAA authorization form before participating sites can collect, use and submit subject information to the study sponsor.

The process of obtaining Informed Consent shall:

- Ensure that the Principal Investigator or an authorized designee conducts the IC process.
- Include all aspects of the EV ICD Pivotal Study that are relevant to the subject's decision to participate throughout the clinical study.
- Avoid any coercion or undue improper influence on, or inducement of the subject to participate.
- Not waive or appear to waive the subject's legal rights.
- Ensure the ICF and Authorization to Use and Disclose Personal Health Information/Research Authorization/HIPAA/other privacy language, as required by law, are given to the subject in a non-technical language the subject is able to read and understand.
- Provide ample time and opportunity for the subject to read and understand the ICF to inquire about details of the study, and to consider participation. All questions about the study should be answered to the satisfaction of the subject.
- Include a personally dated signature of the subject acknowledging that their participation in the study is voluntary.
- Include a personally dated signature of the Principal Investigator or authorized designee responsible for conducting the IC process, as required by local law.
- Include any other locally required signatories, such as witnesses, as indicated by country-specific legislations.
- Provide the subject with a copy of the ICF and Authorization to Use and Disclose Personal Health Information/Research Authorization/HIPAA/other privacy language as required by law, and any other written information, signed and dated if required by local law.
- Ensure subject is notified of any significant new findings about the study that become available during the course of the study which are pertinent to the safety and well-being of the subject, as this could impact a subject's willingness to participate in the study.

If the IC is obtained the same day the subject begins participating in study-related procedures, it must be documented in the subject's case history that consent was obtained prior to participation in any study-related procedures. The IC process shall be documented in the subject's case history, regardless of circumstance.

In the event the subject cannot read and/or write, and if allowed by local law, the IC shall be obtained through a supervised oral process. An independent witness (if applicable as per local regulation) must be present during this process. The ICF and any other information must be read aloud and explained to the prospective subject, and whenever possible, either the witness or prospective subject shall sign and personally date the ICF attesting that the information was accurately explained, and that IC was freely given. The source documentation shall provide the method used for communication with the prospective subject and the specific means by which the prospective subject communicated agreement to participate in the study.

The original signed ICF must be filed in the hospital/clinical chart and/or with the subject's study documents.

The ICF and Authorization to Use and Disclose Personal Health Information/Research Authorization/HIPAA/other privacy language shall be available for monitoring and auditing if required by law. Any Medtronic personnel who support the study procedure must be able to review the subject's signed and dated ICF and verify its completeness prior to proceeding with the study procedure. In the event the Medtronic personnel identify the ICF as being incomplete, the study procedure will not be allowed to occur until the consent of the subject can be adequately and appropriately obtained.

8.4. Enrollment / Baseline

When a patient and the Principal Investigator or authorized designee (if applicable) signs and dates the ICF, the patient is considered a subject enrolled in the study. The date the subject signed the ICF must be documented in the subject's medical records. Enrollment can be a stand-alone visit or can occur on the same day as the baseline visit. Medtronic shall be notified (via Enrollment eCRF) as soon as possible to aid in enrollment tracking. Once consent is obtained, report adverse events, device deficiencies, study deviations, system modifications, and subject exits or deaths as they occur.

The following information is required to be collected at the baseline visit:

- Confirmation of Inclusion/Exclusion Criteria
  - It is recommended to perform a pre-implant anatomy evaluation (see section 8.4.1)
- Demographics
- Physical exam: A basic physical exam will be performed, including height and weight
- Relevant medication and relevant cardiovascular medical history
- Relevant surgical history
- Primary indication for ICD implant
- Echocardiographic data within the last 6 months

- SF-12 quality of life survey
- Chest radiograph, standing tidal inhalation breath hold (see Table 4)
    - Radiographs shall be sent to Medtronic (see section 8.9)

Table 4: Chest Radiograph collection during Baseline Visit

Visit	Image Collection
Baseline	• Standing PA → Tidal inhalation breath hold • Standing LAT → Tidal inhalation breath hold

8.4.1. Subject Pre-implant Anatomy Evaluation

Assess the subject in a supine position to evaluate potential abdominal interference to safely access substernal space and operator's ability to palpate xiphoid process, costal-rib margins and left sternal border to confirm the subject does not meet exclusion criterion 6.

Review the baseline chest radiographs. It is also recommended to review a CT-scan (cardiac gated preferred) or MRI (taken within the last year) for the first 3 subjects at minimum, for each implanter. Imaging may help with pre-procedure planning and assessment of the subject's anatomy. If the implanter feels the subject has unfavorable mediastinal anatomy, the procedure shall not be attempted, and the subject shall be exited from the study (see section 8.19 Subject Withdrawal or Discontinuation).

If collected/reviewed, send CT-scan and/or MRI to Medtronic (see section 8.9). This information will be used to further characterize clinical results and anatomical considerations.

8.5. Implant Visit

It is recommended that the implant visit occurs within 30 days of study enrollment.

8.5.1. Antibiotic and Infection Control Strategies

Prophylactic antibiotic administration per standard of care (e.g., as specified by the site policies) is required. Standard hospital procedures shall be followed regarding antibiotic therapy for ICD implantation.

8.5.2. Anticoagulation

It is required that subjects on anticoagulants have oral and/or systemic anticoagulants withheld peri-procedurally in order to reduce risk of bleeding/hematoma, as follows:

Pre-procedure:

- Withhold anticoagulants per local protocol.
- Follow the treatment procedures suggested by the drug manufacturer for timing of temporary discontinuation.
- Recommendations by anticoagulant type include:
    - Suspension of novel oral anticoagulants (NOACs) ≥24 hours pre-procedure
    - Suspension of heparin ≥6 hours pre-procedure
    - Suspension of low molecular weight heparin ≥72 hours pre-procedure
    - Suspension of warfarin ≥48 hours pre-procedure

Post-procedure:

- It is recommended to resume oral anticoagulation as soon as possible post-procedurally unless clinically contraindicated (e.g. effusion observed).

- Post-procedure anticoagulation should be resumed as soon as possible unless clinically contraindicated in patients who have had AF for ≥ 48 hours in duration prior to the implant procedure and who convert to sinus rhythm during defibrillation testing to diminish the risk of peri-procedural stroke.

Document all medication changes on the Medications eCRF.

8.5.3. Dual antiplatelet therapy

Patients on dual antiplatelet therapy will be treated per standard of care, at physician discretion.

8.5.4. Fluoroscopy and Photography

Prior to inserting the sternal tunneling tool into the mediastinal space, the investigator is required to review AP and Lateral fluoroscopy to determine the best incision location and angle of entry. The investigator should consider the subject's BMI and abdomen when in the supine position, as it may challenge safe tool utilization. If the investigator does not believe he/she can maintain close proximity

to, or contact with, the posterior of the sternum with the tip of tunneling tool, the investigator should not proceed with the EV ICD implant procedure.

In the event that the investigator does not proceed with the implant procedure:

- AP and lateral fluoroscopic images or videos must be sent to Medtronic. These data will help further the understanding of anatomic variances for future procedure development considerations.

In cases where the investigator does proceed with the implant procedure:

- Collect fluoroscopy cine recordings during the substernal tunneling with the sternal tunneling tool and introducer as well as during EV ICD lead placement.
- Two fluoroscopy cine images (AP and Lateral) are required of the final EV ICD lead placement and device placement for one full respiration cycle.
- Fluoroscopy cine recordings and cine images will be will be sent to Medtronic (see section 8.9).

Photography/ Videography

If allowed per local regulations and accepted by the subject in the Informed Consent Form, Medtronic personnel attending the Implant Visit may take pictures of and/or videotape the implant procedure for training, education, and/or research purposes. These photographs and/or video recordings will not display any identifiable features of the subject. The original files will be kept at the hospital and copies will be sent to Medtronic.

8.5.5. Implant Procedure Steps

Prior to performing the implant procedure, it is important that implanting investigators read and understand the Instructions for Use (IFU) that accompanies each device and undergo documented training by Medtronic.

It is strongly recommended to use general anesthesia with cardiac monitoring during the implant procedure to prevent subject movement and minimize the likelihood of adverse events during procedure. Additionally, general anesthesia will afford a greater level of cardiac monitoring compared to what is practiced when patients are under conscious sedation.

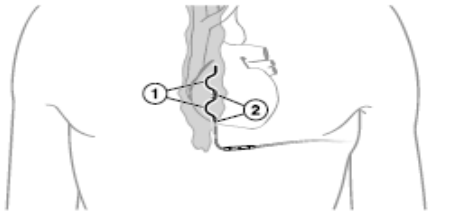
If the procedure is aborted at any point, refer to section 8.19 for additional instructions.

The proposed procedure steps are listed in Table 5. The steps are strongly recommended unless otherwise noted as required steps.

Table 5: Outline of the proposed implant procedure steps

Implant Step	Procedure + Imaging
1. Subject Assessment	• Review pre-procedure chest imaging. • **Required:** Pre-procedural fluoroscopy in both Lateral and AP views is required prior to starting the implant procedure to assist in determining sub-xiphoid incision location for the patient anatomy, to determine whether the sternal tunneling tool tunnel rod curvature needs adjustment based on subject anatomy, to assist in sternal tunneling tool entry into the substernal space to inform the angle of insertion, and identification of appropriate device pocket location. • If the implanter cannot find a way to achieve or maintain consistent contact or close proximity between the distal tip of the tunneling rod and the sternum during insertion or advancement, the procedure should be stopped. • **Required:** If subject presents in atrial fibrillation, perform a pre-procedure TEE to ensure the absence of LA or LV thrombus.
2. Subject Preparation and Drape	• Place 1 set of External Defibrillation Patches in locations that will not compromise the implanted system defibrillation vector or sterile operating field. • Position left arm to allow full lateral fluoroscopy and pocket incision access on left mid-axillary chest. • Determine ICD pocket location using fluoroscopy (AP & Lateral views) and the cardiac silhouette as guidance with demonstration lead and ICD. • Draw surface landmarks on chest, including sternal midline, left sternal border, xiphoid process, costal margins, top of cardiac silhouette and incision location and device pocket location. • Perform sterile preparation of the chest for implant per Standard of Care. • Drape patient chest to provide sterile operating field to access the sub-xiphoid and device pocket incisions.

Implant Step	Procedure + Imaging
3. Sternal Tool and Introducer Preparation	• If needed, manually bend the tunneling rod of the sternal tunneling tool to a curvature suitable for the patient's anatomy. The angle should allow for the tunneling rod tip to remain in contact with (or as close as possible to) the posterior of the sternum during tunneling. • Prepare introducer sheath according to manufacturer's instructions for use and load onto the tunneling rod of sternal tool. • Attach a pre-filled saline syringe (10 cc) to hemostasis valve side-port on introducer with valve open for the implant procedure.
4. Sub-Xiphoid Access	• Make an incision below the xiphoid process and left of sternal midline. Anatomical variation adjustments may be necessary: ○ Consider the margins of the left costal rib and xiphoid process. A lower incision may be required in larger patients to allow for shallow blunt dissection and <30-degree angle of a medical instrument or tunneling rod insertion.
5. Blunt Dissection of Diaphragmatic Attachments	• Use a fingertip and/or curved Kelly hemostat to dissect through diaphragmatic attachments and confirm the tissue plane using lateral fluoroscopy for visualization. • Once the implanter has completed blunt dissection and has entered the mediastinal tissue plane, if resistance is felt (e.g., fibrotic attachments between heart and sternum), abort procedure. • Pre-lay 2 sutures into the rectus fascia (to later secure lead anchoring sleeve).
6. Substernal Tunneling Procedure (Zone 1)	• Insert prepared sternal tunneling rod using full Lateral fluoroscopy into anterior mediastinum. Keep tip of tunneling rod in contact or close to xiphisternal junction and sternum during insertion. • Tunnel approximately midline or just left of sternal midline and no further than the top of cardiac silhouette, as determined by AP Fluoroscopy and surface landmarks. Keep tunneling rod in contact with or close to the posterior of sternum. If any resistance is felt, stop and confirm tunneling tool location in alternate fluoroscopic view. Redirect tunneling rod under the sternum. If patient has COPD or lungs crossing midline are suspected, consider tunneling during

Implant Step	Procedure + Imaging
	end-expiration apnea. • Confirm the pre-filled saline syringe (10 cc) is connected to hemostasis valve side-port on introducer sheath with valve open. • Retain the sheath in position, then slowly remove the sternal tunneling tool from the sheath and incision.
7. EV ICD Lead Insertion and Deployment	• Use AP fluoroscopy to insert the lead to the distal tip of the introducer sheath. • **Required Lead Orientation:** Defibrillation Coils toward subject's right chest; Pace/Sense Rings toward patient's left chest. • Position the lead with respect to the cardiac silhouette and intended ICD location. • Deploy the lead by withdrawing the sheath out of the incision to expose the electrodes over cardiac silhouette for achieving adequate sensing, pacing and defibrillation. Retain the sheath until completion of Step 8. • In the event of the lead deployment in the opposite orientation (Coil 1 and Coil 2 electrodes toward patient's left lateral border), it is recommended to re-advance the introducer over the lead body to the distal tip. • Next, withdraw the lead and reinsert in the required orientation prior to acute testing. • Do not reinsert the lead through the introducer valve more than three times during the procedure. If this occurs, use a new lead.  1 The Coil 1 and Coil 2 electrodes must be oriented toward the patient's right chest. 2 The Ring 1 and Ring 2 electrodes must be oriented toward the patient's left chest.

Implant Step	Procedure + Imaging

8. Assessment of EV ICD Lead	• Evaluate R-wave signal amplitude for Ring1-Ring2 configuration, through one full respiration cycle, using Medtronic CareLink Programmer Model 2090 Analyzer.
	  ○ Set up the 2090 Analyzer to new R-wave filter, ODO mode. Set sensitivity to appropriate setting.
	  ○ Record the measured sensing values.
	• If R-wave amplitude is < 1mV for the Ring1-Ring2 configuration, or P-wave or T-wave oversensing is suspected, attempt repositioning or re-tunneling the lead. If R-wave amplitude remains < 1mV, the implant shall be abandoned, and the implant of an alternative ICD system should be considered.
	• Remove introducer sheath prior to sub-xiphoid suture sleeve fixation.

9. Sub-Xiphoid Suture Sleeve and Lead Fixation	• **Required:** Use a minimum of three non-absorbable sutures with high tension force to fixate anchoring sleeve to lead body in sub-xiphoid incision using each of the three grooves. • **Required:** Tie two non-necrosing sutures to the fascia, then tie to lead anchoring sleeve grooves. Next, tie one suture onto the lead anchoring sleeve to secure to the lead body.
10. Create EV ICD device pocket	• Use fluoroscopy to confirm defibrillation vector based on final lead placement and cardiac silhouette for EV ICD device location. • Create device pocket incision near the left mid-axillary chest to form an optimized vector with the implanted lead.
11. Transverse Subcutaneous Tunneling Procedure (Zone 2)	• Insert distal tip of transverse subcutaneous tunneling rod in sub-xiphoid incision, above/anterior to the costal rib margin and advance into the device pocket incision. • Remove handle to expose lead channel and insert lead connector pin into channel. • Pull tunneling rod with lead inserted in the channel into the device pocket incision. Remove the transverse subcutaneous tunneling rod through the pocket incision.

Implant Step	Procedure + Imaging
12. Device Pocket and Sub-Xiphoid Incision Closure	• Fixate device header against fascial plane using non-absorbable suture in the holes provided. • If the TYRX™ Envelope is used, this shall be documented. • Remove air from incision and close the pocket and sub-xiphoid incisions, at least one layer, prior to device testing. • Final closure of incisions shall be in at least three layers, and wound dressings shall be applied per standard of care.
13. Required Cine of final lead and device placement	• **Required:** Cine, both AP & Lateral views during a full respiration cycle, to document final lead and EV ICD position.
14. EV ICD Device Testing	• Interrogate the EV ICD device and perform electrical testing (sensing, pacing, impedance), as described in section 8.5.6. • Perform defibrillation testing protocol, as described in section 8.5.7.

8.5.6. Implant Testing – EV ICD System

Perform the following tests of the EV ICD System after the EV2401 lead is connected to the EV ICD device and the device is placed into the pocket.

8.5.6.1. Sensing Testing

Perform an RV sensing test. Set ICD RV sensing vector to Ring1-Ring2. Adjust sensing parameters to avoid T-wave oversensing, P-wave oversensing, or other oversensing. Once configured, perform the Sensing Test. Print the Sensing Test Report on the programmer to PDF or paper and store at site. Evaluate alternate sensing vectors as necessary. Program determined sensing settings.

The R-wave amplitude for sensing shall be greater than or equal to 1mV for the Ring1-Ring2 configuration.

If the R-wave amplitude is less than 1mV for the Ring1-Ring2 configuration after all troubleshooting attempts have been exhausted (refer to step 8 in Table 5), the EV ICD implant shall be abandoned and the implant of an alternative ICD system should be considered.

8.5.6.2. Impedance Testing

Subthreshold impedance will be measured for the following electrode pairs:

- Ring1 to Ring2
- Ring1 to Coil2
- High Voltage

Print the Lead Impedance Test Report to PDF or paper and send to Medtronic.

8.5.6.3. Pacing Testing

Pacing capture threshold testing will be performed, potentially in multiple vectors: Ring1-Coil2, Ring1-Ring2, Coil2-Coil1. Pacing capture is defined as at least three consecutive captured beats.

At the conclusion of pacing capture threshold testing, it is recommended to leave pacing settings at the shipped nominal values until pre-hospital discharge.

Print final capture threshold report to PDF or paper and send to Medtronic.

8.5.7. Induction and Defibrillation Testing

To ensure subject safety in an ambulatory setting, sustained shockable ventricular arrhythmia (SSVA) induction and defibrillation testing is required at implant. Adjust device programming to ensure adequate safety margins for sensing and defibrillation during SSVA induction testing.

The testing protocol may require up to six successful SSVA episodes induced and up to 10 EV ICD shocks delivered (Figure 7).

8.5.7.1. General Requirements

Induction of SSVA will be achieved using one of the following methods:

- Burst Induction (Coil2-Coil1, 40V).
- T-shock (up to 20J).

If a subject cannot be induced using these methods, other methods may be employed at the discretion of the investigator (e.g., EP catheter). The investigator may choose to attempt induction on another day prior to discharge. If the investigator determines the subject cannot be induced, the EV ICD System must be removed (refer to section 8.5.8).

Ensure a Wavelet template is collected and EV ICD detection is enabled prior to induction. If the subject's health is at risk, defibrillation testing should be suspended or terminated.

Ensure an external transthoracic defibrillation system is present and ready to deliver rescue shocks during defibrillation testing, and at least one set of rescue patches are in place in locations that will not compromise the implanted system defibrillation vector or sterile operating field.

It is recommended to wait five minutes between the end of an SSVA episode and subsequent induction to ensure that the patient is hemodynamically stable. Waiting period after failed induction attempts is at the investigator's discretion.

Defibrillation testing may continue on a future day if episodes remain within the testing protocol, but lead revision is not permitted on a future day if the subject has resumed anticoagulation.

Anticoagulation should be resumed as soon as possible post-procedurally unless clinically contraindicated (e.g. effusion observed) in subjects who have presented in atrial fibrillation for ≥ 48 hours in duration prior to the implant procedure and who convert to sinus rhythm during defibrillation testing to diminish the risk of peri-procedural stroke.

Reminder: After each induced SSVA episode, save-to-media files shall be collected (see section 8.10). Print the live strip for the duration of each SSVA episode. Retain a copy of the live strip for each episode not recorded by the ICD. If requested, send a copy of the live strip to Medtronic (e.g., a scan). Print the VT/VF episode report to PDF or paper and store at the site.

Record shock outcome and shock impedance (if available) for each EV ICD and rescue shock. A shock will be considered successful if it results in termination of the induced SSVA episode, with termination defined as a return to normal intrinsic rhythm or to a supraventricular tachycardia before the next shock is given. Additional processing of the VF sensing data may be performed after implant data collection.

8.5.7.2. Testing and Programming Defibrillation Therapy

Defibrillation testing success is defined as meeting one of the following criteria:

a. Single SSVA conversion at 20J, or
b. Conversion of two consecutive episodes of SSVA at 30J in final system configuration.

Follow the defibrillation testing as outlined in Figure 7, beginning at Episode 1 (20J). The following requirements shall be observed while conducting defibrillation testing:

- Defibrillation at a given energy will be deemed successful if SSVA is terminated, regardless of whether the shock is delivered manually or automatically by device.
- In one of the two consecutive SSVA episodes, up to two 30J shocks are permitted.

- To achieve final system configuration, changing the position of the ICD generator and/or the lead, or changing shock polarity is permitted.
- If the device or lead position are altered (e.g., position changed as part of troubleshooting), defibrillation success must be demonstrated with the new system configuration.
- If defibrillation protocol episodes are not exhausted, remaining episodes may be used on a subsequent day (e.g., next day or during the admission) to complete the defibrillation testing protocol
- For the first episode following the 20J therapy or the first 30J episode following a "Troubleshoot System" step in Figure 7, program Rx1 polarity to either STD or REV, and program Rx2 polarity the opposite of Rx1 polarity.
- If the episode follows a defibrillation success at 30J, and the previous episode had a defibrillation success with Rx1, program Rx1 and Rx2 to the polarity of Rx1 in the previous episode.
- If the episode follows a defibrillation success at 30J, and the previous episode had a defibrillation success with Rx2, program Rx1 to the same polarity as Rx2 in the previous episode and program Rx2 off.

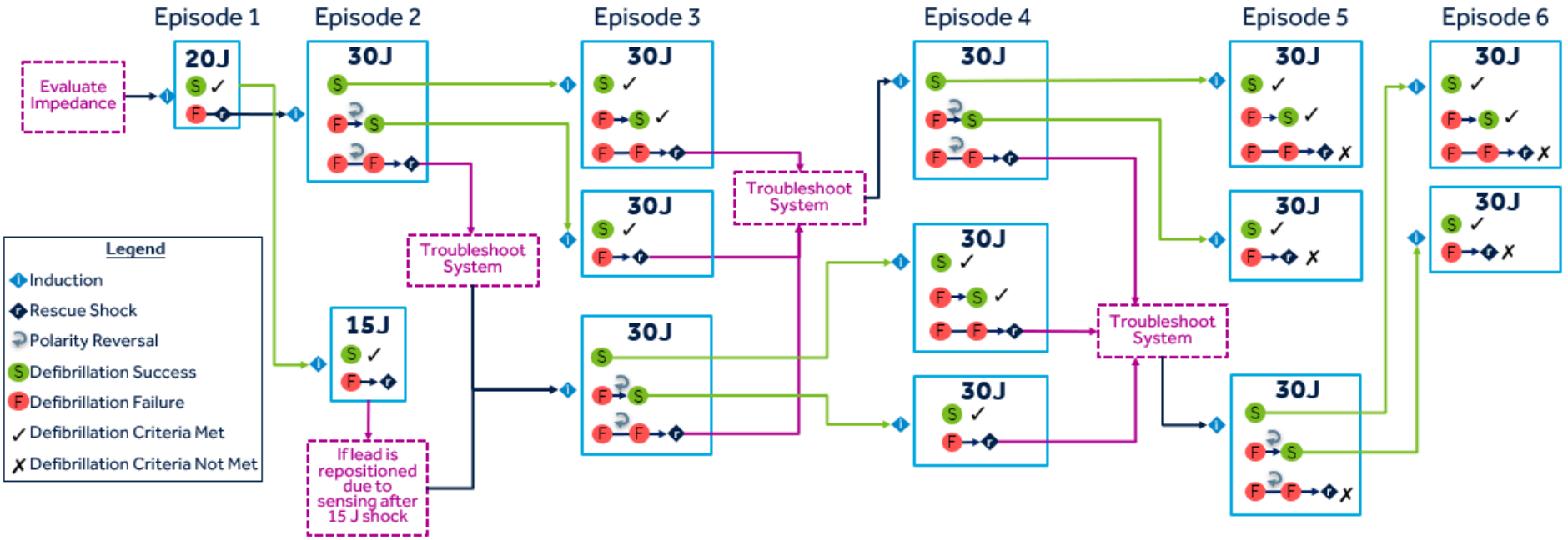


Figure 7: Diagram outlining the process of SSVA induction and defibrillation testing

8.5.7.3. Testing and Programming VF Detection

VF detection success at implant is defined as successful VF detection in a single SSVA episode in the Ring1-Ring2 configuration at a value greater than or equal to 0.2 mV (e.g., 0.2, 0.45, or 0.6 mV). VF detection and defibrillation success do not need to be demonstrated on the same episode(s), but each must be demonstrated in the final system configuration.

Follow the VF detection testing as outlined in Figure 8, beginning at Episode 1. This aligns with Episode 1 for Defibrillation Testing outlined in Figure 7. The following requirements shall be observed while conducting VF detection testing:

- The VF detection shall be demonstrated in the Ring1-Ring2 vector with a Number of Intervals to Detect (NID) setting of 30/40.
    - If VF detection is demonstrated in the Ring1-Ring2 vector, the remaining induction attempts may be programmed with a NID setting of 18/24.
    - Redetect NID shall be programmed to 9/12 when Rx2 is enabled.
- Begin testing with VF Sensitivity programmed to Ring1-Ring2, 0.45 mV.
    - Use this setting when restarting testing to evaluate a new lead position.
- If the first programmed setting is unsuccessful, program VF Sensitivity to Ring1-Ring2, 0.2 mV.
- If the second programmed setting is unsuccessful, reposition the lead and test again with the first programmed VF Sensitivity setting of Ring1-Ring2, 0.45 mV.
- If VF detection is demonstrated in the Ring1-Ring2 vector, program VF Sensitivity to Ring1-Can, 0.45 mV.
- Once VF detection is demonstrated in Ring1-Ring2 and attempted in Ring1-Can, VF detection shall be programmed to the Ring1-Ring2 vector for remaining induction attempts.
    - If desired, additional margin can be assessed by programming VF Sensitivity to 0.6 mV, otherwise it is recommended to complete the remaining induction attempts with Sensitivity programmed to 0.15 mV.[xv]
- Additional inductions beyond those specified in Figure 7 are allowed if needed per medical judgment (e.g., to program sensitivity or to obtain supplementary information on an alternate vector).
- If the VF detection success is demonstrated in the Ring1-Ring2 vector, and the lead position is preserved, it is not necessary to re-demonstrate VF detection in the Ring1-Ring2 configuration, even if the device position is altered (e.g., as part of troubleshooting).

xv In instances where detection has been demonstrated in the Ring1-Ring2 vector at 0.45 mV and the lead is not repositioned, subsequent episodes may be programmed Ring1-Ring2 at 0.15 mV, Ring1-Can at 0.45 mV, or Ring1-Ring2 at 0.6 mV to check for additional margin. Programming VF Sensitivity to 0.6 mV increases the likelihood that VF Detection will not occur, and delivery of a manual shock will be necessary.

- If the lead position is altered (e.g., as part of troubleshooting), previously demonstrated VF detection success is invalidated and success must be demonstrated with the new system configuration with an NID setting of 30/40.

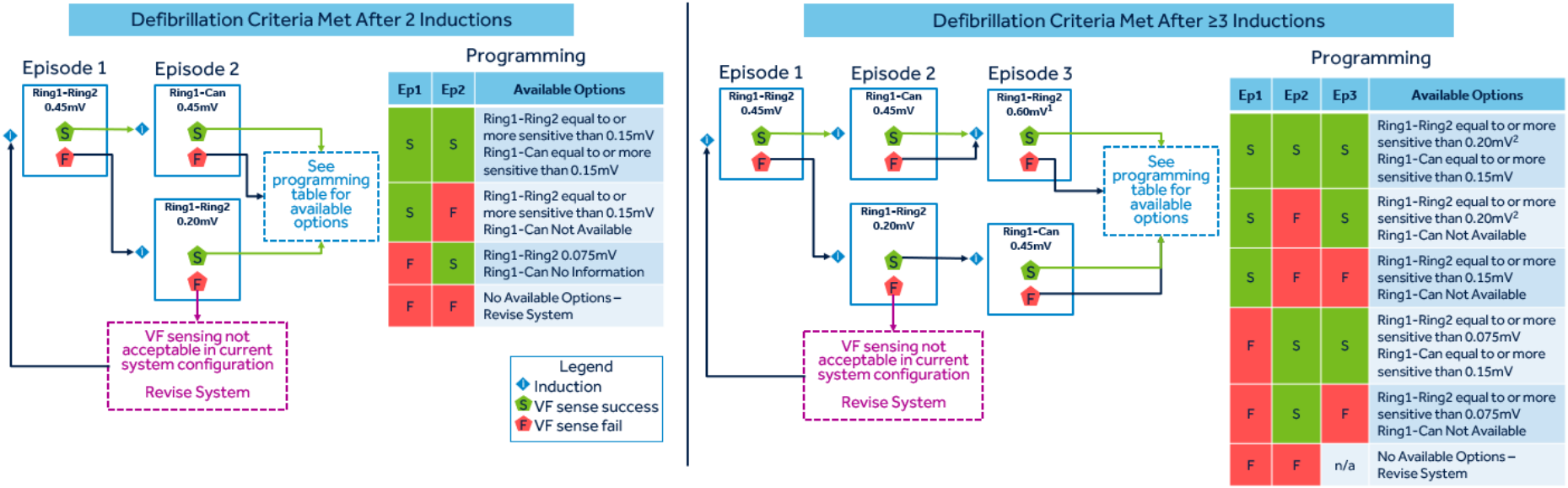


Figure 8: Diagram outlining the process of VF sensing margin testing

1 In instances where detection has been demonstrated in the Ring1-Ring2 vector at 0.45 mV and the lead is not repositioned, VF Sensitivity for subsequent episodes may be programmed to Ring1-Ring2 at 0.15 mV, Ring1-Can at 0.45 mV, or Ring1-Ring2 at 0.6 mV to check for additional margin. Programming VF Sensitivity to 0.6 mV increases the likelihood that VF detection will not occur, and delivery of a manual shock will be necessary.

2 Ring1-Ring2 equal to or more sensitive than 0.20 mV programming option is only available if Ring1-Ring2 was tested successfully at 0.6 mV; Ring1-Ring2 equal to or more sensitive than 0.15 mV programming should be used if 0.6 mV was not successfully tested.

8.5.7.4. Implant Defibrillation Troubleshooting Recommendations

Prior to inducing and throughout the defibrillation protocol, it is recommended to consider the following to improve defibrillation outcome or troubleshooting in the event of failure of first episode(s):

- Check for/resolve pneumothorax
- Check for/resolve high impedance values
- Check for/resolve air in tunnel (e.g., fluoroscopy)
- Check for/resolve air in pocket (e.g., flush with saline or antibiotic wash, massage air out of pocket)
- Check for/resolve gastric bubbles (gas)
- Press on device pocket during testing
- Perform defibrillation during held end tidal expiration (end expiration apnea)
- If all of the above measures are exhausted, evaluate the position of the EV ICD device and the EV ICD Lead. If required, consider repositioning of EV ICD generator or EV ICD lead.[xvi]
- Allow time (e.g., next day or during the admission) to minimize transient factors affecting defibrillation success

Note: Troubleshooting attempts after Episode 5 (Figure 7) may not leave enough remaining episodes to confirm both Defibrillation and VF detection success.

8.5.7.5. Programming Requirements at End of Implant Procedure

At the end of the procedure, VF Detection shall be ON and VF Therapies and Pacing therapies shall be programmed OFF until Pre-Hospital Discharge evaluation to prevent oversensing/undersensing prior to proper evaluation of threshold once the subject is ambulatory. While VF Therapies are OFF, the subject shall have cardiac monitoring.

8.5.8. Subject Exit for Incomplete Implant Visit

The subject shall be exited if any of the following occur during the implant visit:

---

xvi Lead revision is not permitted if the subject has resumed anticoagulation. Post-procedure anticoagulation should be resumed as soon as possible unless clinically contraindicated (e.g. effusion observed) in subjects who have had atrial fibrillation for ≥ 48 hours in duration prior to the implant procedure and who convert to sinus rhythm during defibrillation testing to diminish the risk of peri-procedural stroke.

- Incomplete Placement of Lead and/or Device – The EV ICD System is not fully implanted.
- Incomplete Defibrillation Testing Protocol – The subject cannot complete the entire defibrillation testing protocol because they were not inducible or failed to induce a sufficient number of episodes.
    - Note: If the subject completes the initial implant procedure without completing the defibrillation testing protocol, the subject may be brought back prior to hospital discharge to complete the remainder of the defibrillation testing protocol, as outlined in Figure 7.
- Failure of Defibrillation Testing Protocol – The subject completes the defibrillation testing protocol but does not meet the criteria for success for defibrillation testing.
- Inadequate Sensing – The subject cannot achieve an R-wave ≥ 1 mV for the Ring1-Ring2 sensing vector after troubleshooting methods are exhausted.
- Inadequate SSVA Detection – The subject cannot achieve successful VF detection in a single SSVA episode in the Ring1-Ring2 configuration at a value greater than or equal to 0.2 mV after troubleshooting methods are exhausted.

If the subject does not complete the implant visit due to any of the reasons specified above, the EV ICD System shall be explanted, and the subject shall be followed and assessed for AEs through 30 days or until procedure or system related AEs have been resolved, at which point the subject can be exited (see section 8.19). If the subject receives an alternative system (e.g., S-ICD or TV ICD), any AEs related to the alternate system will be recorded during the course of subject participation, but will not be considered related to the EV ICD System.

Incomplete placement of the lead and/or device, and incomplete or failed electrical or defibrillation testing (including prolongation of hospital stay by allowing time to minimize transient factors affecting defibrillation) are not considered adverse events; however, any adverse events occurring during an unsuccessful implant attempt (e.g., subject allergy to electrodes used during implant) must be recorded and classified on an AE eCRF. Unsuccessful EV ICD system implants and/or failed defibrillation testing shall be evaluated for reporting as a device deficiency.

If the EV ICD System is explanted or repositioned after initial implant procedure but prior to pre-hospital discharge, this shall be captured on a System Modification eCRF.

8.6. Pre-Hospital Discharge

Perform the following pre-hospital discharge tests of the EV ICD System at any time after implant, but prior to discharge. Prior to the subject being discharged, VF Therapies shall be programmed ON and pacing therapies, as appropriate, should be programmed ON.

Programming requirements and recommendations at PHD are outlined in Table 6.

Table 6: PHD Programming Requirements and Recommendations

Required Programming		Recommended Programming	
Initial NID for VF Therapies	Minimum 30/40	VF Sensing	Per implant testing results (most sensitive setting)
All Rx	40 J	VF Sensing if PHD Troubleshooting is required	Per PHD testing results (most sensitive setting)
Pause Prevention	Monitor, 5 s	Post Shock Pacing	Per physician recommendation; 4 V margin minimum
		ATP	At physician discretion; 4 V margin minimum

An initial interrogation save-to-media file shall be collected at the beginning of the visit, and a final (interrogate all) save-to-media file shall be collected at the end of the visit (see section 8.10).

8.6.1. Sensing Testing

At the Pre-Hospital Discharge visit, perform the Sensing Test in the following postures:

- Sitting
- Supine
- Lying on left
- Lying on right

Print the Sensing Test Report to PDF or paper and send a copy of the report to Medtronic.

8.6.2. Impedance Testing

Perform the Impedance Test in a sitting posture. If necessary, impedance testing in additional postures may be performed. Print the Impedance Test Report to PDF or paper and send a copy of the report to Medtronic.

8.6.3. Pacing Testing

Perform pacing testing in a supine posture. If necessary, pacing testing in additional postures may be performed. The following configurations may be evaluated: Ring1-Coil2, Ring1-Ring2, Coil2-Coil1. Pacing capture is defined as at least three consecutive captured beats.

The clinician will evaluate for pacing sensation during testing. Note: Pacing sensation or discomfort observed during testing will not be considered a reportable adverse event.

If post pace oversensing is observed, sensing parameters should be adjusted to eliminate or minimize oversensing. Print the final capture threshold report to PDF or paper and send a copy to Medtronic.

8.6.4. Imaging

Collect the chest radiographs at Prehospital Discharge (PHD) per Table 7 and send to Medtronic (see section 8.9). Additional radiographs may be collected at the discretion of the physician at any post-implant time point if electrical testing at follow-up reveals deterioration in sensing or pacing performance.

Table 7: Chest Radiograph collection during Pre-Hospital Discharge Visit

Visit	Image Collection
Pre-hospital Discharge Visit	• Standing PA → Tidal inhalation breath hold • Standing LAT → Tidal inhalation breath hold

Collection of echocardiogram at pre-hospital discharge may be performed per physician discretion, for example, if suspicion of potential pericardial effusion exists.

If additional images (CT scans, radiographs, TEE, MRI or other imaging modalities) are collected at physician discretion throughout the duration of the study, it is requested that a copy of the images be sent to Medtronic (see section 8.9).

8.7. Scheduled Follow-up Visits

Subjects will undergo assessments at scheduled follow-up visits to characterize the safety and efficacy of the EV ICD System.

Medtronic will provide the target dates and windows for each follow-up visit to the implanting site. Follow-up visit windows open on the Window Start date and remain open as defined in Table 8. It is recommended that subjects are scheduled as close as possible to the target date for a given follow-up visit.

Table 8: Scheduled visit windows

Study Follow-up Visit	Window (Calculated days post-implant procedure)		
	Window Start (days post-procedure)	Target (days post-procedure)	Window End (days post-procedure)
2 Week	7	14	50
3 Month	90	90	120
6 Month	182	182	210
12 Month (1 Year)	335	365	395
18 Month	518	548	578
24 Month (2 Year)	701	730	760
30 Month	883	913	943
36 Month (3 Year)	1066	1096	1126
42 Month	1248	1278	1308
48 Month (4 Year)	1431	1461	1491

All subjects with an implanted EV ICD System will remain in the study and be followed at pre-defined study visits until official study closure. After their study participation ends, the EV ICD System will remain implanted and the subject will be provided with standard medical care by their physician.

At all follow-up visits, photographs of the device pocket and sternal incision are recommended in case an infection related to the EV ICD System is suspected or diagnosed. These photographs will not display any identifiable features of the subject. The original files will be kept at the hospital and copies will be sent to Medtronic. Report any adverse events, including infections, per section 10.5.

8.7.1. 2-Week Follow-up Visit

The following data will be collected at the 2-week follow-up visit:

- Electrical Testing (Sensing, Impedance, and Pacing tests (see section 8.7.6)
- Initial (interrogation) and final (interrogate all) save-to-media files (see section 8.10)
- Adverse Event assessment
- Device Deficiencies assessment
- Healthcare Utilizations
- Study Deviations
- Other Cardiac Imaging

- Medication Log updates

8.7.2. 3-Month Follow-up Visit

The following data will be collected at the 3-month follow-up visit:

- Electrical Testing (Sensing, Impedance, and Pacing tests (see section 8.7.6))
- Initial (interrogation) and final (interrogate all) save-to-media files (see section 8.10)
- Adverse Event assessment
- Device Deficiencies assessment
- Healthcare Utilizations
- Study Deviations
- Other Cardiac Imaging
- Medication Log updates

8.7.3. 6-Month Follow-up Visit

The following data will be collected at the 6-month follow-up visit:

- Electrical Testing (Sensing, Impedance, and Pacing tests (see section 8.7.6))
- Initial (interrogation) and final (interrogate all) save-to-media files (see section 8.10)
- Adverse Event assessment
- Device Deficiencies assessment
- Healthcare Utilizations
- Study Deviations
- Other Cardiac Imaging
- Medication Log updates
- SF-12 quality of life survey
- Florida Patient Acceptance Survey (FPAS) (only for subjects who complete their ICF in English)
- Chest Radiographs per Table 9 (required for subjects participating in chronic defibrillation testing, for other subjects this is recommended) (see section 8.9)

- Chronic Defibrillation Testing, for those subjects who consent to this testing (see CIP Addendum for 6-Month Defibrillation Testing and Appendix I: Chronic Defibrillation Testing Protocol)

Table 9: Chest Radiograph collection during 6-Month Follow-up Visit.

Visit	Image Collection
6-Month Visit	• Standing PA → Tidal inhalation breath hold • Standing LAT → Tidal inhalation breath hold

Chest radiographs should be reviewed by the physician for lead stability at the six-month visit. Chest radiographs for subjects participating in chronic defibrillation testing shall be sent to Medtronic (see section 8.9), and for all other subjects shall be retained at the site and may be sent to Medtronic upon request.

Prior to chronic defibrillation testing, both chest radiographs and the EV ICD System's electrical performance should be considered to decide whether or not to proceed with chronic defibrillation testing. If there is evidence for deterioration of electrical performance or significant movement of the lead, the clinician may consider either changing the device programming or moving the lead (Note: lead repositioning involves a system modification and overall subject health and safety should be considered before proceeding) to ensure adequate functioning of the EV ICD System.

8.7.4. Long-term follow-up Visits

Subjects will be followed up at 12 months post-implant and every 6 months thereafter until the study is closed. The following data will be collected at these visits:

- Electrical Testing (Sensing, Impedance, and Pacing tests; see section 8.7.6)
- Initial (interrogation) and final (interrogate all) save-to-media files (see section 8.10)
- Adverse Event assessment
- Device Deficiencies assessment
- Healthcare Utilizations
- Study Deviations
- Other Cardiac Imaging
- Medication Log updates

8.7.5. Device Troubleshooting

Device troubleshooting is generally required per standard of care for ICD systems and may require additional testing. Additional imaging or data collection may be necessary, and a DR220 Digital Holter Recorder (North East Monitoring, Inc.; investigational in Australia, Canada, New Zealand, and Japan) may be used for up to 24 hours of Holter monitoring. If additional data are collected, data shall be submitted to Medtronic.

If troubleshooting includes a chronic defibrillation test, it is recommended to follow the steps outlined in Appendix I: Chronic Defibrillation Testing Protocol. After conducting a chronic defibrillation test, it is required to complete a Chronic Defibrillation Testing eCRF.

8.7.6. Electrical Testing

Subjects' medical records shall be made available prior to performing electrical testing. An initial interrogation save-to-media file shall be collected at the beginning of the visit, and a final (interrogate all) save-to-media file shall be collected at the end of the visit (see section 8.10).

8.7.6.1. Sensing Testing

At the 2-Week, 3-Month, 6-Month, and Long-Term follow up visits, perform the Sensing Test in a sitting posture. If necessary, sensing testing in additional postures may be performed. Print the Sensing Test Report to PDF or paper and send a copy of the report to Medtronic.

8.7.6.2. Impedance Testing

At the 2-Week, 3-Month, 6-Month, and Long-Term follow up visits, perform the Impedance Test in a sitting posture. If necessary, impedance testing in additional postures may be performed. Print the Impedance Test Report to PDF or paper and send a copy of the report to Medtronic.

8.7.6.3. Pacing Testing

At the 2-Week, 3-Month, 6-Month, and Long-Term follow up visits, perform pacing testing in a sitting posture. If necessary, pacing testing in additional postures may be performed. The following configurations may be evaluated: Ring 1-Coil2, Ring1-Ring2, Coil2-Coil1. Pacing capture is defined as at least three consecutive captured beats. If post pace oversensing is observed, sensing parameters should be adjusted to eliminate or minimize oversensing. Print the final capture threshold report to PDF or paper and send a copy to Medtronic.

8.8. Unscheduled Visits

An Unscheduled follow-up visit is defined as any non-standard of care visit by the subject to the investigative study site due to the EV ICD System between CIP-required visits.

If an Unscheduled Visit occurs:

- Document any adverse events and/or device deficiencies on the associated eCRFs, as applicable.
- Where possible, initial (beginning of the visit) and final (end of the visit) device interrogation data should be collected via a save-to-media file (see section 8.10).
- If electrical testing is conducted, print the Testing Reports to PDF or paper and send a copy of the reports to Medtronic.

8.9. Images and recordings

All images and recordings shall be retained in the subject's file. Copies of images sent to Medtronic shall be transferred in DICOM format.

8.10. Save-to-Media Files

When a save-to-media file/save-to-media files should be collected, a device interrogation (full summary interrogation/interrogate all is best practice) must be performed and saved in a digital format (.pdd) on a USB or other removable electronic media. Save-to-media files shall be sent to Medtronic, with a copy being maintained at the site in the subject's file. It is recommended that data are not cleared during any interrogation.

8.11. CareLink Transmissions

At the time of CIP approval, CareLink will not be available for subjects implanted with the EV ICD System. In the event it becomes available, it is acceptable to collect and utilize data via CareLink transmissions. A CareLink file collected within a visit window will be considered equivalent to an in-office save-to-media file, but a save-to-media file for in-office visits is preferred. If review of a CareLink transmission results in a subject visit to the study center between scheduled visit windows, an Unscheduled Visit eCRF shall be completed.

8.12. Healthcare Utilizations

Health Care Utilization (HCU) information will be collected when the utilizations are related to the following characteristics of the EV ICD System:

- All procedure, system, and accessory related adverse events
- Shocks delivered by the EV ICD System (inclusive of inappropriate shocks and appropriate shocks delivered to treat ventricular arrhythmias)
- Cardiovascular syncope

All inpatient hospitalizations, outpatient hospital encounters, emergency department visits, clinic visits, urgent care, or rehab center utilizations associated with the characteristics listed above are considered reportable HCUs for this study. CIP-required utilizations (except unscheduled visits) should not be reported on HCU eCRFs.

8.13. System Modification

A System Modification eCRF form shall be completed in the event the EV ICD System requires an invasive modification after the subject has been transported out of the procedure room from their initial implant (e.g., explant, replacement, repositioning).

Prior to a system revision a save-to-media file (initial, see section 8.10) shall be collected and the physician should consider the following actions:

- Evaluate electrical performance
- Reprogramming
- Imaging (e.g., chest radiographs), images reviewed by the physician shall be sent to Medtronic (see section 8.9).
- Chronic defibrillation test, it is recommended to follow the steps outlined in Appendix I: Chronic Defibrillation Testing Protocol. After conducting a chronic defibrillation test, it is required to complete a Chronic Defibrillation Testing eCRF.
- Risk-benefit to subject

Unless urgent, the physician should consult with a member of the steering committee for questions about moving forward with a system modification.

In the event of a system modification where an EV ICD System remains in the body, the follow up schedule for the subject will remain unchanged. In cases where an EV ICD System is explanted and not replaced with an EV ICD System, the subject will be exited according to section 8.19.

If the system modification involves replacing or repositioning the lead, the procedure shall be completed by a physician who has undergone EV ICD implant procedure training as specified by Medtronic. It is recommended to demonstrate at least a 10J safety margin. Repeat all data collection from the PHD visit (see section 8.6), including a final save-to-media file (see section 8.10).

8.14. Role of the Sponsor Representatives

Sponsor representatives will provide support as required for the study under supervision of the Principal Investigator, including:

- Provide study training, including but not limited to training on the: CIP, Informed Consent process, data collection tools, and regulations
- Technical support in installing/uninstalling the programmer software into/from the Programmer manually or via the SDN
- Technical support at all study visits under the supervision of the Principal Investigator, including device programming, but no data entry on eCRFs shall be performed by Medtronic personnel or their representatives at sites
- A trained Medtronic representative may support a study investigator at the Implant Visit by proactively providing support and feedback during the implant procedure.
- Sponsor representatives may conduct monitoring and auditing activities for this study.

8.15. Assessment of Efficacy

Efficacy of the EV ICD System with regards to defibrillation testing success will be assessed per the primary efficacy objective at the implant visit (see section 12.5). In addition, efficacy of ATP and shock for termination of spontaneous ventricular arrhythmias will be characterized as part of the ancillary objectives (see sections 12.6 and 12.10).

8.16. Assessment of Safety

Safety of the EV ICD System with regard to major complications related to the system or procedure will be assessed by way of the primary safety objective (see section 12.4). All Adverse Events will be collected throughout the study duration, starting at the time of signing the Informed Consent Form. The prevalence of these adverse events will further be summarized by MedDRA key terms (see section 12.11). Additionally, any device deficiencies related to the EV ICD system or accessory will be collected. Further information on the collection of Adverse Events is discussed in section 10.

8.17. Recording Data

This study will be conducted using an electronic data capture system (e.g., Oracle Clinical Remote Data Capture system, or OC RDC). The electronic data capture system, which allows the study sites to enter study data into the sponsor's database over a secure internet connection, will be used to capture study

required eCRF information. The Principal Investigator or an individual delegated by the Principal Investigator is responsible for entering data for the study on the eCRFs. The Principal Investigator or Sub-Investigator designee (if allowed by local regulation) is required to approve all data on eCRFs via electronic signature. The data reported on the eCRFs shall be derived from source documents, and any discrepancies shall be explained in writing.

Save-to-media files will be collected and stored at the site. Copies submitted to Medtronic should be sent via secure and compliant electronic file transfer services (e.g., Box) and/or secure mail.

Programmer printouts will be collected in hard or electronic copy and stored at the site. Copies submitted to Medtronic shall be sent via secure and compliant electronic file transfer services (e.g., Box) and/or secure mail.

Fluoroscopy /radiograph/ CT images, if collected, shall be stored on a CD/DVD or USB flash drive at the site. Copies submitted to Medtronic shall be sent via secure and compliant electronic file transfer services (e.g., Box) and/or secure mail.

8.18. Deviation Handling

A study deviation is defined as an event within a study that did not occur according to the Clinical Investigation Plan or the Clinical Trial Agreement.

Prior approval by Medtronic is expected in situations where the investigator anticipates, contemplates, or makes a conscious decision to deviate. Prior approval is not required when a deviation is necessary to protect the safety, rights or well-being of a subject in an emergency or in unforeseen situations beyond the investigator's control (e.g., subject failure to attend scheduled follow-up visit, inadvertent loss of data due to computer malfunction, inability to perform required procedures due to subject illness).

For medically justifiable conditions which preempt a subject's ability to complete a study-required procedure, it may be permitted to report only one deviation which will apply to all visits going forward. This may also apply for other unforeseen situations (e.g., the subject permanently refuses to complete a study required procedure and the data will not contribute to the primary endpoint analysis). However, prior approval from Medtronic is required for such situations.

All study deviations must be reported on an eCRF regardless of whether medically justifiable, pre-approved by Medtronic, an inadvertent occurrence, or taken to protect the subject in an emergency. In the occurrence of a corrupted device interrogation file, Medtronic may request a deviation to document that a readable interrogation file is unavailable.

Refer to section 14.7.2 for deviation reporting requirements and timeframes for reporting to Medtronic, Ethics Committee and/or regulatory bodies, as required per local law.

Medtronic is responsible for analyzing deviations, assessing their significance, and identifying any additional corrective and/or preventive actions (e.g., amend the Clinical Investigation Plan, conduct additional training, terminate the investigation). Repetitive or serious investigator compliance issues may result in initiation of a corrective action plan with the investigator and site, and in some cases, necessitate suspending enrollment until the problem is resolved or ultimately terminating the investigator's participation in the study. Medtronic will provide site-specific reports to investigators summarizing information on deviations that occurred at their investigational site on a periodic basis.

Examples of study deviations include but are not limited to:

- Failure to obtain proper Informed Consent
- Failure to collect required study data (e.g., required imaging)
- Inclusion criteria not met/exclusion criteria met at enrollment
- Missing required save-to-media files

8.19. Subject Withdrawal or Discontinuation

Subjects may be exited from the study for reasons such as:

- Subject has completed the study
- Subject lost to follow-up
- Subject death
- Subject did not meet inclusion or met exclusion criteria or meets exclusion due to change since initial evaluation
- Subject chooses to withdraw (e.g., consent withdrawal, relocation to another geographic location)
- Subject does not have or no longer has EV ICD System implanted
- Subject completes but does not pass defibrillation testing prior to pre-hospital discharge
- Investigator deems withdrawal necessary (e.g., medically justified)

A withdrawn subject will be treated according to standard of medical care and will not be replaced. Subjects will be included in the analyses up to the time that consent was withdrawn, or up to the time that the subject is exited.

Subjects who had undergone an implant attempt and did not have an EV ICD System implanted or had their EV ICD System removed without replacement with an EV ICD System may be exited by phone at

the end of 30 days following implant attempt or system removal, or once all system and procedure-related AEs are resolved.

The following information is required to be collected at study exit:

- Reason for exit (this shall be documented on the Study Exit eCRF and in the subject's medical record)
- Save-to-media

In the case that the subject is determined to be lost to follow-up, details of a minimum of two attempts and the method of attempt (e.g., one letter and one phone record or two letters) to contact the subject must be recorded. In addition, follow the regulations set forth by the governing Ethics Committee. Upon withdrawal from the study, no further study data will be collected, and no additional study visits will occur for the subject.

9. Risks and Benefits

9.1. Potential Risks

Medtronic follows rigorous Quality Assurance and Control procedures throughout the development and clinical study of a research system. The formal Hazard/ Risk Analysis for the EV ICD System is performed according to ISO 14971:2012 (Medical Device Risk Management) and is used to ensure that the level of risk is acceptable and reduced as low as possible prior to starting the EV ICD Pivotal Study.

The EV ICD System is assessed via a System Hazard Analysis to ensure all potential risks, at individual component and at system-levels, are evaluated and minimized via risk controls. The subject risk assessment evaluates potential risks associated with: system implant/explant, biological compatibility, therapy delivery, diagnostic data integrity and security, and potential failure modes associated with the finished devices. Risk control strategies for the EV ICD Pivotal Study risks were developed by a cross-functional team and in accordance with the Risk Management process. Risk controls are implemented via safety design inputs, and acceptable safety performance is demonstrated via system design verification and validation activities. During the course of the study, risks will be continuously monitored, assessed and documented by the investigators. It is the Principal Investigator's decision to assess whether to continue the study at the respective site, should safety-related concerns arise.

The risks are reduced as much as possible, with residual risk being documented within the Risk Management Report (DSN028279, Version 2.0 or currently approved version) and disclosed in the Informed Consent Forms provided to subjects. A summary of the risk analysis and risk assessment will

also be listed in the EV ICD Pivotal Investigator's Brochure.

A summary of potential risks and risk mitigation strategies associated with the EV ICD System and EV ICD Pivotal Study is presented in Table 10. Potential risks associated with the study are further minimized by selecting qualified investigators and training site personnel on the CIP and hands-on training program.

Table 10: Potential Risks and Mitigation Strategies

Risks	Mitigation Strategies
Procedural risks such as acute trauma, infection, or chronic trauma	i. Procedural technique instructions intended to optimize safety are provided in the CIP ii. The CIP requires that the EV ICD implant procedure is to be performed by an investigator who has received timely hands-on training on all aspects of the implant procedure iii. Medtronic intends to use a proctorship strategy during the EV ICD implant in order to ensure the knowledge and skills are transferred to a non-surgical physician specialty (EP/Cardiologist). Cardiothoracic surgeons will also provide emergency support during the clinical study.
Failure to provide effective high voltage shock therapy when needed by the subject	i. An external defibrillation system(s) is required to be present and ready at all times during the implant defibrillation testing procedure. The external defibrillator(s) is to be prepared to be used in case of emergency. ii. Exclusion of subjects with current implantation of a pacemaker, ICD, neurostimulator or any other chronically implanted device which delivers current in the body, that may interfere with therapy delivery iii. Testing during the implant procedure to ensure proper system set-up connections and lead integrity iv. Defibrillation therapy configuration instructions provided in the protocol which help promote optimal tachyarrhythmia detection and therapy v. EV ICD System design verification and end-to-end system design validation ensuring defibrillation therapy as specified
Inappropriate delivery of high voltage	i. Exclusion of subjects with current implantation of a

Risks	Mitigation Strategies
shock therapy	pacemaker, ICD, neurostimulator or any other chronically implanted device which uses current in the body, that may interfere with therapy delivery ii. Testing during the implant procedure to ensure proper system set-up connections and lead integrity iii. Defibrillation therapy configuration instructions provided in the protocol and training which help avoid oversensing and resulting inappropriate therapy delivery iv. EV ICD System design verification and end-to-end system design validation ensuring defibrillation therapy as specified
Failure to provide effective bradycardia pacing therapy when needed by the subject	i. Exclusion of subjects with current implantation of a pacemaker, ICD, neurostimulator or any other chronically implanted device which delivers current in the body, that may interfere with therapy delivery ii. Testing during the implant procedure to ensure proper system set-up connections and lead integrity iii. Pacing therapy configuration instructions provided in the CIP and training which help avoid oversensing and resulting failure to deliver pacing therapy when needed (e.g., post-shock) iv. EV ICD System design verification and end-to-end system design validation ensuring pacing therapy as specified
Delivery of bradycardia pacing therapy at an excessive rate causing symptoms	i. EV ICD System reliability analysis ensuring freedom from failures as specified
Arrhythmia induction (pacing during vulnerable period, proarrhythmic pauses, electrical/mechanical stimulus)	i. An external defibrillation system(s) is required to be present and ready at all times during the implant defibrillation testing procedure. The external defibrillator(s) is to be prepared to be used in case of emergency. ii. EV ICD System reliability analysis ensuring freedom from failures as specified
Acceleration of an existing tachyarrhythmia	i. Defibrillation therapy configuration instructions provided in the protocol and training which help avoid ineffective shock therapy and resulting arrhythmia acceleration ii. EV ICD System design verification and end-to-end system

Risks	Mitigation Strategies
	design validation ensuring defibrillation therapy as specified
Extracardiac stimulation	i. Clinician training and CIP procedures for preventive measures regarding pain/ stimulation thresholds, including the use of general anesthesia, for the potential discomfort or pain associated with the pacing stimulation outputs and shocks ii. Pacing therapy configuration instructions provided in the CIP and training which help avoid unnecessary therapy energy delivery such that extracardiac stimulation can be minimized/avoided iii. EV ICD System design verification and end-to-end system design validation ensuring pacing therapy as specified
Thermal/electrical injury to subject tissues	i. EV ICD System reliability analysis ensuring freedom from failures as specified
Subject exposure to toxic materials	i. EV ICD System design utilizes materials that have sufficient biological compatibility and performance as demonstrated by a biocompatibility assessment
Subject exposure to allergic materials	i. EV ICD System design utilizes materials that have sufficient biological compatibility and performance as demonstrated by a biocompatibility assessment
Product degradation due to bio instability	i. EV ICD System design utilizes materials that have sufficient biological compatibility and performance as demonstrated by years of successful field performance in products using equivalent materials
Missing or misleading data pertaining to diagnostic data or system integrity is presented to user	i. EV ICD System design verification and end-to-end system design validation ensuring data corruption monitoring as specified
Catastrophic failure of implanted product necessitating procedural revision of implanted components	i. EV ICD System reliability analysis ensuring freedom from failures as specified ii. EV ICD System design verification and end-to-end system design validation ensuring system integrity monitoring mechanisms as specified
Exposure to radiation energy via diagnostic imaging modalities	i. Expected medical practice includes shielding the subject against unnecessary radiation exposure during diagnostic imaging.

Risks	Mitigation Strategies
	ii. Practicing as low as reasonably achievable (ALARA) principles during the device implantation.
During travel, subjects may not have immediate access to programmers with applicable software	i. Subjects will be provided with subject ID cards. Software may be downloaded upon request by contacting subject's doctor or Medtronic.

If a subject becomes pregnant during the study, there may be risks that are not yet known. Radiation exposure may cause miscarriage, birth defects or other unforeseen medical conditions.

There may be other discomforts and risks related to the EV ICD System and/or this study that are not foreseen at this time.

The potential adverse events related to the EV ICD System and procedure and the EV ICD Pivotal Study procedures identified from the risk assessment are listed in Table 11. The additional procedural steps beyond traditional ICD implant such as increased radiation due to additional required radiographs and the substernal placement of the lead were considered in the creation of this list. In addition, the risks associated with the optional 6-month defibrillation testing (see CIP Addendum for 6-Month Defibrillation Testing) are the same as for the implant defibrillation testing and therefore also included in the list.

Table 11: EV ICD System/Procedure- and EV ICD Pivotal Study-related Potential Adverse Events

EV ICD System/Procedure-related Potential Adverse Events	EV ICD Pivotal Study-related Potential Adverse Events
Acute tissue trauma	Acute tissue trauma
Allergic reaction of local tissues	Allergic reaction of local tissues
Bradyarrhythmia	Cardiac arrest
Cardiac arrest	Chronic tissue trauma
Cardiac perforation	Discomfort associated with implant
Cardiac tamponade	Dizziness
Chronic tissue trauma	Dyspnea
Death	Hiccups
Device migration	Infection
Discomfort associated with fibrotic growth	Mental anguish*
Discomfort associated with implant	Organ damage (liver, mammary arteries, diaphragmatic arteries)
Discomfort associated with product migration	Pain

EV ICD System/Procedure-related Potential Adverse Events	EV ICD Pivotal Study-related Potential Adverse Events
Dizziness	Palpitations
Dyspnea	Radiation sickness
Electrical/thermal tissue damage	Skeletal muscle twitching
Erosion	Syncope
Extracardiac stimulation	Tachyarrhythmia
Failure to provide necessary therapy	
Hematoma	
Haemorrhage	
Hemothorax	
Hiccups	
Hospitalization	
Inappropriate shocks	
Infection	
Lead abrasion	
Lead fracture	
Lead insulation failure	
Lead migration	
Lethargy	
Mental anguish*	
Organ damage (liver, mammary arteries, diaphragmatic arteries)	
Pain	
Palpitations	
Pericardial effusion	
Pericarditis	
Pneumothorax	
Radiation sickness	
Return of cardiac symptoms	
Seroma	
Skeletal muscle twitching	
Syncope	
Tachyarrhythmia	

EV ICD System/Procedure-related Potential Adverse Events	EV ICD Pivotal Study-related Potential Adverse Events
Toxic reaction to implant	
Twiddler's syndrome	
Wound dehiscence	

*Subjects susceptible to frequent shocks despite medical management could develop psychological intolerance to an ICD system that might include the following conditions:

- Dependency
- Depression
- Fear of premature battery depletion
- Fear of shocking while conscious
- Fear that shocking capability may be lost
- Imagined shocking (phantom shock)

9.2. Potential Benefits

The EV ICD Pivotal Study provides access to ICD therapy for patients who are unable to receive a transvenous system because they have occluded vessels or anatomical anomalies, and for patients that can benefit from preservation of cardiac vasculature. For other patients, there is no proven benefit. Furthermore, the EV ICD System introduces additional potential benefits as compared to subcutaneous ICD systems currently on the market, specifically:

- Better signal to noise ratio from the substernal space as compared to a subcutaneous configuration, resulting in better detection/discrimination algorithms for sensing arrhythmias (and potentially fewer inappropriate shocks)
- Reduced defibrillation energy required to defibrillate as compared to a subcutaneous configuration, resulting in improved battery longevity
- Longer battery longevity and corresponding reduction in adverse events associated with device replacement
- Asystole pacing
- Anti-tachycardia pacing
- Smaller device which increases patient comfort and acceptance

The information gained from this study could result in the improved management of patients with the EV ICD System. Additionally, information collected from this study may assist in the design of new product(s)/therapy(ies) and/or instructions for use.

9.3. Risk-Benefit Rationale

The majority of the risks associated with the EV ICD System are similar to the risks associated with existing transvenous and subcutaneous ICD systems on the market. The unique risks introduced by the EV ICD System include: unique harms associated with procedural complications (e.g., liver laceration, cardiac trauma/ tamponade), unique harms associated with defibrillating from a substernal lead position (e.g., tissue heating/necrosis), unique harms from chronic lead implant in the substernal space (e.g., dislodgment due to absence of fibrosis), and the general risk that an EV ICD System has not yet been chronically implanted in humans for greater than 12 months. The results of the System Hazard Analysis confirm that the patient risks are reduced as far as possible and the residual risks are deemed acceptable.

The foreseeable benefits of the EV ICD System for patients with occluded vessels or anatomical anomalies and for patients that can benefit from preservation of cardiac vasculature include: a reduction in procedural risk as compared to transvenous systems, enhanced tachyarrhythmia therapies as compared to subcutaneous systems (i.e., improved signal/noise, reduced shock energy, and offering of ATP), and improved patient comfort and acceptance due to the smaller size of device as compared to subcutaneous systems. Although there is no proven benefit for patients who are able to receive a transvenous system, there may be benefits specific to the novel design of the EV ICD System. As compared to a transvenous system, the EV ICD System is expected to result in fewer extraction complications. Since the EV ICD System avoids implanting a lead in the heart, risks such as: systemic infection, embolism, vascular/SVC tears, and lead extraction injuries are expected to be significantly reduced or eliminated.

10. Adverse Events and Device Deficiencies

Timely, accurate, and complete reporting and analysis of safety information for clinical studies are crucial for the protection of subjects. Reporting and analysis of safety data are mandated by regulatory authorities worldwide. Medtronic has established procedures in conformity with worldwide regulatory requirements to ensure appropriate reporting of safety information. The study is conducted in accordance with these procedures and regulations.

Since the safety reporting requirements and classification systems vary for each regulatory agency, requirements from all geographies are taken into account for the collection and reporting of safety information.

10.1. Assessment

10.1.1. Adverse Events Assessment

Adverse Event (AE) definitions are provided in Table 12. All AEs will be collected throughout the study duration, starting at the time the Informed Consent Form is signed. For purposes of reporting, events shall be captured on an AE eCRF.

All instances of shocks delivered by the EV ICD will be considered associated with a reportable AE. Shocks delivered appropriately to treat a ventricular arrhythmia should be noted as treatment delivered within the AE for the ventricular arrythmia(s) experienced. If shocks are delivered inappropriately due to an EV ICD issue, the issue should be reported as the underlying system related AE.

Reporting of these events to Medtronic will occur on an Adverse Event eCRF, including a description of AE, date of onset of AE, date of awareness of site, treatment, resolution, assessment of both the seriousness and the relatedness to the system and/or procedure. Each AE must be recorded on a separate AE Form. Subject deaths are also required to be reported. Refer to section 10.7 for Subject Death collection and reporting requirements.

Documented pre-existing conditions are not considered AEs unless the nature or severity of the condition has worsened. Worsening may be identified if there is a change in frequency, associated symptoms, or the need for new/additional treatment (e.g., ventricular arrhythmias would be considered worsened if there are new associated symptoms or treatment/shock is warranted). In all geographies, Unavoidable Adverse Events, listed in Table 12 need not be reported unless the adverse event worsens or is present outside the stated timeframe post-implant procedure. Adverse events impacting users or other persons are also reportable during the course of the study.

For AEs that require immediate reporting, initial reporting may be done by phone, fax, or on the eCRF by completing as much information as possible. The AE eCRF must be completed as soon as possible.

10.1.2. Device Deficiencies Assessment

Device deficiency information will be collected throughout the study and reported to Medtronic. An eCRF should be completed for each device deficiency that did not lead to an Adverse Event.

Note that device deficiencies that result in an adverse device effect (ADE) to the subject should be captured as an AE only. Device deficiencies that did not lead to an AE but could have led to a Serious

Adverse Device Effect (SADE) (i.e., if suitable action had not been taken, if intervention had not been made, or if the circumstances had been less fortunate) require immediate reporting.

Examples of instances that may be considered device deficiencies in the absence of an untoward clinical occurrence to the subject may include, but are not limited to:

- Damaged components observed out of packaging
- Unsuccessful EV ICD System implant and/or failed defibrillation testing
- Pervasive/persistent sensing issues occurring outside of device testing
- System placement outside of labeling (e.g., lead in pleural space)

10.2. Processing Updates and Resolution

For any changes in status of a previously reported AE (i.e., change in actions taken, change in outcome, change in relatedness), information needs to be updated on or added to the original AE form. All AEs must be followed until the AE has been resolved, the subject exits the study, or until study closure, whichever occurs first.

All efforts should be made to continue following subjects until all system or procedure related AEs that are not resolved, as classified by the investigator, are resolved.

At the time of study exit, all collected AEs with an outcome of “not recovered/not resolved”, “recovering/resolving” or “unknown” must be reviewed and updates provided as applicable.

10.3. Adverse Events and Device Deficiency Definitions

For the purposes of the clinical report, Medtronic will classify each AE according to ISO 14155:2011.

Where the definition indicates “device”, it refers to any device used in the study. This might be the device under investigation, or any market released component of the EV ICD System or accessory.

Table 12: Adverse Event and Device Deficiency definitions

General	
Adverse Event (AE)	Any untoward medical occurrence, unintended disease or injury, or untoward clinical signs (including abnormal laboratory findings) in subjects, users or other persons, whether or not related to the investigational medical device. Note: This definition includes events related to the investigational medical device or the comparator. Note: This definition includes events related to the procedures involved. Note: For users or other persons, this definition is restricted to events related to investigational medical devices. (ISO 14155:2011 section 3.2)
Adverse Device Effect (ADE)	AE related to the use of an investigational medical device. Note: This definition includes AEs resulting from insufficient or inadequate instructions for use, deployment, implantation, installation, or operation, or any malfunction of the investigational medical device. Note: This definition includes any event resulting from use error or from intentional misuse of the investigational medical device. (ISO 14155:2011 section 3.1)
Device Deficiency (DD)	Inadequacy of a medical device with respect to its identity, quality, durability, reliability, safety or performance. Note: Device deficiencies include malfunctions, use errors, and inadequate labeling. (ISO 14155:2011, 3.15)
Relatedness	
Procedure Related	An adverse event that is directly related to the implantation or modification of the EV ICD System. NOTE: In general, this excludes events that are inherent to any surgical procedure (e.g., anesthesia complications, anticoagulation interruption) as well as indirect subsequent consequences of the procedure (e.g., reaction to pain medication).
System Related	An adverse event that results from the presence or performance of any component of the EV ICD System. Device Related: An adverse event that results from the presence or performance (intended or otherwise) of the device. Lead Related: An adverse event that results from the presence or performance (intended or otherwise) of the lead.

Accessory Related	An adverse event that results from the presence or performance of the EV ICD System accessory. Sternal Tunneling Tool Related: An adverse event that results from the presence or performance (intended or otherwise) of the sternal tunneling tool. Transverse Tunneling Tool Related: An adverse event that results from the presence or performance (intended or otherwise) of the transverse tunneling tool. Safesheath II Related: An adverse event that results from the presence or performance (intended or otherwise) of the SafeSheath II. Programmer Related: An adverse event that results from the presence or performance (intended or otherwise) of the programmer. Programmer Software Related: An adverse event that results from the presence or performance (intended or otherwise) of the programmer software. MyCareLink Patient Monitor Related: An adverse event that results from the presence or performance (intended or otherwise) of the patient monitor.
Not Related	Relationship to the device or procedures can be excluded when: • The event is not a known side effect of the product category the device belongs to or of similar devices and procedures; • The event has no temporal relationship with the use of the device or the procedures; • The serious event does not follow a known response pattern to the medical device (if the response pattern is previously known) and is biologically implausible; • The discontinuation of medical device application or the reduction of the level of activation/exposure – when clinically feasible – and reintroduction of its use (or increase of the level of activation/exposure) do not impact the serious event; • The event involves a body-site or an organ not expected to be affected by the device or procedure; • The serious event can be attributed to another cause (e.g., an underlying or concurrent illness/clinical condition, an effect of another device, drug, treatment, or other risk factors); • The event does not depend on a false result given by the device used for diagnosis (when applicable); • Harm to the subject are not clearly due to use error; • In order to establish the non-relatedness, not all the criteria listed above might be met at the same time, depending on the type of device/procedures and the event.

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

Seriousness	
Serious Adverse Event (SAE)	Adverse event that a) led to death, b) led to serious deterioration in the health of the subject, that either resulted in 1) a life-threatening illness or injury, or 2) a permanent impairment of a body structure or a body function, or 3) in-patient or prolonged hospitalization, or 4) medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function, c) led to fetal distress, fetal death or a congenital abnormality or birth defect NOTE: Planned hospitalization for a pre-existing condition, or a procedure required by the CIP, without serious deterioration in health, is not considered a serious adverse event. (ISO 14155:2011, 3.37)
Serious Adverse Event (SAE) – Germany Definition	A serious adverse event is an event that occurs in a clinical investigation subject to approval or occurring in a performance evaluation which led, might have led or could lead directly or indirectly to death or serious deterioration of health of the subject, the user or a third party, without consideration if the event has been caused by the medical device itself; this applies accordingly to serious adverse events occurring in a clinical investigation or performance evaluation for which an exemption of the approval authorization as per MPG § 20 paragraph 1 sentence 2 has been granted. (MPSV § 2 Definitions Abs 5)
Serious Adverse Device Effect (SADE)	ADE that has resulted in any of the consequences characteristic of a SAE. (ISO 14155:2011 section 3.36)
Unanticipated Adverse Device Effect (UADE)	Any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death, was not previously identified in a nature, severity, or degree of incidence in the investigational plan or application (including a supplementary plan or application), or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects. (21 CFR 812.3(s))
Unanticipated Serious Adverse Device Effect (USADE)	SADE which by its nature, incidence, severity or outcome has not been identified in the current version of the risk analysis report. Note: Anticipated Serious Adverse Device Effect (ASADE) is an effect which by its nature, incidence, severity or outcome has been identified in the risk analysis report. (ISO 14155:2011 section 3.42)
Significant Safety Issue (SSI)	A safety issue that could adversely affect the safety of participants or materially impact on the continued ethical acceptability or conduct of the trial.

Urgent Safety Measure (USM)	A measure required to be taken in order to eliminate an immediate hazard to a participant's health or safety. Note: This type of significant safety issue can be instigated by either the investigator or sponsor and can be implemented before seeking approval from HRECs or institutions.
Complication	An adverse event that includes the following is considered a complication: • Results in death, • Involves any termination of significant device function (i.e., defibrillation therapy), or • Requires an invasive intervention Non-invasive (21 CFR 812.3(k)): when applied to a diagnostic device or procedure, means one that does not by design or intention: Penetrate or pierce the skin or mucous membranes of the body, the ocular cavity, or the urethra, or enter the ear beyond the external auditory canal, the nose beyond the nares, the mouth beyond the pharynx, the anal canal beyond the rectum, or the vagina beyond the cervical os For purposes of this part, blood sampling that involves simple venipuncture is considered non-invasive, and the use of surplus samples of body fluids or tissues that are left over from samples taken for non-investigational purposes is also considered non-invasive. Note: Only system or procedure related AEs will be classified as complication (major, minor) or observation.
Major complication	A system or procedure-related complication which results in: • Death • Permanent loss of defibrillation function due to mechanical or electrical dysfunction of the device • Hospitalization • Prolongation of an existing hospitalization by at least 48 hours • System revision (reposition, replacement, explant) Note: Only system or procedure related AEs will be classified as complication (major, minor) or observation.
Minor complication	Any complication that is not a major complication (e.g., event classified as a complication solely based on intravenous drug administration). Note: Only system or procedure related AEs will be classified as complication (major, minor) or observation.
Observation	Any adverse event that is not a complication. Note: Only system or procedure related AEs will be classified as complication (major, minor) or observation.

<table>
<tr><th colspan="2">Timing</th></tr>
<tr><td>Pre-Implant Procedure</td><td>Occurs after the IC has been signed but before the skin incision during the EV ICD implant procedure.</td></tr>
<tr><td>During Implant Procedure</td><td>Occurs during the EV ICD implant procedure, after skin incision and prior to completion of skin closure.</td></tr>
<tr><td>Post-Implant Procedure</td><td>Occurs after the completion of skin closure for the EV ICD implant procedure.</td></tr>
<tr><th colspan="2">Other</th></tr>
<tr><td>Unavoidable Adverse Event</td><td>An Adverse Event inherent to a surgical procedure that is expected to occur in all subjects for a projected duration according to the Investigator's opinion, including, but not limited to:
<table>
<tr><th>Event Description</th><th>Timeframe (hours) from the Surgical Procedure</th></tr>
<tr><td>Anesthesia related nausea / vomiting</td><td>24</td></tr>
<tr><td>Low-grade fever (oral temperature >98.6°F (>37°C) but <100.4°F (<38.0°C))</td><td>48</td></tr>
<tr><td>Pocket site / Incisional pain</td><td>72</td></tr>
<tr><td>Mild to moderate bruising / ecchymosis</td><td>168</td></tr>
<tr><td>Sleep problems (insomnia)</td><td>72</td></tr>
<tr><td>Back pain related to laying on table</td><td>72</td></tr>
<tr><td>Shoulder pain/discomfort/stiffness related to shoulder immobilization during procedure</td><td>72</td></tr>
</table></td></tr>
<tr><td>Hospitalization</td><td>A therapeutic inpatient hospitalization (excludes observation unit, emergency room and outpatient visits) lasting greater than or equal to 24 hours.</td></tr>
</table>

10.4. Adverse Event and Deficiency Classification

All adverse events and device deficiencies will be reviewed by a Medtronic representative. AEs will be classified according to the definitions provided in section 10.3.

Upon receipt of AEs at Medtronic, a Medtronic representative will review the adverse event/device deficiency for completeness and accuracy and when necessary will request clarification and/or additional information from the Investigator. Medtronic will utilize MedDRA, the Medical Dictionary for Regulatory Activities, to assign a MedDRA term for each AE based on the information provided by the investigator.

Regulatory reporting of AEs and device deficiencies that could have led to a SADE will be completed according to local regulatory requirements. Refer to section 14.7 for a list of additional required

investigator and Medtronic reporting requirements and timeframes. It is the responsibility of the investigator to abide by any additional AE reporting requirements stipulated by the Ethics Committee responsible for oversight of the study.

For a list of Foreseeable Adverse Event List, refer to Appendix E: Foreseeable Adverse Event List. The Foreseeable Adverse Event List consists of observed adverse device effects in similar Medtronic studies, adverse events reported in published literature and other special considerations. An evaluation of potentially anticipated events, adverse device effects observed in previous clinical studies, and reported events in literature may be used in combination with device labeling, current event reporting information, and other published data to assess if an adverse event is unexpected.

Adverse Events and Deaths will be classified according to the standard definitions as outlined in Table 12.

Table 13: Adverse Event classification responsibilities

What is classified	Who classifies	Classification Parameters
Timing of the Event	Investigator	Pre-implant procedure, During implant procedure, Post-implant procedure
Relatedness	Investigator	Procedure, Device, Lead, Sternal Tunneling Tool, Transverse Tunneling Tool, SafeSheath II, Programmer, Programmer Software, Patient Monitor
	Sponsor	Procedure, Device, Lead, Sternal Tunneling Tool, Transverse Tunneling Tool, SafeSheath II, Programmer, Programmer Software, Patient Monitor
Severity	Investigator	SAE, Device Deficiency with SADE potential
	Sponsor	SAE, UADE/USADE, Device Deficiency with SADE potential
Diagnosis	Investigator	Based on presenting signs and symptoms and other supporting data
	Sponsor	MedDRA term assigned based on the data provided by Investigator
Death Classification	Investigator	Sudden Cardiac, Non-sudden Cardiac, Non-Cardiac, Unknown

An independent Clinical Events Committee (CEC) will review and adjudicate, at a minimum, all events classified by the investigator or Medtronic as procedure or system related to determine relatedness and complication (major, minor) or observation classifications. In addition, the CEC will also review and adjudicate all Adverse Events resulting in death.

When determining whether a USADE has occurred, where the sponsor's causality assessment conflicts with the assessment made by the site investigator, the site investigator's assessment cannot be downgraded by the sponsor (i.e., altered from 'related' to 'not related'). In this case, if an investigator's judgment triggers the reporting of a USADE, the opinion of both the investigator and the sponsor should be provided with any report sent to regulatory reporting as required.

10.5. Reporting of Adverse Events

Adverse events and Device Deficiencies will be reported according to local regulatory requirements. It is the responsibility of the investigator to abide by the AE/DD reporting requirements stipulated by local law and the Ethics Committee. Reporting requirements in Table 14 have been summarized at the time of CIP creation; however, changes may occur during the course of the study. Updates may be provided under separate cover and it is the investigator's responsibility to comply with current local regulatory and institutional reporting requirements.

Refer to section 14.7 for a list of additional required investigator and Medtronic reporting requirements and timeframes.

For AEs/DDs that require immediate reporting, initial reporting may be done by contacting the study sponsor per the sponsor contact information provided in this document. For emergency contact regarding a UADE/USADE, SAE and/or SADE, contact a clinical study representative immediately (refer to the study contact list provided in the site's study documents binder/investigator site file or refer to the contact information provided on the title page).

Table 14: Adverse Event Reporting Requirements

Serious Adverse Events (SAEs)	
Investigator submit to:	
Medtronic	**Australia:** Without unjustified delay. (The National Health and Medical Research Council (NHMRC) Safety monitoring and reporting in clinical trials involving therapeutic goods November 2016 section C.2.b) **Europe:** To the sponsor in acceptable timely conditions, but not later than within 3 calendar days after investigational site study personnel's awareness of the event, including new information in relation to an already reported event (ISO 14155:2011 and local law) **Japan:** Immediately (no later than 72 hours) (Japan GCP Article 68) **All geographies:** Submit per local reporting requirements
Ethics Committee	**All geographies:** Submit per local reporting requirements
Regulatory authorities	**All geographies:** Submit per local reporting requirements
Head of Medical Institution (HOMI)	**Japan:** Immediately (Japan GCP Article 68)
Sponsor submit to:	
Investigators	**Japan:** Annually (Japan GCP Article 28) **All geographies:** Submit per local reporting requirements
Regulatory authorities	**Europe:** No later than 7 calendar days after awareness; Report immediately, but no later than 2 calendar days after awareness by sponsor for SAE and/or DD that may have led to a SADE which indicates an imminent risk of death, serious injury, or serious illness and that requires prompt remedial action for other patients/subjects, users or other persons or a new finding to it (occurred in the study under same CIP*) **Japan:** Annually (Enforcement Regulation of the PMDL Article 274- 2) **All geographies**: Submit per local reporting requirements
Ethics Committee	**All geographies:** Submit per local reporting requirements
HOMI	**Japan:** Annually (Japan GCP Article 28)
Serious Adverse Device Effects (SADEs)	
Investigator submit to:	
Medtronic	**Australia:** Without unjustified delay. (NHMRC Safety monitoring and reporting in clinical trials involving therapeutic goods November 2016 section C.2.b) **Canada:** SADEs on the patient, the user or any other person must be reported to the regulator and to the Sponsor within 72 hours after it comes to the attention of the qualified investigator. **Japan:** Immediately (no later than 72 hours) (Japan GCP Article 68) **All geographies:** Submit per local reporting requirements
Ethics Committee	**All geographies:** Submit per local reporting requirements
Regulatory authorities	**Canada:** SADEs on the patient, the user or any other person must be reported to the regulator and to the Sponsor within 72 hours after it comes to the attention of the qualified investigator. **All geographies:** Submit per local reporting requirements
HOMI	**Japan:** Immediately (Japan GCP Article 68)
Sponsor submit to:	
Investigators	**Japan:** Annually (Japan GCP Article 28) **All geographies:** Submit per local reporting requirements

Regulatory authorities	**Canada:** Report within 10 days after the sponsor becomes aware. **Japan:** [Life threatening or death] Individual reporting within 15 calendar days after awareness, and [All SADEs] Annually (Enforcement Regulation of the PMDL Article 274- 2) **Saudi Arabia:** Within 15 working days **All geographies:** Submit per local reporting requirements
Ethics Committee	**All geographies:** Submit per local reporting requirements
HOMI	**Japan:** Annually (Japan GCP Article 28)
Unanticipated Adverse Device Effects (UADEs) and Unanticipated Serious Adverse Device Effects (USADEs)	
Investigator submit to:	
Medtronic	**Canada:** USADEs on the patient, the user or any other person must be reported to the regulator and to the Sponsor within 72 hours after it comes to the attention of the qualified investigator. **US:** An investigator shall submit to the sponsor and to the reviewing IRB a report of any UADE occurring during an investigation as soon as possible, but in no event later than 10 working days after the investigator first learns of the effect. (21 CFR 812.150(a)) **Europe:** Immediately after the investigator learns of the event or of new information in relation to an already reported event. (ISO 14155:2011 and local law) **Japan:** Immediately (no later than 72 hours) (Japan GCP Article 68) **All geographies:** Submit per local reporting requirements
Regulatory Authority	**Canada:** USADEs on the patient, the user or any other person must be reported to the regulator and to the Sponsor within 72 hours after it comes to the attention of the qualified investigator. **All geographies:** Submit per local reporting requirements
Ethics Committee	**Australia:** Report USADE to their institution without undue delay and no later than 72 hours of the Principal Investigator becoming aware of the event. (NHMRC Safety monitoring and reporting in clinical trials involving therapeutic goods November 2016 section C.2.g) **US:** An investigator shall submit to the sponsor and to the reviewing IRB a report of any UADE occurring during an investigation as soon as possible, but in no event later than 10 working days after the investigator first learns of the effect. (21 CFR 812.150(a)) **All geographies:** Submit per local reporting requirements
Institution	**Australia:** Report USADE to their institution without undue delay and no later than 72 hours of the Principal Investigator becoming aware of the event. (NHMRC Safety monitoring and reporting in clinical trials involving therapeutic goods November 2016 section C.2.g)
HOMI	**Japan:** Immediately (Japan GCP Article 68)
Sponsor submit to:	
Investigator	**US:** Notification as soon as possible, but not later than 10 working days after the sponsor first learns of the effect. (21 CFR 812.150(b)) **Japan:** Immediately (Japan GCP Article 28) **All geographies:** Submit per local reporting requirements

Regulatory authorities	**Australia:** Fatal or life-threatening Australian USADE – No later than 7 calendar days after being made aware of the case with any follow up information within a further 8 calendar days. Other Australian USADEs- No later than 15 calendar days after being made aware of the case. (NHMRC Safety monitoring and reporting in clinical trials involving therapeutic goods November 2016 section C.1.f) **Canada:** Report within 10 days after the sponsor becomes aware. **Japan:** [Life-threatening or death) Individual reporting within 7 calendar days after awareness, [Non-life threatening or death) Individual reporting within 15 calendar days after awareness, and [All USADE] Annually. (Enforcement Regulation of PMDL Article 274-2) **US:** Notification as soon as possible to FDA, but not later than 10 working days after the sponsor first receives notice of the effect. (21 CFR 812.150(b)) **All geographies:** Submit per local reporting requirements
Ethics Committee	**US:** Notification as soon as possible, but not later than 10 working days after the sponsor first learns of the effect. (21 CFR 812.150(b)) **All geographies:** Submit per local reporting requirements
HOMI	**Japan:** Immediately (Japan GCP Article 28)
Significant Safety Issue (SSI): Sponsor reporting in Australia	
Events to Report	**Reporting Requirement and Timeframe**
Significant Safety Issue	• Urgent Safety Measure (USMs): within 24 hours (where possible) to TGA and without undue delay to investigators & HREC and in any case, no later than 72 hours of the measure being taken. - Reasons for the urgent safety measure, Measures taken, Further actions planned - Reasons for the termination, Measures taken, Further actions planned (NHMRC Safety monitoring and reporting in clinical trials involving therapeutic goods November 2016 section C.1.k)
Significant Safety Issue (continued)	Submit to TGA • Other significant safety measures: Without undue delay and no later than 15 calendar days of the sponsor being aware of the issue. Details of significant safety issue, Further actions planned • Notification of an amendment: Without undue delay and no later than 15 calendar days Note: TGA should receive notification that a SSI has occurred but the amendment revising trial documentation should be submitted to the HREC only • Action taken with respect to safety that has been taken by another country's regulatory agency (relevant to an ongoing clinical trial in Australia): Without undue delay and no later than 72 hours of the trial sponsor becoming aware of the action (Australian clinical trial handbook version 2.2)
Significant Safety Issue (continued)	Submit to TGA, any Australian investigator and HREC • Temporary halt of a trial for safety reasons: Without undue delay and no later than 15 calendar days of the sponsor's decision to halt the trial. Reasons for the halt, the scope of the halt, Measures taken, Further actions planned • Early termination of a trial for safety reasons: Without undue delay and no later than 15 calendar days of the sponsor's decision to termination the trial.

Significant Safety Issue (SSI): Investigator Reporting in Australia	
Events to Report	**Reporting Requirements and Timeframe to submit to Sponsor, HREC and institution**
Significant Safety Issues	• Urgent Safety Measure (USMs): Within 24 hours (NHMRC Safety monitoring and reporting in clinical trials involving therapeutic goods November 2016 section C.2.c) • All other significant safety issues: without undue delay and no later than 72 hours of the principal investigator becoming aware of the event (NHMRC Safety monitoring and reporting in clinical trials involving therapeutic goods November 2016 section C.2.g)
Device Deficiencies with SADE potential	
Investigator submit to:	
Medtronic	**Australia:** Without unjustified delay. (NHMRC Safety monitoring and reporting in clinical trials involving therapeutic goods November 2016 section C.2.b) **Canada:** DDs that have resulted in any of the consequences characteristic of an SAE on the patient, the user or any other person or could do so were it to reoccur must be reported to the regulator and the Sponsor within 72 hours after it comes to the attention of the qualified investigator. **Europe**: To the sponsor in acceptable timely conditions, but not later than within 3 calendar days after investigational site study personnel's awareness of the event , including new information in relation to an already reported event (ISO 14155:2011 and local law) **Japan:** Immediately (no later than 72 hours) (Japan GCP Article 68) **All geographies:** Submit per local reporting requirements
Regulatory authorities	**Canada:** DDs that have resulted in any of the consequences characteristic of an SAE on the patient, the user or any other person or could do so were it to reoccur must be reported to the regulator and the Sponsor within 72 hours after it comes to the attention of the qualified investigator. **All geographies:** Submit per local reporting requirements
Ethics Committee	**All geographies:** Submit per local reporting requirements
HOMI	**Japan:** Immediately (Japan GCP Article 68)
Sponsor submit to:	
Investigator	**Japan:** Immediately per the direction of PMDA and/or annually (Japan GCP Article 28) **All geographies:** Submit per local reporting requirements
Regulatory authorities	**Canada:** Submit to regulatory authorities within 30 calendar days of awareness by Sponsor. **Japan:** Within 30 calendar days after awareness and annually (Enforcement Regulation of PMDL Article 274-2) **Europe:** No later than 7 calendar days after awareness; Report immediately, but no later than 2 calendar days after awareness by sponsor for SAE and/or DD that may have led to a SADE which indicates an imminent risk of death, serious injury, or serious illness and that requires prompt remedial action for other patients/subjects, users or other persons or a new finding to it (occurred in the study under same CIP*) **Saudi Arabia:** Within 15 working days **All geographies:** Submit per local reporting requirements
Ethics Committee	**All geographies:** Submit per local reporting requirements
HOMI	**Japan:** Immediately per the direction of PMDA and/or annually (Japan GCP Article 28)
All other Adverse Events, Device Deficiencies, and new information that may adversely affect safety of the subjects or the conduct of the study	
Investigator submit to:	

Medtronic	**Europe:** Submit in a timely manner after the investigator first learns of the event **All geographies:** Submit per local reporting requirements
Regulatory Authorities	**All geographies:** Submit per local reporting requirements
Ethics Committee	**All geographies:** Submit per local reporting requirements
Sponsor submit to:	
Investigator	**All geographies:** Submit per local reporting requirements
Regulatory authorities	**All geographies:** Submit per local reporting requirements
Ethics Committee	**All geographies:** Submit per local reporting requirements

10.6. Subject Death

All subject deaths must be reported by the investigator to Medtronic on an AE eCRF (AE with fatal outcome) as soon as possible after the investigator first learns of the death. In case of death, there should be one SAE with an outcome of fatal.

A de-identified copy of the death certificate, if available and allowed by state/local law, should be sent to the Medtronic clinical study team. When a death occurs in a hospital, a copy of the death summary report and all relevant hospital records should be sent to Medtronic, if available. If an autopsy is conducted, the autopsy report should also be sent to Medtronic if available and allowed by state/local law. When the death occurs at a remote site, it is the investigative site's responsibility to attempt retrieval of information about the death. In summary, the following data will be collected:

- Date of death
- Detailed description of death
- Cause of death
- Relatedness to system and/or procedure
- Device interrogation (if available)
- Death summary/hospital records (if available and allowed by state/local law)
- Autopsy report (if available and allowed by state/local law)
- Death certificate (if available and/or allowed by state/local law)

10.7. Death Classification and Reporting

Sufficient information will be required in order to properly classify the subject's death. The Investigator shall classify each subject death per the following definitions:

Cardiac Death: A death directly related to the electrical or mechanical dysfunction of the heart.

- Sudden Cardiac Death (SCD): Natural death due to cardiac causes, indicated by abrupt loss of consciousness within one hour of the onset of acute symptoms; preexisting heart disease may have been known to be present, but the time and mode of death are unexpected. If time of onset cannot be determined, SCD will alternatively be defined as any unexpected cardiac death occurring out of the hospital or in the emergency room as dead on arrival.
- Non-sudden Cardiac Death: All cardiac deaths that are not classified as sudden deaths, including all cardiac deaths of hospitalized subjects on inotropic support.

Non-cardiac Death: A death not classified as a cardiac death.

Unknown Cardiac Classification: Unknown death classification is intended for use only when there is insufficient or inadequate information to classify the death.

The Clinical Events Committee will also review all deaths and provide an adjudication of the death classification. See section 11.1 for handling events where the adjudication of the investigator and the CEC differ.

10.8. Product Complaint Reporting

The reporting of product complaints is not part of the EV ICD Pivotal Study and should be done in addition to the AE/DD reporting requirements. It is the responsibility of the investigator to report all product complaints associated with a medical device distributed by Medtronic, regardless of whether they are related to intended use, misuse or abuse of the product. Reporting must be done immediately and via the regular channels for market-released products.

Product Complaint: any written, electronic or oral communication that alleges deficiencies related to the identity, quality, durability, reliability, safety, effectiveness or performance of a medical device that has been placed on the market.

11. Data Review Committees

11.1. Clinical Events Committee

The study will utilize an independent Clinical Events Committee (CEC). At regular intervals, an independent CEC will review events and adjudicate at a minimum all system and procedure-related events. Additionally, the CEC will provide an adjudication of the death classification for all reported deaths.

The CEC will consist of a minimum of three (3) non-Medtronic-employed physicians whose site is not participating in the study, including a CEC chairperson.

Medtronic personnel may facilitate and participate in CEC meetings but will be non-voting members.

For AEs and deaths reviewed by the CEC, Medtronic will provide the CEC with the Investigator's description and supportive documentation (when available). The CEC is responsible for reviewing the Investigator's description and supportive documentation (when available), reviewing applicable definitions, and determining final classifications for all adjudication parameters. For AEs, classification includes system/procedure relatedness and complication (major, minor) or observation. Additionally, the CEC will provide an adjudication for all reported deaths, including system/procedure relatedness and cardiac relatedness.

If the CEC disagrees with the investigator's classification of the event, the difference will be provided to the investigator. If the investigator agrees with the CEC's adjudication, the eCRF documenting the AE will be updated accordingly.

If the investigator does not agree with the CEC's adjudication classification, both determinations will be provided within the final report; however, the CEC's adjudication will be used for data analysis. The disagreement will also be included in reporting to ethics committees and regulatory authorities, if required.

11.2. Data Monitoring Committee

An independent Data Monitoring Committee will be established by Medtronic to periodically review the total incidence of adverse events and follow trends of these events in this study, and make recommendations to Medtronic and/or the Steering Committee regarding study conduct and subject safety. The DMC for this study will consist of a minimum of three and up to seven non-Medtronic members with study related backgrounds and not from sites participating in the study. Medtronic will appoint members of the Committee and the Chairperson. Up to two additional investigators participating in this study may participate in the meetings to offer clarification of events, but none will be given voting privileges. Medtronic personnel may facilitate the DMC meeting (e.g., study manager, statistician), but they will not be voting members.

A quorum of the committee may review interim analyses in which the results are analyzed against the primary objective. A summary of adverse events will be reviewed at this time also. Review and consensus by the entire committee is required to recommend to the sponsor that the study should be stopped for safety reasons.

The DMC Member list will be under a separate cover and available upon request.

11.3. Episode Review Committee

An Episode Review Committee (ERC) will be established to evaluate device-treated ventricular episodes according to an ERC Charter. Committee membership, meeting frequency, roles and responsibilities and procedures will also be described in the ERC Charter. Device-treated ventricular episodes in the device episode log with EGM will be reviewed by the ERC and adjudicated based on appropriateness of therapy (shocks and ATP) delivered to subjects and success of the therapy. Inappropriate therapy will be identified based on adjudication rhythm truth and device episode log information.

This committee may include independent physicians and/or Medtronic personnel. The ERC Member list will be under a separate cover and available upon request.

12. Statistical Design and Methods

12.1. General Considerations

Data analysis will be performed by a Medtronic statistician or designee.

The cohort will include all enrolled subjects who undergo the study procedures unless the subject does not complete the required testing, and there are no pre-specified subgroups for assessment. For endpoints involving only measurements collected at follow-up visits, only subjects who complete those visits will be included in the analysis of those endpoints.

Any tests of treatment effects will be conducted at a two-sided alpha level of 0.05 unless otherwise stated.

A Statistical Analysis Plan will be developed and kept under separate cover and will include a comprehensive description of the statistical methods and reports to be included in the final study report, as well as a description of how missing, unused, and spurious data will be accounted. Any change to the data analysis methods described in the CIP will require an amendment only if it changes a principal feature of the CIP. Any other change to the data analysis methods described in the CIP, and the justification for making the change, will be described in the clinical study report.

12.2. Analysis for market approval outside the US

Human clinical data may be needed to support marketing applications in CE Mark countries and other geographies outside the US. Therefore, Medtronic plans to analyze the accumulated data once 60 subjects undergoing implant of the EV ICD System have completed their 3 Month follow-up visit. This analysis will include characterizing both defibrillation efficacy at implant and incidence of major EV ICD

System/procedure-related complications through at least 3 months. All subjects will continue to be followed and the timeline for other marketing applications will not be impacted by this analysis.

12.3. Sample Size

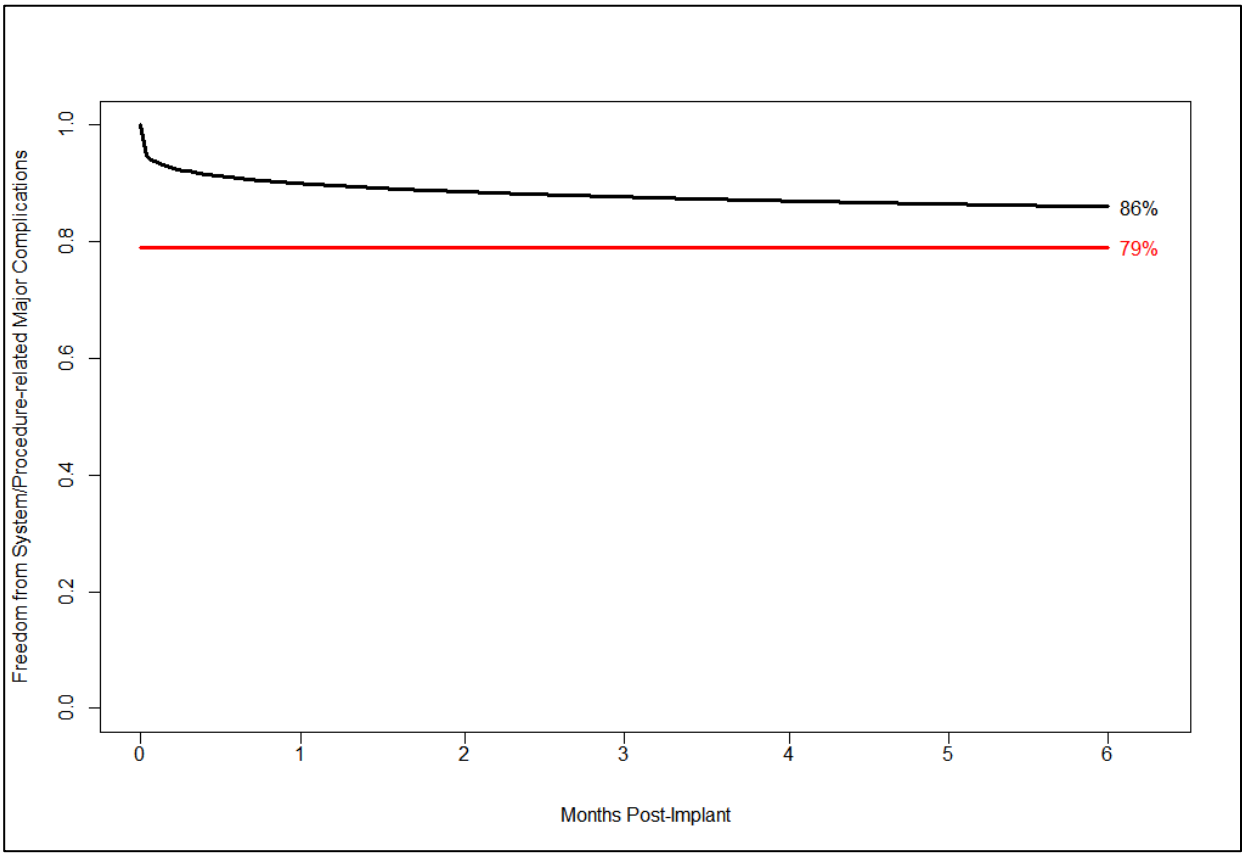
There are two primary objectives (safety and efficacy), and each objective requires 292 subjects to, in the case of the safety objective, undergo an implant attempt of the EV ICD System, and in the case of the efficacy objective, complete the pre-specified defibrillation testing protocol (see section 8.5.7 for details). Since the defibrillation protocol may not be initiated until an implant attempt occurs, the overall sample size requirement will be derived from the efficacy objective; at least 292 subjects will undergo the defibrillation testing protocol, which may result in more than 292 subjects undergoing an implant attempt to satisfy this requirement. To further account for subjects who enroll in the study but exit prior to an implant attempt (19% of 26 enrolled subjects in the EV ICD Pilot study did not undergo an implant attempt), up to 400 subjects may be enrolled.

12.3.1. Primary Objective #1: Safety

An Objective Performance Criterion (OPC) of 79% was chosen based on prior precedent to evaluate the primary safety objective metric of the EV ICD System/procedure-related major complication-free rate at 6 months. The estimated EV ICD System/procedure-related major complication-free rates through 6 months are provided in Figure 9. They are modeled using a Weibull distribution assuming a rate of 90% at one month and 86% at 6 months. A solid line denoting the Objective Performance criterion of 79% is also provided. It is also assumed that attrition (exit or death) will follow a Weibull distribution, with an attrition rate of 9% at one month (allowing for unsuccessful implants) and 16% through one-year post-implant.

The trial was simulated 10,000 times. Each time a sample size of 292 subjects had a time to safety endpoint simulated and a time to attrition simulated using the assumptions above. Using these data, a lower confidence bound for the 6-month Kaplan-Meier freedom from safety endpoint rate was generated using the log scale for each simulation of the trial. It was determined that based on these assumptions and the requirements of a false positive rate (alpha) controlled at 2.5%, a sample size of 292 subjects undergoing an implant attempt is required to allow for 90% power of assessing this objective.

Figure 9: Estimated Freedom from System/Procedure-related Major Complications



12.3.2. Primary Objective #2: Efficacy

An OPC of 88% was chosen to evaluate the primary efficacy objective metric of implant testing success defined as successfully terminating one or more induced ventricular fibrillation episodes (see sections 8.5.7 and 12.5.2 for more details). Each subject who completes the defibrillation protocol will be counted as a success or failure; it is assumed the true success rate is 93.5%. The required sample size to evaluate this objective using a two-sided exact binomial 95% confidence bound and OPC of 88% with 90% power is 292 subjects completing the defibrillation protocol.

12.4. Primary Objective #1: Safety

Demonstrate the freedom from major complications related to the EV ICD System and/or procedure at 6 months post-implant exceeds an OPC of 79%.

12.4.1. Hypothesis

The hypotheses for this objective are as follows, with π_6 denoting the 6-month freedom from major EV ICD System/procedure-related complications rate:

$H_O: \pi_6 \leq 0.79$
$H_A: \pi_6 > 0.79$

12.4.2. Performance Requirements

Performance requirements for this objective define both the endpoint and the OPC. The endpoint is defined as a subject's first occurrence of a major complication related to the EV ICD System and/or procedure as determined by the independent Clinical Event Committee (CEC) that occurs on or prior to 6 months (182 days) post-implant.

For an adverse event to meet the endpoint, the event must have occurred within 182 days (inclusive) of the EV ICD System implant attempt and be adjudicated by the CEC as being a major complication related to the EV ICD System and/or procedure. Major complications are those complications resulting in:

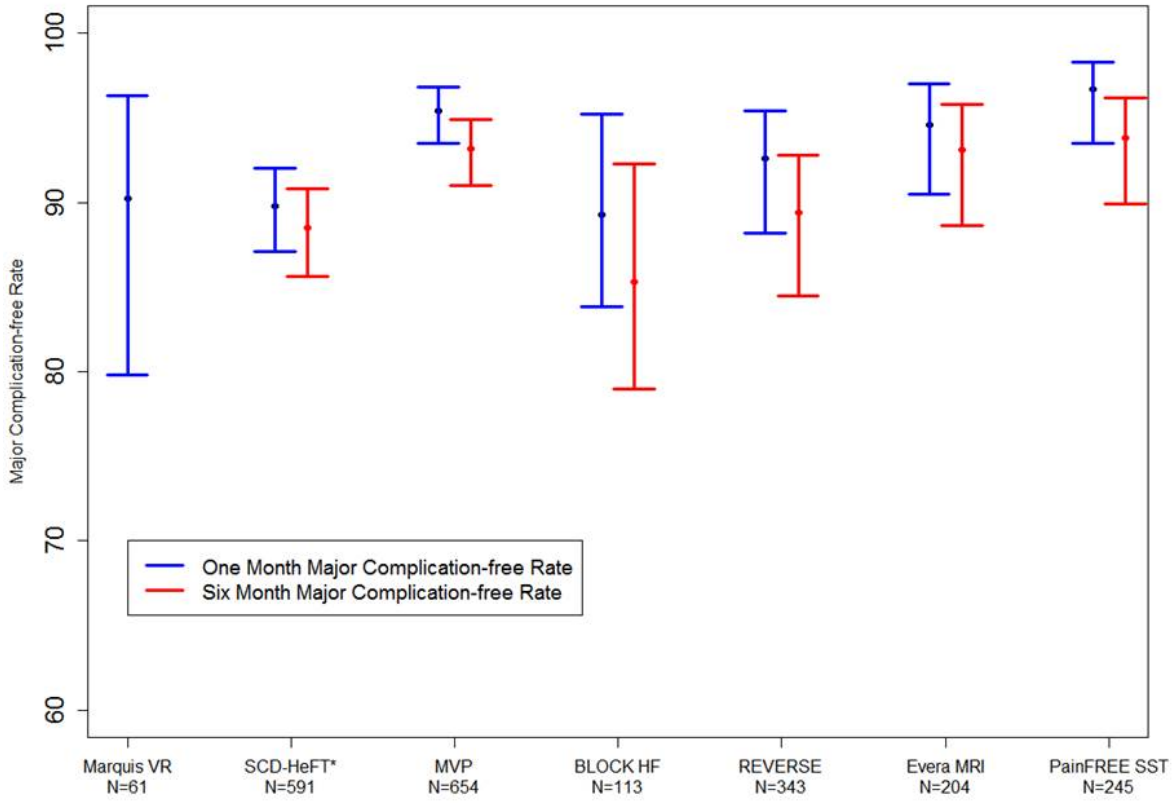
- Death
- Permanent loss of defibrillation function due to mechanical or electrical dysfunction of the device
- Hospitalization (see Table 12 for Hospitalization definition)
- Prolongation of an existing hospitalization by at least 48 hours
- System revision (reposition, replacement, explant)

The pre-specified OPC for the major complication free rate at 6 months is 0.79, meaning the 95% lower confidence bound for the freedom from EV ICD major complication incidence rate must exceed 0.79.

12.4.3. Rationale for Performance Criteria

The determination of the pre-specified OPC (79%) for the major complication objective was based on review of internal Medtronic transvenous ICD trial data as well as literature involving alternative devices. An assessment of comparable major complication-free rates at 6 months for Medtronic transvenous devices showed observed rates as low as 85% (Figure 10). In each such study, only ICD subjects with no history of CABG or valve surgery were analyzed, as that subset of subjects was considered representative of the possible EV ICD population.

Figure 10: Historical ICD Generator/RV Lead/Procedure-related Major Complication-free Rates



*SCD-HeFT rates may include major and minor complications

The following table provides further detail regarding these trials.

Table 15: Historical Medtronic Transvenous ICD Trial Major System/Procedure Complication-free Rates

Study	Study Description	30-day Freedom Rate (95% CI)	6-Month Freedom Rate (95% CI)
Marquis VR[xvii]	Medtronic Market Release Study Evaluating Marquis VR ICD	90.2% (79.8%, 96.3%)	N/A, subjects not followed to 6 months
SCD-HeFT[xviii]	Randomized study comparing ICD therapy to placebo	89.8%* (87.1%, 92.0%)	88.5%* (85.6%, 90.8%)
MVP[xix]	Post-market study comparing MVP to VVI pacing in ICD population without pacing indication	95.4% (93.5%, 96.8%)	93.2% (91.0%, 94.9%)
BLOCK HF[xx]	IDE (G030156) study comparing efficacy of CRT to RV pacing in AV block patients	89.3% (83.8%, 95.2%)	85.3% (79.0%, 92.3%)
REVERSE[xxi]	IDE (G040004) study comparing efficacy of CRT to ICD/OMT therapy in NYHA II patients	92.6% (88.2%, 95.4%)	89.4% (84.5%, 92.8%)
Evera MRI[xxii]	IDE (G140039) study evaluating safety and efficacy of the Medtronic Evera MRI ICD System	94.6% (90.5%, 97.0%)	93.1% (88.6%, 95.8%)
PainFREE SST[xxiii]	Randomized study to evaluate the Medtronic Protecta ICD System	96.7% (93.5%, 98.3%)	93.8% (89.9%, 96.2%)

*Included both major and minor complications

xvii Data on file.

xviii Bardy G, et al. Amiodarone or an Implantable Cardioverter-Defibrillator for Congestive Heart Failure. *NEJM*. 2005; 352:3: 225-237.

xix Sweeney M, et al. Atrial pacing or ventricular backup-only pacing in implantable cardioverter-defibrillator patients. *Heart Rhythm*. 2010; 7(11); 1552-1560.

xx Curtis A, et al. Biventricular Pacing for Atrioventricular Block and Systolic Dysfunction. *NEJM*. 2013; 368:17: 1585-1593.

xxi Linde C, et al. Randomized trial of cardiac resynchronization in mildly symptomatic heart failure patients and in asymptomatic patients with left ventricular dysfunction and previous heart failure symptoms. *JACC*. 2008; 52(23): 1834-1843.

xxii Gold MR, et al. Full-Body MRI in Patients With an Implantable Cardioverter-Defibrillator: Primary Results of the Randomized Study. *JACC*. 2015; 65(24):2581-2588.

xxiii Auricchio A, et al. Low inappropriate shock rates in patients with single- and dual/triple-chamber implantable cardioverter-defibrillators using a novel suite of detection algorithms; PainFree SST trial primary results. *Heart Rhythm.* 2015; 12(5):926-936.

Additionally, the OPC threshold of 79% has been used to evaluate only system-related complications in a pivotal trial for an alternative subcutaneous defibrillation device[xxiv], and so there is precedent for 79% being considered an acceptable criterion for evaluating safety at 6 months for defibrillation products. In that S-ICD study the observed 6-month freedom from system-related or procedure-related complications was 92.1% with a lower confidence limit of 88.9%. A pooled analysis of the S-ICD IDE and EFFORTLESS Post Market S-ICD Registry[xxv] reported that 92.3% of subjects were free of a system or procedure-related complication through 6 months. Since Medtronic is evaluating both EV ICD System and procedure-related complications, an OPC of 0.79 at 6 months for establishing freedom from such complications is appropriate.

12.4.4. Analysis Methods

Results will be summarized in aggregate using descriptive statistics. The total number of major complications experienced by subjects for whom an implant is attempted will be summarized. Subjects not experiencing an event will be censored at their last point of contact. The 182-day freedom from major complication rate will be generated using the Kaplan-Meier method, along with a two-sided 95% confidence bound. If the lower bound is at least 0.79 (79%), the objective will be considered met.

12.4.5. Determination of Subjects/Data for Analysis

All subjects with an implant attempt of the investigational product will be included in the analysis.

12.5. Primary Objective #2: Efficacy

Demonstrate the EV ICD defibrillation testing success rate at implant is greater than an OPC of 88%.

12.5.1. Hypothesis

The hypotheses for this objective are as follows, with P_I denoting the probability of EV ICD defibrillation success at implant:

$H_O: P_I \leq 0.88$
$H_A: P_I > 0.88$

xxiv Weiss R, et al. Safety and Efficacy of a Totally Subcutaneous Implantable-Cardioverter Defibrillator. *Circulation*. 2013; 128: 944-953.

xxv Burke M, et a. Safety and Efficacy of the Totally Subcutaneous Implantable Defibrillator: 2-Year Results From a Pooled Analysis of the IDE Study and EFFORTLESS Registry. JACC (April 2015); 65 (16).

12.5.2. Performance Requirements

Performance requirements for this objective define both the endpoint and the OPC. The endpoint, defibrillation testing success, is defined as:

- Single SSVA conversion at 20J, or
- Conversion of two consecutive episodes of SSVA at 30J in final system configuration.

Notes:

- In one of the two consecutive SSVA episodes, up to two 30J shocks are permitted.
- To achieve final system configuration, changing the position of the ICD generator and/or the lead or changing shock polarity is permitted.
- Subjects can return for testing on another day if testing is not fully completed on the day of implant.

The pre-specified OPC for this objective is 0.88 (88%), meaning the 95% lower confidence bound for the proportion of EV ICD pts who achieve defibrillation testing success at implant must exceed 0.88.

12.5.3. Rationale for Performance Criteria

Defibrillation implant success for transvenous devices, though no longer routinely performed, has historically been shown to be as low as 88% (Table 16). A literature search combined with prior Medtronic trial data showed transvenous defibrillation testing rates commonly in the 90-93% range, which is in line with the hypothesized defibrillation efficacy of EV ICD.

Table 16: Historical Transvenous ICD Defibrillation Testing Success Rates

Reference	Sample Size	Defibrillation Implant Success
Medtronic 6932 Lead Study (MDL #13520, Data on file)	N=165 Model 6932 leads N=166 Model 6936 leads	87.7% 83.5%
Medtronic 6944 Lead Study (MDL #24416, Data on file)	N=112 Model 6944 leads N=122 Model 6942 leads	91.1% 91.8%
Leong-Sit AMJ: 2006; 152:1104-8	N=168	90.5%
Pires JCE 2006; 17:1-6	DFT at implant (N=129) Safety Margin Testing at Implant (N=503) No Testing at Implant (N=203)	77% 93% N/A
Michowitz Europace 2011; 13:683-88	N=204	91.7%
SIMPLE Study Lancet 2015; 385:785-91	Safety Margin Testing at Implant (N=1218)	91.8%

Reference	Sample Size	Defibrillation Implant Success
	No Testing at Implant (N=1227)	N/A

The OPC threshold of 88% has also been used in a pivotal trial for an alternative defibrillation device (S-ICD), so there is precedent for an OPC of 88% being considered an acceptable criterion for evaluating termination of induced ventricular rhythms at implant. The S-ICD literature shows acute defibrillation testing results less than 93% when testing at 65J (applying a 15J safety margin).

Defibrillation results in the post market setting support the belief of S-ICD efficacy being 91-94%. The first results from the EFFORTLESS Study[xxvi] provided a report on the full patient cohort and study endpoint with follow-up ≥1 year. The pre-defined endpoints of this registry are 30- and 360-day complications, and shocks for atrial fibrillation or supraventricular tachycardia. These results provide more data on the efficacy of the S-ICD over time, during both induced and spontaneous arrhythmias. In the first 30 days following implantation, 861 patients had at least 1 evaluable acute conversion test, with 777 of these tests (91.6%) using a defibrillation energy of ≤65 J, which allows for a safety margin.

In a retrospective analysis, Friedman et al[xxvii] reported on trends and in-hospital outcomes associated with early adoption of the S-ICD compared to single- and dual-chamber transvenous ICD implants. Table 17 provides in-hospital outcomes associated with the S-ICD implants. Among 2791 patients with S-ICD who underwent DFT testing, 2588 (92.7%), 2629 (94.2%), 2635 (94.4%), and 2784 (99.7%) were successfully defibrillated (≤65, ≤70, ≤75, and ≤80 J, respectively). The 92.7% defibrillation efficacy at 65J is the best comparator, as it offers a 15J safety margin.

Additionally, there have been other studies and sub-analyses that have reported on the defibrillation threshold testing performance of the S-ICD device. Frankel DS et al[xxviii] evaluated 65J first shock success in acute DFT testing in the S-ICD IDE trial among subgroups define by BMI, while Peddareddy L et al[xxix] reported acute DFT testing results at their site only. These studies show evidence of defibrillation

xxvi Boersma L, et al. Implant and Midterm Outcomes of the Subcutaneous Implantable Cardioverter-Defibrillator Registry – The EFFORTLESS Study. JACC (August 2017); 70(7): 830-841.

xxvii Friedman D, et al. Trends and In-Hospital Outcomes Associated with Adoption of the Subcutaneous Implantable Defibrillator in the United States. JAMA Cardiol (November 2016); 1(8): 900-911.

xxviii Frankel DS et al. Impact of Body Mass Index on Safety and Efficacy of the Subcutaneous Implantable Cardioverter-Defibrillator. JACC: Clinical Electrophysiology (May 2018): 4(5): 652-659.

xxix Peddareddy L et al. Effect of Defibrillation Threshold Testing on Effectiveness of the Subcutaneous Implantable Cardioverter Defibrillator. Pacing Clin Electrophysiol (PACE) June 12 2018. doi: 10.1111/pace.13416 [epub]

testing performance of less than the OPC of 88% in subgroups of patients, further justifying the clinical relevance of such a threshold.

Table 17: S-ICD EFFORTLESS Defibrillation Testing Results

Final Conversion Result	Without Repositioning	With Repositioning	Total
EFFORTLESS Trial Results (N=861)			
Success ≤ 65J (15J Safety Margin)	777 (90.2%)	12 (1.4%)	789 (91.6%)
Success at 70-80J (0-10J Safety Margin)	36 (4.2%)	2 (0.2%)	38 (4.4%)
Success at Unknown Energy	29 (3.4%)	1 (0.1%)	30 (3.5%)
Summary of Success Conversion	842 (97.8%)	15 (1.7%)	857 (99.5%)
Friedman et al Retrospective Analysis (N=2791)			
Success ≤ 65J (15J Safety Margin)	N/A	N/A	2588 (92.7%)
Success ≤ 70J (10J Safety Margin)	N/A	N/A	2629 (94.2%)
Success ≤ 75J (5J Safety Margin)	N/A	N/A	2635 (94.4%)
Success ≤ 80J	N/A	N/A	2784 (99.7%)
Frankel DS et al Assessment of S-ICD IDE by BMI (Evaluating 65J First Shock Success)			
BMI < 25.0 kg/m^2 (N=79)	N/A	N/A	75 (94.9%)
BMI 25.0-29.9 kg/m^2 (N=105)	N/A	N/A	91 (86.7%)
BMI ≥ 30.0 kg/m^2 (N=137)	N/A	N/A	114 (83.2%)
Peddareddy L et al Single Site DFT Success (N=135)	N/A	N/A	113 (83.7%)

12.5.4. Analysis Methods

Results will be summarized in aggregate using descriptive statistics. Subjects will be partitioned by the results of their defibrillation testing (e.g., no rescue shocks required, one rescue shock required), with counts and percentage falling into each subgroup reported. Each subject who completes the defibrillation protocol will be determined to either have successfully met the defibrillation endpoint or not met the endpoint. A 95% two-sided binomial confidence interval for the proportion of subjects who met the endpoint will be generated. If the lower bound exceeds 0.88, the objective will be met. Subjects who do not complete the defibrillation protocol will be reported separately and will not be included in the calculation of the 95% confidence interval.

12.5.5. Determination of Subjects/Data for Analysis

All subjects who complete the defibrillation protocol will be included in the analysis.

12.6. Ancillary Objective #1

Characterize appropriate and inappropriate shocks.

12.6.1. Hypothesis

There are no hypotheses for this objective. Spontaneous episodes receiving shocks will be summarized.

12.6.2. Performance Requirements

Performance requirements are not pre-specified for this objective. The endpoint is defined as a shock delivered by the EV ICD. Spontaneous arrhythmic episodes resulting in a shock will be adjudicated to determine the underlying rhythm.

12.6.3. Rationale for Performance Criteria

Due to the minimal number of appropriate and inappropriate shocks expected for spontaneous arrhythmias, this objective is intended to only characterize device performance with regard to sensing ventricular arrhythmias and delivering shocks when the episode either does not self-terminate or is not terminated by ATP. There are no pre-specified performance criteria.

12.6.4. Analysis Methods

Results will be summarized in aggregate using descriptive statistics. All shocks delivered by the device for spontaneous arrhythmias will be partitioned by whether the treated rhythm was a VT/VF episode, and by the specific rhythm of the episode. Both the number of episodes and the number of subjects experiencing such episodes will be reported, as well as the energy delivered. Kaplan-Meier curves for time to first appropriate shock and time to first inappropriate shock may be provided to demonstrate shock incidence.

12.6.5. Determination of Subjects/Data for Analysis

All subjects successfully implanted with an EV ICD having at least one device interrogation post-implant will be included in the analysis. At minimum, all episodes occurring by the date at which all implanted subjects have had the opportunity to be followed for 6 months post-implant will be included.

12.7. Ancillary Objective #2

Characterize electrical performance (pacing capture thresholds, pacing impedance, sensing amplitudes) over time.

12.7.1. Hypothesis

There are no hypotheses for this objective. Pacing capture performance, as well as pacing impedance and sensing amplitudes, will be summarized.

12.7.2. Performance Requirements

Performance requirements are not pre-specified for this objective. The endpoints are defined as pacing capture threshold, pacing impedance, and sensing amplitude. The pacing testing will be performed at pre-hospital discharge, as well as visits at 2 weeks, 3- and 6-months post-implant and every 6 months thereafter.

12.7.3. Rationale for Performance Criteria

This objective is for the purpose of characterizing device performance with regard to achieving pacing capture and determining sensing performance over time. There are no pre-specified performance criteria.

12.7.4. Analysis Methods

Results will be summarized in aggregate using descriptive statistics. For each follow-up visit, the proportion of subjects undergoing pacing testing will be reported, as well as the proportion for whom capture is obtained. Mean impedance and R-wave amplitudes will also be reported at each follow-up for which the testing occurs (pre-hospital discharge, 2 weeks, 3- and 6-months post-implant, and every 6 months thereafter).

12.7.5. Determination of Subjects/Data for Analysis

All subjects successfully implanted with an EV ICD having relevant data (pacing tests, impedance, sensing amplitudes) will be included in the analysis of that endpoint at that timepoint.

12.8. Ancillary Objective #3

Characterize extracardiac pacing sensation.

12.8.1. Hypothesis

There are no hypotheses for this objective.

12.8.2. Performance Requirements

Performance requirements are not pre-specified for this objective. The endpoint will be defined as whether pacing therapies were programmed OFF due to pacing sensation.

12.8.3. Rationale for Performance Criteria

There are no pre-specified performance criteria; pacing sensation at follow-up will be summarized and reported.

12.8.4. Analysis Methods

Results will be summarized in aggregate using descriptive statistics. Descriptive statistics will be used to summarize distribution among the subjects who completed each follow-up visit, and whether pacing therapies, specifically ATP, were programmed OFF due to the subject reporting pacing sensation. This objective will be analyzed using data from the pre-hospital discharge, 2 weeks, 3- and 6-month, and long-term visits.

12.8.5. Determination of Subjects/Data for Analysis

For each visit (e.g., PHD, 2 weeks), all subjects successfully implanted with an EV ICD who complete that visit will be included in the analysis.

12.9. Ancillary Objective #4

Characterize asystole pacing.

12.9.1. Hypothesis

There are no hypotheses for this objective, as the purpose of this objective is simply to characterize prevalence of asystole pacing in this population.

12.9.2. Performance Requirements

Performance requirements are not pre-specified for this objective. The endpoint is the amount of pacing for asystole the subject received.

12.9.3. Rationale for Performance Criteria

This objective is for the purpose of characterizing prevalence of need for asystole pacing in this population. There are no pre-specified performance criteria.

12.9.4. Analysis Methods

Descriptive statistics will be used to summarize the number of subjects and amount of asystole pacing experienced during follow-up.

12.9.5. Determination of Subjects/Data for Analysis

All subjects successfully implanted with an EV ICD with at least one device interrogation post-implant will be eligible for the analysis. At minimum, all instances occurring on or before the date at which all implanted subjects have had the opportunity to be followed for 6 months post-implant will be included.

12.10. Ancillary Objective #5

Summarize ATP performance with spontaneous arrhythmias.

12.10.1. Hypothesis

There are no hypotheses for this objective, as the purpose is to characterize defibrillation performance through use of ATP.

12.10.2. Performance Requirements

Performance requirements are not pre-specified for this objective. The endpoint is defined as whether a spontaneous ventricular tachycardia episode for which ATP was delivered by the EV ICD was terminated by ATP. Spontaneous arrhythmias will be adjudicated to determine the underlying rhythm and whether they were terminated by ATP.

12.10.3. Rationale for Performance Criteria

It is projected that only a small subset of implanted subjects may experience one or more ventricular arrhythmias during follow-up. Therefore, device performance regarding such episodes will be characterized only. There are no pre-specified performance criteria.

12.10.4. Analysis Methods

Results will be summarized in aggregate using descriptive statistics. All monomorphic and polymorphic ventricular arrhythmias with EGM will be partitioned by whether the treated rhythm received ATP and/or shock, whether it successfully terminated as a result, and by the specific rhythm of the episode (monomorphic vs. polymorphic VT/VF). Both the number of episodes and the number of subjects experiencing such episodes will be reported. A 95% confidence interval will be provided for the percentage of monomorphic VT episodes successfully terminated by ATP.

12.10.5. Determination of Subjects/Data for Analysis

All subjects successfully implanted with an EV ICD having at least one device interrogation post-implant will be included in the analysis. At minimum, all VT/VF episodes occurring on or prior to the date by which all implanted subjects have had the opportunity to be followed for 6 months post-implant will be included in the analysis.

12.11. Ancillary Objective #6

Summarize adverse events.

12.11.1. Hypothesis

There are no hypotheses for this objective, as safety of the EV ICD System is being evaluated by Primary Objective #1 (see section 12.4). This objective is to provide a comprehensive summary of adverse events experienced during follow-up.

12.11.2. Performance Requirements

Performance requirements are not pre-specified for this objective. The endpoint is an adverse event (see Table 12 for definition of adverse event) experienced by a subject post-enrollment and prior to exit. Adverse events will be adjudicated by a Clinical Events Committee for relatedness to the EV ICD System and procedure.

12.11.3. Rationale for Performance Criteria

This objective is for the purpose of gathering comprehensive data pertaining to subject health over at least the first six months post-implant. There are no pre-specified performance criteria.

12.11.4. Analysis Methods

Results will be summarized in aggregate using descriptive statistics. Counts and percentages of subjects experiencing system and/or procedure-related adverse events will be reported, as well as, in the case of system-related events, the specific component of the system to which the event was related. Adverse Events will be broken out by MedDRA keyterm, with both counts of events and counts of subjects experiencing each type of event reported.

12.11.5. Determination of Subjects/Data for Analysis

All subjects for whom an implant of the investigational product is attempted will be included in the analysis. At minimum, all adverse events recorded by the date by which all implanted subjects have been followed at least 6 months post-implant will be included.

12.12. Ancillary Objective #7

Characterize the EV ICD defibrillation testing success rate at 6 months post-implant.

12.12.1. Hypothesis

No statistical hypotheses will be tested for this objective.

12.12.2. Performance Requirements

The performance requirement for this objective is that the observed proportion of subjects, among those with an induced VF episode at their 6-month visit, for whom the episode is successfully terminated with a shock is at least 0.88. The endpoint, defibrillation testing success, is defined as successful completion of the chronic defibrillation testing protocol at the 6-month visit.

12.12.3. Sample Size

Consecutive subjects at centers that agree with and obtain approval from their EC and associated regulatory authority if applicable will be approached for consent to undergo chronic defibrillation testing (see CIP Addendum for 6-Month Defibrillation Testing) until a minimum of 17 and up to 34 subjects have completed testing. Subjects who have consented to participate in this testing will have their chronic defibrillation testing included in the analysis.

12.12.4. Rationale for Performance Criteria

Chronic defibrillation testing is rarely done as standard of care, and places burden on the subject. Therefore, this trial will gather minimal chronic defibrillation testing data to assess efficacy of the EV ICD System in a chronic defib testing, as defined by an observed chronic defibrillation success rate meeting the primary efficacy Objective Performance Criterion of 0.88.

12.12.5. Analysis Methods

Results will be summarized in aggregate using descriptive statistics. Subjects will be partitioned by the results of their defibrillation testing (e.g., no rescue shocks required, one rescue shock required), with counts and percentage falling into each subgroup reported. As supplemental data of chronic performance, if spontaneous VF episodes treated with a shock by the EV ICD System and occurring at least 120 days post-implant are available, they will be summarized separately. Additionally, subjects who do not consent to chronic defibrillation testing but who undergo chronic defibrillation testing at 6-month or later follow-up per physician discretion will be analyzed separately.

12.12.6. Determination of Subjects/Data for Analysis

All subjects for whom defibrillation testing is attempted at 6 months or who experience a spontaneous VF episode treated with a shock by the EV ICD System at least 120 days post-implant will be included in the analysis.

12.13. Supplemental Analysis

Quality of Life/patient acceptance will also be measured through the SF-12 Questionnaire at baseline and 6 months and FPAS at 6 months. These tools will be administered so that subject response in this study may be compared to response to such tools in other ICD studies.

13. Ethics

13.1. Statement(s) of Compliance

The study will be conducted according to the Declaration of Helsinki, CIP, Good Clinical Practice (GCP) and in accordance to the national and local laws, regulations, standards, and requirements of the countries/geographies in which the study is conducted. The principles of the Declaration of Helsinki are implemented in this study by means of the Informed Consent process, Ethics Committee approval, study training, clinical trial registration, and risk benefit assessment.

The clinical investigation shall not begin until all required approvals and documents from the Ethics Committee and regulatory authorities, if needed, have been received. Any additional requirements imposed by the Ethics Committee or regulatory authority shall be followed, if appropriate.

This EV ICD Pivotal Study will be conducted in compliance with international ethical and scientific quality standards, known as good clinical practice (GCP). GCP includes review and approval by an independent Ethics Committee before initiating a study, continuing review of an ongoing study by an Ethics Committee, and obtaining and documenting the freely given Informed Consent of a subject before initiating the study.

The EV ICD Pivotal Study is designed to reflect the GCP principles outlined in ISO 14155:2011 and other international clinical requirements outlined below. These include the protection of the rights, safety and well-being of human subjects, controls to ensure the scientific conduct and credibility of the clinical investigation and the definition of responsibilities of the sponsor and investigators. In accordance with ISO 14155:2011, the sponsor shall avoid improper influence on, or inducement of, the subject, monitor, any investigator(s) or other parties participating in, or contributing to, the clinical investigation. All investigators shall avoid improper influence on or inducement of the subject, sponsor, monitor, other investigator(s) or other parties participating in or contributing to the clinical investigation. Adverse Event and Device Deficiency handling in the EV ICD Pivotal Study is ISO 14155:2011 compliant for all participating geographies.

Ultimately, all sites in all geographies will follow and comply with:

- The Clinical Trial Agreement
- The procedures described within this CIP
- Local Ethics Committee Requirements

In addition to the requirements outlined above, the study will be conducted according to federal, national and local laws, regulations, standards, and requirements of the countries/geographies where the study is being conducted. These include but are not limited to the following:

- In Australia and New Zealand: local laws will be complied with and below will be followed:
    - Principles of Declaration of Helsinki and all of its subsequent amendments, including the latest version 2013
    - ISO 14155:2011
    - 21 CFR Part 11: Electronic Records, Electronic Signatures
    - 21 CFR Part 54: Financial Disclosure by Clinical Investigators

- In Canada below will be followed:
    - SOR/98-282, Section 59-88

- Principles of Declaration of Helsinki and all of its subsequent amendments, including the latest version 2013
- 21 CFR Part 11: Electronic Records, Electronic Signatures
- 21 CFR Part 54: Financial Disclosure by Clinical Investigators

- In Europe, Middle East, Africa, the study will be conducted in compliance with:
  - ISO 14155:2011
  - Active Implantable Medical Device Directive (AIMDD)
  - Principles of Declaration of Helsinki and all of its subsequent amendments, including the latest version 2013
  - 21 CFR Part 11: Electronic Records, Electronic Signatures
  - 21 CFR Part 54: Financial Disclosure by Clinical Investigators

- In Hong Kong, the study will be conducted in compliance with:
  - ISO 14155:2011
  - Principles of Declaration of Helsinki and all of its subsequent amendments, including the latest version 2013
  - 21 CFR Part 11: Electronic Records, Electronic Signatures
  - 21 CFR Part 54: Financial Disclosure by Clinical Investigators

- In Japan, the study will be conducted in compliance with:
  - Ministerial Ordinance Concerning Good Clinical Practice for Medical Devices (The Ministry of Health, Labour and Welfare (MHLW) Ministerial Ordinance No.36 in 2005 revised on 26 Oct 2017)
  - 21 CFR Part 11: Electronic Records, Electronic Signatures
  - 21 CFR Part 54: Financial Disclosure by Clinical Investigators
  - Principles of Declaration of Helsinki and all of its subsequent amendments, including the latest version 2013
- In the United States, the study will be conducted under an FDA Investigational Device Exemption (IDE) in compliance with:
  - 21 CFR Part 11: Electronic Records, Electronic Signatures
  - 21 CFR Part 50: Protection of Human Subjects
  - 21 CFR Part 54: Financial Disclosure by Clinical Investigators
  - 21 CFR Part 56: Institutional Review Boards
  - 21 CFR Part 812: Investigational Device Exemptions

- Principles of Declaration of Helsinki and all of its subsequent amendments, including the latest version 2013

The study will be publicly registered prior to first enrollment in accordance with the 2007 Food and Drug Administration Amendments Act (FDAAA) and Declaration of Helsinki on http://clinicaltrials.gov (PL 110-85, section 810(a)). In addition, the study may be registered in local regulatory databases where required by local law.

Approval of the CIP and CIP amendments, if applicable, is required from the following groups prior to any study procedures at a study site:

- Medtronic
- Principal Investigators
- Geography-specific regulatory authorities (if regulatory approval is required)
- Ethics Committees

Similarly, approval of subsequent revisions to the CIP is required from the above-mentioned groups prior to implementation of the revised CIP at each study site.

14. Study Administration

14.1. Monitoring

It is the responsibility of Medtronic to ensure proper monitoring of this clinical study. Trained Medtronic personnel or delegates appointed by Medtronic may perform study monitoring at the study site to ensure the study is conducted in accordance with the CIP, the Clinical Trial Agreement, and applicable regulatory and local requirements. Medtronic, or delegates, must therefore have access to the subjects' case histories (clinic and hospital records, and other source data/documentation) upon request as per the Informed Consent Form, Authorization to Use and Disclose Personal Health Information/Research Authorization/HIPAA/other privacy language (where applicable) and Clinical Trial Agreement. The Principal Investigator should also be available during monitoring visits.

Frequency of monitoring visits may be based upon subject enrollment, duration of the study, study compliance, number of adverse events, number of deviations, findings from previous monitoring visits and any suspected inconsistency in data that requires investigation. Monitoring for the study, including site initiation visits, interim monitoring visits, and closeout visits, will be done in accordance to the study-specific monitoring plan.

Monitoring visits may be conducted periodically in accordance with the study monitoring plan to assess site study progress, the investigator's adherence to the CIP, regulatory compliance including but not limited to Ethics Committee approval and review of the study, maintenance of records and reports, and review of source documents against eCRFs. Monitors review site regulatory and study compliance by identifying findings of non-compliance and communicating those findings along with recommendations for preventative/corrective actions to site personnel. Monitors may work with study personnel to determine appropriate corrective action recommendations and to identify trends within the study or at a particular site.

14.2. Data Management

Data will be collected using an electronic data management system for clinical studies. Electronic Case Report Form (eCRF) data will be stored in a secure, password-protected database which will be backed up nightly. Data will be reviewed using programmed and manual data checks. Data queries will be made available to sites for resolution. Study management reports may be generated to monitor data quality and study progress. At the end of the study, the data will be frozen and will be retained by Medtronic.

The data reported on the eCRFs shall be derived from source documents and be consistent with these source documents. Source documents, which may include patient medical records, device interrogation files, programmer printouts, and worksheets, must be created and maintained by site personnel. The eCRF may be considered as source for the following data points:

- Adverse Event: date site became aware of event
- Non-Subject Adverse Event: date site became aware of event
- Device Deficiency: date site became aware of deficiency
- Protocol Deviation: reason for deviation
- EV ICD Device Accountability eCRFs:
    - DVEX3E4 EV ICD (except for date used/date explanted)
    - EV2401 EV ICD Lead (except for date used/date explanted)
    - EAZ101 and EAZ201 Tunneling Tools (except for date used)
    - Oscor SafeSheath® II Model SSCL9 introducer (except for date used)
    - SW041 Programmer Software
    - DR220 NorthEast Monitoring Digital Holter Recorder

Device data from transmissions provided to Medtronic will be uploaded to secure servers and made accessible to the study team. Save-to-media files and other non-eCRF data such as Radiographs and Fluoroscopies collected via electronic media at office visits may be sent to Medtronic. Upon receipt via

transmission or electronic media, non-eCRF data will be securely maintained, and stored, and retrieved for analysis and reporting.

14.3. Direct Access to Source Data/Documents

The sponsor or a regulatory authority may audit or inspect the study site to evaluate the conduct of the study. The clinical investigator(s)/institution(s) shall allow study related monitoring, audits, Ethics Committee review, and regulatory inspection(s) by providing direct access to source data/documents. If study site's documents are electronic, these must be made available in their original form (or printouts signed and dated with the statement that this is complete and true reproduction of the original source document) if requested by the sponsor and/or regulatory authority. Study sites should inform Medtronic upon notification of an audit by a regulatory body immediately.

14.4. Confidentiality

All records and other information about subjects participating in this study will be treated as confidential. Data will be transferred and processed by Medtronic or a third party designated by Medtronic in a key coded form, unless it is impossible to make it anonymous, for instance, where the subject's name cannot be removed from the data carrier, such as fluoroscopy images. Participating subjects will not be identified by name in any published reports about the study.

14.5. Liability

Medtronic Australasia Pty Ltd is a wholly owned subsidiary of Medtronic, Inc., which as the parent company of such entity maintains appropriate clinical study liability insurance coverage as required under applicable laws and regulations and will comply with applicable local law and custom concerning specific insurance coverage. If required, a Clinical Study insurance statement/certificate will be provided to the Ethics Committee.

Medtronic New Zealand Ltd. is a wholly owned subsidiary of Medtronic, Inc., which as the parent company of such entity maintains appropriate clinical study liability insurance coverage as required under applicable laws and regulations and will comply with applicable local law and custom concerning specific insurance coverage. If required, a Clinical Study insurance statement/certificate will be provided to the Ethics Committee.

Medtronic Bakken Research Center B.V. (Europe, Middle East) is a wholly owned subsidiary of Medtronic, Inc., which as the parent company of such entity maintains appropriate clinical study liability

insurance coverage as required under applicable laws and regulations and will comply with applicable local law and custom concerning specific insurance coverage. If required, a Clinical Trial insurance statement/certificate will be provided to the Ethics Committee.

Medtronic International (Hong Kong), Ltd. is a wholly owned subsidiary of Medtronic, Inc., which as the parent company of such entity maintains appropriate clinical trial liability insurance coverage as required under applicable laws and regulations and will comply with applicable local law and custom concerning specific insurance coverage. If required, a Clinical Trial insurance statement/certificate will be provided to the Ethics Committee.

Medtronic Japan Co., Ltd is a wholly owned subsidiary of Medtronic, which as the parent company of such entity maintains appropriate clinical study liability insurance coverage as required under applicable laws and regulations and will comply with applicable local law and custom concerning specific insurance coverage. If required, a clinical study insurance statement/certificate will be provided to the Institutional Review Board.

14.6. CIP Amendments

Approval of CIP amendments is required from the following groups prior to any study procedures at a study site:

- Medtronic
- Principal Investigators (where required by local law)
- Geography-specific regulatory authorities (if regulatory approval is required)
- An independent Ethics Committee.

14.7. Required Records and Reports

14.7.1. Investigator Records

The investigator is responsible for the preparation and retention of the records cited below. All of the below records, with the exception of case history records and case report forms, should be kept in the Investigator Site File (e.g., the study binder provided to the investigator) or Subject Study Binder. Electronic CRFs must be maintained and signed electronically within the electronic data capture system during the study. The following records are subject to inspection and must be retained:

- All correspondence between the Ethics Committee, sponsor, monitor, regulatory authority and the investigator that pertains to the investigation, including required reports.

- Subject's case history records, including:
  - Signed and dated Informed Consent Form.
  - Observations of adverse events/adverse device effects/device deficiencies.
  - Medical history.
  - Implant and follow-up data (if applicable).
  - Documentation of the dates and rationale for any deviation from the CIP.
- Subject identification log.
- List of investigation sites.
- Financial disclosure.
- All approved versions of the CIP, IC, other information given to the subject and Investigator's Brochure.
- Signed and dated Clinical Trial Agreement.
- Current signed and dated curriculum vitae of Principal Investigator and key members of the investigation site team (as required by local law).
- Documentation of delegated tasks.
- Ethics Committee approval documentation. Written information that the investigator or other study staff, when member of the Ethics Committee, did not participate in the approval process. Approval documentation must include the Ethics Committee composition, where required per local law.
- Regulatory authority notification, correspondence and approval, where required per local law.
- Study training records for site staff.
- Insurance certificates.
- Shipping records of investigational devices.
- Equipment maintenance records, if applicable.
- Any other records that local regulatory agencies require to be maintained.
- Final Study Report including the statistical analysis.

The above-mentioned documentation shall be kept for a period of at least 15 years after the clinical investigation with the device in question has ended, or, in the event that the device is subsequently placed on the market, at least 15 years after the last device has been placed on the market or longer as local law or hospital administration requires.

14.7.2. Investigator Reports

The investigator is responsible for the preparation (review and signature) and submission to the sponsor of all case report forms, including adverse events and adverse device effects (reported per the

country-specific collection requirements), device deficiencies, deaths, and any deviations from the CIP. If any action is taken by an Ethics Committee with respect to this clinical study, copies of all pertinent documentation must be forwarded to Medtronic in a timely manner. Reports are subject to inspection and to the retention requirements as described above for investigator records.

Safety data investigator reporting requirements are listed in Table 14 of the Adverse Event section 10.5. The investigator shall prepare and submit in a complete, accurate and timely manner the reports listed in this section.

Table 18: Investigator reports applicable for all geographies per Medtronic requirements

Report	Submit to	Description/Constraints
Withdrawal of Ethics Committee approval	Sponsor and Relevant Authorities, where applicable per local requirements	The investigator must report a withdrawal of approval by the reviewing Ethics Committee of the investigator's part of the investigation within 5 working days, or sooner as required per local requirements.
Study Deviations	Sponsor Ethics Committee and Relevant Authorities, where applicable per local requirements	Any deviation from the Clinical Investigation Plan shall be reported together with the explanation of the deviation as soon as possible upon the site becoming aware of the deviation. Notice of deviations from the CIP involving a failure to obtain a subject's consent, or is made to protect the life or physical well-being of a subject in an emergency shall be given within 5 working days, or sooner if required by local requirements. Except in such emergency, prior approval is required for changes in the plan or deviations. Reporting of serious breaches as per requirements in Australia must be complied with. **Australia:** Report any suspected breaches to the sponsor and confirmed serious breaches to their institution (research governance office) within 72 hours of becoming aware or notified of the same; provide any follow-up information as required and work with the institution or sponsor, as appropriate, to implement any corrective and preventative actions.
Progress report	Sponsor and Ethics Committee	As required by local requirements.
Final Report	Ethics Committees and Relevant Authorities	This report must be submitted per local requirements.

Table 19: Investigator reports applicable to the United States per FDA regulations

Report	Submit to	Description/Constraints
Withdrawal of Ethics Committee approval (either suspension or termination)	Sponsor	The investigator must report a withdrawal of approval by the reviewing Ethics Committee of the investigator's part of the investigation within 5 working days. *(21 CFR 812.150(a)(2))* For any action taken by an EC with respect to the investigation information will be forwarded to the sponsor.
Progress report	Sponsor and Ethics Committee	The investigator must submit this report to the sponsor and Ethics Committee at regular intervals, but in no event less than yearly. *(21 CFR 812.150 (a)(3))*.
Study deviations	Sponsor and Ethics Committee	Notice of deviations from the CIP to protect the life or physical wellbeing of a subject in an emergency shall be given as soon as possible, but no later than 5 working days after the emergency occurred. Except in such emergency, prior approval is required for changes in the plan or deviations. If the deviation may affect the scientific soundness of the plan or the rights, safety and welfare of the subjects, the deviation must be approved by Medtronic, the EC, and the FDA/applicable regulatory authorities. If the deviation does not affect these issues then only Medtronic must approve it. *(21 CFR 812.150(a)(4))*
Failure to obtain Informed Consent prior to investigational device use	Sponsor and Ethics Committee	If an investigator uses a device without obtaining Informed Consent, the investigator shall report such use within 5 working days after device use. *(21 CFR 812.150(a)(5))*
Final report	Sponsor Ethics Committee Relevant Authorities	This report must be submitted within 3 months of study completion or termination of the investigation or the investigator's part of the investigation. *(21 CFR 812.150(a)(6))*
Other	Ethics Committee and FDA	An investigator shall, upon request by a reviewing Ethics Committee or regulatory agency, provide accurate, complete, and current information about any aspect of the investigation. *(21 CFR 812.150(a)(7))*

Table 20: Investigator reports applicable to Europe, Middle East and Africa per ISO 14155:2011

Report	Submit to	Description/Constraints
Progress Report	Sponsor and Ethics Committee	Provide if required by local law or Ethics Committee.
Study Deviations	Sponsor and Ethics Committee	Any deviation from the CIP shall be recorded together with an explanation for the deviation. Deviations shall be reported to the sponsor who is responsible for analyzing them and assessing their significance. Note: When relevant, Ethics Committees, competent authorities or the appropriate regulatory bodies should be informed.
Failure to obtain Informed Consent	Sponsor and Ethics Committee	Informed Consent shall be obtained in writing and documented before a subject is enrolled into the clinical investigation.

Table 21: Investigator reports applicable to Japan

Report	Submit to	Description/Constraints
Co-Investigator/ Clinical Trial Collaborator List	Head of Medical Institution (HOMI)	When the principal Investigator assigns important parts of the clinical trial duties to co-Investigators and/or clinical trial collaborators, he or she shall prepare a list of the assigned duties and the individual performing the assigned duties, submit the list to the HOMI on the list, and receive the appointments of such individuals. (MHLW Ordinance 36, 2005 Article 63)
Study Deviations	Sponsor and HOMI	The Investigator may implement a deviation from, or a change in, the CIP to eliminate an immediate hazard(s) to study subjects without prior Ethics Board approval. In this case, the Investigator shall immediately submit to the sponsor, the HOMI, and to the Ethics Board via the HOMI, the description and reason for the deviation and the proposed revision to the CIP, if one is necessary, to receive agreement. All deviations, regardless of the reason, shall be submitted to the sponsor. (MHLW Ordinance 36, 2005 Article 66)
Summary of the Clinical Study Status	HOMI	The principal Investigator shall submit a summary of the clinical study status to the HOMI in writing once a year, or more frequently if requested by the Ethics Board, to receive the continuation review by the institutional review board. (MHLW Ordinance 36, 2005 Article 68)
Premature Termination or Suspension of the Clinical Investigation	HOMI	When the principal Investigator discontinues or suspends the clinical study, he or she shall promptly notify the HOMI thereof in writing, and explain in detail in writing the discontinuation or suspension. (MHLW Ordinance 36, 2005 Article 69)
Completion of the Clinical Investigation	HOMI	When the clinical study is completed, the principal Investigator shall notify the HOMI thereof in writing and report on a summary of the clinical study results in writing. (MHLW Ordinance 36, 2005 Article 69)

Additional reporting requirements and if stricter timelines of reporting are required per EC and/or local regulation, the same should be complied with, including any reporting needs to regulators, when required by local law.

14.7.3. Sponsor Records

Medtronic shall maintain the following accurate, complete, and current records:

- All correspondence which pertains to the investigation.
- Investigational device traceability records.
- Software traceability records.
- Signed Clinical Trial Agreements, financial disclosure and current signed and dated (Europe, ANZ, and Hong Kong only) curriculum vitae of Principal Investigator and key members of the investigation site team (as required by local law), delegated task list.
- All approved Informed Consent templates, and other information provided to the subjects, including translations.
- Copies of all Ethics Committee approval letters and relevant Ethics Committee correspondence and Ethics Committee voting list/roster/letter of assurance.
- Names of the institutions in which the clinical study will be conducted.
- Regulatory authorities' correspondence, notification and approval as required by national legislation.
- Insurance certificates (if applicable per local law).
- Names/contact addresses of monitors.
- Site visit reports and follow-up letters.
- Statistical analyses and underlying supporting data.
- Final report of the clinical study.
- The Clinical Investigation Plan, Investigator's Brochure and study related reports, and revisions.
- eCRFs, including AE and Device Deficiency (DD) forms and eCRF corrections.
- Study training records for site personnel and Medtronic personnel involved in the study.
- Any other records that local regulatory agencies require to be maintained.

14.7.4. Sponsor Reports

Medtronic shall prepare and submit the following complete, accurate, and timely reports listed in the tables below (by geography). In addition to the reports listed below, Medtronic shall, upon request of reviewing Ethics Committee or regulatory agency, provide accurate, complete and current information about any aspect of the investigation. Safety data Medtronic reporting requirements are listed in Table 14 of the Adverse Event section 10.5.

Table 22: Sponsor reports for Australia and New Zealand

Report	Submit to	Description/Constraints
Premature termination or suspension of the clinical study	Investigators, Ethics Committee, and relevant authorities	Provide prompt notification of termination or suspension and reason(s).
Recall and device disposition	Investigators, Ethics Committee, relevant authorities,	Notification as required per local regulations in country
Study deviation	Investigators	Ensure that all deviations from the Clinical Investigation Plan are reviewed with the appropriate clinical investigator(s), are reported on the case report forms and the final report of the clinical investigation. Site specific study deviations will be submitted to investigators periodically. Reporting of serious breaches to required parties in Australia as per local requirements will be done.
Annual safety reports and single case Adverse events	TGA	Submit upon request from TGA
USADEs for Australia and international / Safety Report / updated IB / approved Product Information	Investigator and HREC	Per EC requirements, but at least annually: • Annual safety report including; - a summary of the evolving safety profile of the trial, a brief description and analysis of new/relevant findings, implications of safety data to the risk-benefit ratio for the trial, a description of any measures taken or proposed to minimize risks (NHMRC Safety monitoring and reporting in clinical trials involving therapeutic goods November 2016 section C.1.i) • An updated/addenda of IB or IFU, if appropriate (e.g., when an IB is no longer maintained). (NHMRC Safety monitoring and reporting in clinical trials involving therapeutic goods November 2016 section C.1.h)

Table 23: Sponsor reports for Canada

Report	Submit to	Description/Constraints
Premature termination or suspension of the clinical study	Investigators, Ethics Committee, Relevant authorities, and Head of the Institution	Provide prompt notification of termination or suspension and reason(s).
Recall and device disposition	Investigators, Head of Institution, Ethics Committee, relevant authorities, and FDA	Notification within 30 working days and will include the reasons for any request that an investigator return, repair, or otherwise dispose of any devices.
Study deviation	Investigators	Ensure that all deviations from the Clinical Investigation Plan are reviewed with the appropriate clinical investigator(s), are reported on the case report forms and the final report of the clinical study. Site specific study deviations will be submitted to investigators periodically.

Table 24: Sponsor reports for Europe, Middle East, Africa

Report	Submit to	Description/Constraints
Premature termination or suspension of the clinical study	Investigators, Ethics Committee, Relevant authorities and Head of the Institution	Provide prompt notification of termination or suspension and reason(s). *(ISO 14155:2011)*
Withdrawal of Ethics Committee approval	Investigators, Head of Institution, Ethics Committee and relevant authorities	Investigators, Ethics Committee will be notified only if required by local laws or by the Ethics Committee.
Withdrawal of CA approval	Investigators, Head of Institution, Ethics Committee, and relevant authorities	Investigators, Ethics Committee will be notified only if required by local laws or by the Ethics Committee.

Report	Submit to	Description/Constraints
Progress Reports	Ethics Committee and regulatory authorities	This will be submitted to the Ethics Committee only if required by the Ethics Committee.
Final report	Investigators, Ethics Committee, and Regulatory authorities upon request	For studies with sites complying to ISO 14155:2011: • The investigator shall have the opportunity to review and comment on the final report. • If a clinical investigator does not agree with the final report, his/her comments shall be communicated to the other investigator(s). • The coordinating investigator shall sign the report. If no coordinating investigator is appointed, then the signature of the Principal Investigator in each site should be obtained. *(ISO 14155:2011)*
Study deviation	Investigators	Ensure that all deviations from the Clinical Investigation Plan are reviewed with the appropriate clinical investigator(s), are reported on the case report forms and the final report of the clinical investigation. *(ISO 14155:2011)* Site specific study deviations will be submitted to investigators periodically.

Table 25: Sponsor reports for Hong Kong

Report	Submit to	Description/Constraints
Premature termination or suspension of the clinical study	Investigators, Ethics Committee	Provide prompt notification of termination or suspension and reason(s).
Recall and device disposition	Investigators, Ethics Committee, relevant authorities	Notification within 30 working days and will include the reasons for any request that an investigator return, repair, or otherwise dispose of any devices.
Study deviation	Investigators	Ensure that all deviations from the CIP are reviewed with the appropriate clinical investigator(s), are reported on the case report forms and the final report of the clinical study.

Table 26: Sponsor reports for the United States

Report	Submit to	Description/Constraints
Withdrawal of Ethics Committee approval	Investigators, Ethics Committee, FDA, and relevant authorities	Notification within five working days. *(21 CFR 812.150(b)(2))*
Withdrawal of FDA approval	Investigators, Ethics Committee, and relevant authorities	Notification within five working days. *(21 CFR 812.150(b)(3))*
Investigator List	FDA	Submit at 6-month intervals, a current list of the names and addresses of all investigators participating in the investigation. *(21 CFR 812.150(b)(4))*
Progress Reports	Ethics Committee and FDA	Progress reports will be submitted at least annually. *(21 CFR 812.150(b)(5), 812.36(f)*
Recall and device disposition	Investigators, Head of Institution, Ethics Committee, relevant authorities, and FDA	Notification within 30 working days and will include the reasons for any request that an investigator return, repair, or otherwise dispose of any devices. *(21 CFR 812.150(b)(6))*
Failure to obtain Informed Consent	FDA	Investigator's report will be submitted to FDA within five working days of notification. *(21 CFR 812.150(b)(8))*
Final report	Investigators, Ethics Committee, Regulatory authorities upon request, and FDA	Medtronic will notify FDA within 30 working days of the completion or termination of the investigation. A final report will be submitted to the FDA, investigators, and Ethics Committee within six months after completion or termination of this study. *(21 CFR 812.150(b)(7))*
Study deviation	Investigators	Ensure that all deviations from the Clinical Investigation Plan are reviewed with the appropriate clinical investigator(s), are reported on the case report forms and the final report of the clinical study. Site specific study deviations will be submitted to investigators periodically.
Other	IRB, FDA	Accurate, complete, and current information about any aspect of the investigation. *(21 CFR 812.150(b)(10))*

Table 27: Sponsor reports for Japan

Report	Submit to	Description/Constraints

Premature termination or suspension of the clinical investigation	HOMI PMDA	When the sponsor suspends or discontinues the clinical trial, he or she shall promptly notify the heads of all the medical institutions and regulatory authorities thereof and the detailed reason therefor in writing. (MHLW Ordinance 36, 2005 Article 32)
Suspension of development of investigational device	HOMI PMDA	When the sponsor decides not to attach the documents concerning clinical trial records collected in the clinical trial to the authorization application, he or she shall promptly notify the heads of all the medical institutions other facilities engaged in the clinical trial thereof and the detailed reason therefor in writing. (MHLW Ordinance 36, 2005 Article 32)
Investigator List	HOMI PMDA	The sponsor shall beforehand submit the list of Investigators to PMDA and HOMI. (Pharmaceutical and Medical Device Act Enforcement Regulations) The sponsor shall submit the list of Investigators to PMDA and HOMI when making any changes in the list. (Pharmaceutical and Medical Device Act Enforcement Regulations)
Important information concerning the quality, effectiveness, and safety of the investigational device	Investigators HOMI PMDA	When new, important information is obtained, the sponsor shall revise the Investigator's brochure. In addition, prior to revising the Investigator's brochure, the sponsor shall report the information to the principal Investigator, HOMI, and regulatory authorities. (MHLW Ordinance 36, 2005 Article 28)
Clinical Trial Report	PMDA upon request	The sponsor shall prepare, according to the procedure, a clinical study report that summarizes the results, etc., of a clinical study when it is completed or discontinued. (MHLW Ordinance 36, Article 33)
Study deviation	Investigators HOMI as necessary	Ensure that all deviations from the Clinical Investigation Plan are reviewed with the appropriate clinical Investigator(s), are reported on the case report forms and the final report of the clinical investigation. (ISO 14155:2011) Site specific study deviations will be submitted to Investigators periodically. When the monitor confirms deviation as a result of monitoring, the monitor shall notify the principal Investigator and, as necessary, the HOMI thereof. The monitor shall also request for appropriate measures to be taken to prevent such deviation in the future. (MHLW Ordinance 36, 2005 Article 30)

Medtronic records and reports will be maintained in a password-protected document management system, and paper documents (where applicable) will be stored in secured file cabinets at Medtronic during the course of this study.

After closure of the study, Medtronic will archive records and reports and these will be retained per Medtronic standard and applicable regulations.

14.8. Suspension or Early Termination

Early Termination is the closure of a clinical study that occurs prior to meeting defined endpoints. This is possible for the whole study or a single site. Suspension is a temporary postponement of study

activities related to enrollment and distribution of the product. This is possible for the whole study or a single site.

14.8.1. Study-wide Suspension or Early Termination

Possible reasons for considering study suspension or termination of the study include but are not limited to:

- Adverse events associated with the system or product under investigation which might endanger the safety or welfare of the subject
- Observed/suspected performance different from the product's design intent
- Decision by Medtronic or regulatory body (where the study is operating under regulatory body authority)
- Technical issues during the manufacturing process

14.8.2. Investigator/Site Suspension or Early Termination

Possible reasons for clinical investigator or site termination or suspension include but are not limited to:

- Failure to obtain initial Ethics Committee approval or annual renewal of the study approval
- Persistent non-compliance to the CIP (e.g., failure to adhere to inclusion/exclusion criteria, failure to follow subjects per scheduled follow-ups)
- Lack of enrollment
- Noncompliance to regulations and the terms of the Clinical Trial Agreement (e.g., failure to submit data in a timely manner, failure to follow-up on data queries and monitoring findings in a timely manner)
- Ethics Committee suspension of the site
- Fraud or fraudulent misconduct is discovered (as defined by local law and regulations)
- Investigator request (e.g., no longer able to support the study)

14.8.3. Procedures for Suspension or Early Termination

Below procedures will apply in addition to any other specific requirement per local regulations.

Medtronic-initiated and regulatory authority-initiated

- Medtronic will promptly inform the clinical investigators of the termination or suspension and the reasons and inform the regulatory authority(ies) where required

- In the case of study termination or suspension for reasons other than a temporary EC approval lapse, the investigator will promptly inform the EC. A detailed written explanation of the termination or suspension will be provided, where required per regulatory requirements.
- In the case of study termination, the investigator must inform the subjects and may inform the personal physician of the subjects to ensure appropriate care and follow-up is provided
- In the case of a study suspension, subject enrollment must stop until the suspension is lifted by Medtronic
- In the case of a study suspension, enrolled subjects should continue to be followed out of consideration of their safety, rights and welfare

Investigator-initiated

- The investigator will immediately or promptly inform Medtronic and provide a detailed written explanation of the termination or suspension
- The investigator will promptly inform the institution (where required per regulatory requirements)
- The investigator will promptly inform the EC, along with a detailed written explanation of the termination or suspension (where required per regulatory requirements)
- The investigator will promptly inform the subjects and/or the personal physician of the subjects to ensure appropriate care and follow-up is provided
- In the case of a study suspension, subjects enrolled should continue to be followed out of consideration of their safety, rights and welfare

Ethics Committee-initiated

- The investigator will inform Medtronic and provide a detailed written explanation of the termination or suspension within 5 business days, or sooner if required per local requirements
- Subject enrollment must stop until the suspension is lifted
- Subjects already enrolled should continue to be followed in accordance with EC policy or its determination that an overriding safety concern or ethical issue is involved
- The investigator will inform his/her institution (where required per local requirements)
- The investigator will promptly inform the subjects and/or the personal physician of the subjects, with the rationale for the study termination or suspension to ensure appropriate care and

follow-up is provided

15. References

1. Weiss R, et al., Safety and efficacy of a totally subcutaneous implantable-cardioverter defibrillator, Circulation, 2013;128:944-53
2. U.S. Food and Drug Administration. (2012). A Patient Guide - Living with your S-ICD System. U.S. Food and Drug Administration/Devices@FDA. Retrieved 16-Jan-2018 from: http://www.accessdata.fda.gov/cdrh_docs/pdf11/P110042c.pdf.
3. U.S. Food and Drug Administration. (2012). FDA Circulatory Systems Device Panel Transcript for April 26, 2012. U.S. Food and Drug Administration Medical Device Advisory Committees. Retrieved 26-Jan-2018 from: https://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/MedicalDevices/MedicalDevicesAdvisoryCommittee/CirculatorySystemDevicesPanel/ucm124182.htm.
4. Ellenbogen KA, Wood MA, Shepard RK, Clemo HF, Vaughn T, et al. 2003. Detection and management of an implantable cardioverter defibrillator lead failure: incidence and clinical implications. J Am Coll Cardiol 41:73-80.
5. Kleemann T, Becker T, Doenges K, Vater M, Senges J, Schneider S, Saggau W, Weisse U, Seidl K. Annual Rate of Transvenous Defibrillation Lead defect in Implantable Cardioverter-Defibrillators over a Period of >10 Years. Circulation. 2007;115:2474-2480.
6. Bardy GH, et al., An entirely subcutaneous implantable cardioverter-defibrillator, N Engl J Med., 2010;363:36-44.
7. Cappato R, Smith WM, Hood MA, Crozier IG, Jordaens L, Spitzer SG, Ardashev AV, Boersma L, Lupo P, Grace AA, Bardy GH. Subcutaneous chronic implantable defibrillation systems in humans, J Interv Card Electrophysiol., 2012;34:325–332. https://doi.org/10.1007/s10840-012-9665-6.
8. Tomaske M, Prêtre R, Rahn M, Bauersfeld U. Epicardial and pleural lead ICD systems in children and adolescents maintain functionality over 5 years. Europace. 2008 Oct;10(10):1152-6.
9. Molina JE, Benditt DG. An epicardial subxiphoid implantable defibrillator lead: superior effectiveness after failure of standard implants. Pacing Clin Electrophysiol. 2004 Nov;27(11):1500-6.
10. Tung SK, Bennett M, Yeung-Lai-wah JA, Ling H. Minimal invasive extra cardiac placement of high voltage defibrillator leads. Heart Rhythm 2007; 4(5, Suppl.):S200

11. Bauersfeld U, Tomaske M, Dodge-Khatami A, Rahn M, Kellenberger CJ, Prêtre R. Initial experience with implantable cardioverter defibrillator systems using epicardial and pleural electrodes in pediatric patients. Ann Thorac Surg 2007;84:303-5.
12. Gold, M., Aasbo, J., El-Chami, M. et al., Subcutaneous implantable cardioverter-defibrillator Post-Approval Study: Clinical characteristics and perioperative results. Heart Rhythm. 2017;14:1456–1463.
13. Boersma L, Barr C, Knops R et al. Implant and Midterm Outcomes of the Subcutaneous Implantable Cardioverter-Defibrillator Registry: The EFFORTLESS Study. J Am Coll Cardiol 2017;70:830-841.
14. Jacob S, Lieberman RA. Percutaneous epicardial defibrillation coil implantation: a viable technique to manage refractory defibrillation threshold. Circ Arrhythm Electrophysiol. 2010 Apr;3(2):214-7.
15. Haydin S, Saygi M, Ergul Y, Ozyilmaz I, Ozturk E, Akdeniz C, Tuzcu V. Subxiphoid approach to epicardial implantation of implantable cardioverter defibrillators in children. Pacing Clin Electrophysiol. 2013 Aug;36(8):926-30.
16. Hajj-Chahine J, Houmaida H, Tomasi J, Corbi P. Epicardial defibrillation patch or coil lead? Interact Cardiovasc Thorac Surg. 2011 Apr;12(4):630.
17. Guenther M, Kolschmann S, Knaut M. Letter to the Editors: Substernal lead implantation: A Novel Option to Manage DFT failure in S-ICD Patients. Clin Res Cardiol, DOI 10.1007/s00392-014-0764-5.
18. Boyle TA, Cohen J, Carrillo R. Substernal implantation of a subcutaneous implantable cardioverter-defibrillator in a patient with preexisting Hemodialysis Reliable Outflow graft. HeartRhythm Case Rep 2016;2:412-414.
19. Bhagwandien RE, Kik C, Yap SC, Szili-Torok T. Substernal ICD lead implantation in a patient not suitable for subcutaneous ICD implantation without venous access due to superior vena cava syndrome. HeartRhythm Case Rep 2017;3:97-99.
20. Hata H, Sumitomo N, Nakai T, Amano A. Retrosternal Implantation of the Cardioverter-Defibrillator Lead in an Infant. Ann Thorac Surg 2017;103:e449-e451.
21. Chan JYS, Lelakowski J, Murgatroyd FD, Boersma LV, Cao J, Nikolski V, Wouters G, Hall MCS. Novel Extravascular Defibrillation Configuration With a Coil in the Substernal Space: The ASD Clinical Study, JACC: Clinical Electrophysiology, Volume 3, Issue 8, 2017, Pages 905-910, ISSN 2405-500X, https://doi.org/10.1016/j.jacep.2016.12.026.
22. Sholevar DP, Tung S, Kuriachan V, et al. Feasibility of extravascular pacing with a novel substernal electrode configuration: The Substernal Pacing Acute Clinical Evaluation

Study. Heart Rhythm. Published online 29Nov2017. DOI: http://dx.doi.org/10.1016/j.hrthm.2017.11.030

23. Boersma LV, Merkely B, Neuzil P, Crozier IG, Akula DN, Timmers L, Kalarus Z, Sherfesee L, DeGroot PJ, Thompson AE, Lexcen DR, Knight BP. Therapy from a Novel Substernal Lead: The ASD2 study. JACC: Clinical Electrophysiology, Volume 5, Issue 2, 2019, Pages 186-196.
24. Blatt JA, Poole JE, Johnson GW, et al. No benefit from defibrillation threshold testing in the SCD-HeFT (Sudden Cardiac Death in Heart Failure Trial). J Am Coll Cardiol. 2008 Aug 12;52(7):551-6.
25. Neuzner J, Hohnloser SH, Kutyifa V, et al. Effectiveness of single- vs. dual-coil implantable defibrillator leads: An observational analysis from the SIMPLE study. J Cardiovasc Electrophysiol. 2019 Apr 4. doi: 10.1111/jce.13943.
26. Crozier IG, Haqqani H, Kotschet E, Shaw D, Prabhu A, Roubos N, Alison J, Melton I, Denman R, Lin T, Almeida A, Portway B, Sawchuk B, Sherfesee L, Liang S, BENG, Thompson AE, Lentz L, DeGroot PJ, O'Donnell D. First-in-human Chronic Implant Experience of the Substernal Extravascular Implantable Cardioverter Defibrillator. Heart Rhythm 2018 S-LBCT04-01.

16. Appendices

Appendix A: Draft Data Collection Elements (Case Report Forms)

Draft Case Report Forms for the EV ICD Pivotal Study will be provided under separate cover. Final eCRFs will be provided to sites via the electronic data management system after the site has fulfilled all requirements for database access.

Appendix B: Preliminary Publication Plan

Publications from the EV ICD Pivotal Study will be handled according to the sponsor's Standard Operating Procedures and as indicated in the Clinical Trial Agreement.

Publication Committee

The Steering Committee will serve as the Publication Committee as they will play a role in disseminating the study outcomes to the broader medical community. Additional members of the Publication Committee may include representation from Medtronic study management, statistics, marketing, research, etc. This committee will manage study publications with the goal of publishing findings from the data. Together with Medtronic representatives, the Publication Committee will develop a final Publication Plan as a separate document.

The Publication Committee's role is to:

1) manage elements addressed in the publication plan as outlined in this appendix,
2) develop the final Publication Plan under separate cover,
3) finalize the Publication Plan,
4) oversee the publication of primary and ancillary study results,
5) review and prioritize publication proposals,
6) provide input on publication content, and
7) determine authorship.

In addition, the committee will apply and reinforce the authorship guidelines set forth in the Publication Plan. Membership in the Publication Committee does not guarantee authorship. The committee will meet as needed.

Management of Primary and Ancillary Publications

The Publication Committee reviews, prioritizes, and manages all publications including primary and ancillary publications. Primary and ancillary publications are those that address analyses of any or all primary objectives or ancillary objectives, respectively, as specified in the Clinical Investigation Plan.

An ancillary publication is any publication that does not address the study objectives identified in the Clinical Investigation Plan. They include publications proposed and developed by other Medtronic departments or entities, clinicians participating in this clinical study, and clinicians not participating in this clinical study. The committee will work with Medtronic to ensure that requests do not present conflicts with other proposals, are not duplicative, and to determine which ancillary publication proposals, if any, will be supported.

The committee may decide that no publications, including abstracts, will be published prior to the end of the study or with individual site data. Requests for publications on study objectives utilizing subset data (e.g., regional) will be evaluated for scientific validity and the ability of Medtronic to provide resources.

Criteria for Determining Authorship

Publications will adhere to authorship criteria defined by the International Committee of Medical Journal Editors (ICMJE, Uniform requirements for manuscripts submitted to biomedical journals, www.icmje.org). Individual authorship criteria defined by the target journal or conference will be followed when it differs from ICMJE criteria.

Authors, including Medtronic personnel, must at a minimum meet all conditions below:

- Substantial contribution to conception and design, or acquisition of data, or analysis and interpretation of data; and
- Drafting the article or revising it critically for important intellectual content; and
- Final approval of the version to be published; and
- Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Decisions regarding authorship and contributor-ship will be made by the committee. The selected authors will be responsible for drafting the publication. All selected authors must fulfill the authorship conditions stated above to be listed as authors, and all contributors who fulfill the conditions must be listed as authors.

Contributors who make substantial contributions, but do not meet authorship criteria may be considered for inclusion in an Acknowledgement section of the publication. Depending on the degree, these contributions might merit contributor-ship in the publication.

Transparency

Transparency of study results will be maintained by the following means:

- a final report, describing the results of objectives and analysis, will be distributed to all investigators, Ethic Committees and Regulatory Authorities of participating countries when required by local law
- registering and posting the study results on ClinicalTrials.gov based on the posting rules stipulated

- Medtronic intends to publish the primary study results in a manner that is sensitive to the commercial application of the results. Publication may be delayed until closer to the potential release of a device feature
- disclosing conflicts of interest (e.g., financial) of the co-authors of publications according to the policies set forth by the corresponding journals and conferences
- making an individual site's study data accessible to the corresponding investigator after the completion of the study, if requested.

Appendix C: Instructions for Use

Instructions for Use (IFU) for the components of the EV ICD System and accessories, and equipment are provided with each component under separate cover. The cover of each IFU will have a clinical statement on the cover indicating the device is an investigational device.

Appendix D: Informed Consent Templates

Medtronic legal-approved Informed Consent Templates for each geography where the study will be conducted will be distributed under separate cover.

Appendix E: Foreseeable Adverse Event List

Potential risks associated with the implantation of the EV ICD System, associated harms and adverse events, as well as risk minimization are discussed in more detail within section 9, Risks and Benefits. The information provided in this section includes additional reference information and may collectively assist in identifying those events for a given device or therapy that are unexpected in nature. The foreseeable adverse event information consists of three parts: (1) rates of adverse events reported from previous Medtronic studies evaluating transvenous ICD systems, (2) adverse event rates reported in published literature for procedures similar to EV ICD, and (3) additional adverse events for consideration. An evaluation of potentially anticipated events, adverse device effects observed in previous clinical studies, and reported events in literature may be used in combination with device labeling, current event reporting information, and other published data to assess for an unexpected occurrence.

The implantation of the EV ICD System involves surgery; therefore, standard adverse events associated with a surgical procedure may be experienced (e.g., anesthesia complications, injury, infections, bleeding, exacerbation of pre-existing conditions, healing complications). However, the focus of this section is to address in more detail, those events that are foreseeable due to the implantation, use, performance, and/or presence of the system under investigation or comparable systems.

Treatment required for procedure and/or system related adverse events may include medication, device reprogramming, device modification (e.g., repositioning, electrical abandonment, surgical removal), or other surgical and medical remedies.

Adverse Events Reported in Previous Clinical Studies of Transvenous ICD Systems

Table 28 provides examples of adverse events associated with the use of transvenous ICD systems reported in three previous Medtronic studies. These three predicate studies were selected as a reference for EV ICD performance as they were contemporary and used adverse event definitions consistent with those utilized in the EV ICD Pivotal Study. The three predicate Medtronic studies include BLOCK HF, REVERSE, and Evera MRI. These studies collected adverse event data from 1035 subjects that underwent an ICD implant. The average follow-up time exceeded 9 months in all three trials. Table 28 displays the adverse event rates classified as related to the implanted system and/or procedure. To characterize the safety profile of a single lead ICD system, all adverse events related to an atrial or left ventricular pacing lead were excluded from consideration. Kaplan-Meier estimates and associated 95% confidence intervals of the adverse event rates are provided in the Table below at 30-days and 12-months (365 days) post-implant to characterize both peri-procedural and long-term adverse events related to the procedure or implanted system.

Table 28: System and/or Procedure Related AEs Associated with Transvenous ICD Systems (n=1035)

	Within 30-days of Implant		Within 12-months of Implant	
MedDRA Preferred Term	**No. Events (No. Subjects, %)**	**95% CI**	**No. Events (No. Subjects, %)**	**95% CI**
ACUTE PULMONARY OEDEMA	2 (2, 0.19%)	0.05% - 0.77%	2 (2, 0.19%)	0.05% - 0.77%
ADVERSE DRUG REACTION	5 (5, 0.39%)	0.15% - 1.03%	5 (5, 0.39%)	0.15% - 1.03%
ANGINA UNSTABLE	1 (1, 0.10%)	0.01% - 0.68%	1 (1, 0.10%)	0.01% - 0.68%
ANXIETY	0 (0, 0%)	--	1 (1, 0.13%)	0.02% - 0.93%
ARRHYTHMIA SUPRAVENTRICULAR	1 (1, 0.10%)	0.01% - 0.68%	2 (1, 0.10%)	0.01% - 0.68%
ATELECTASIS	3 (3, 0.29%)	0.09% - 0.90%	3 (3, 0.29%)	0.09% - 0.90%
ATRIAL FIBRILLATION	8 (7, 0.68%)	0.32% - 1.41%	8 (7, 0.68%)	0.32% - 1.41%
ATRIAL FLUTTER	1 (1, 0.10%)	0.01% - 0.68%	1 (1, 0.10%)	0.01% - 0.68%
ATRIAL THROMBOSIS	0 (0, 0%)	--	1 (1, 0.10%)	0.01% - 0.74%
ATRIOVENTRICULAR BLOCK COMPLETE	3 (2, 0.19%)	0.05% - 0.77%	3 (2, 0.19%)	0.05% - 0.77%
ATRIOVENTRICULAR BLOCK THIRD DEGREE	6 (6, 0.58%)	0.26% - 1.29%	6 (6, 0.58%)	0.26% - 1.29%
BACTERAEMIA	0 (0, 0%)	--	1 (1, 0.10%)	0.01% - 0.71%
BODY TEMPERATURE INCREASED	1 (1, 0.10%)	0.01% - 0.68%	1 (1, 0.10%)	0.01% - 0.68%
BRADYCARDIA	2 (2, 0.19%)	0.05% - 0.77%	2 (2, 0.19%)	0.05% - 0.77%
BRONCHITIS	1 (1, 0.10%)	0.01% - 0.68%	1 (1, 0.10%)	0.01% - 0.68%
CARDIAC FAILURE	16 (16, 1.55%)	0.95% - 2.52%	16 (16, 1.55%)	0.95% - 2.52%
CARDIAC FAILURE CHRONIC	1 (1, 0.10%)	0.01% - 0.68%	1 (1, 0.10%)	0.01% - 0.68%
CARDIAC PERFORATION	2 (2, 0.19%)	0.05% - 0.77%	2 (2, 0.19%)	0.05% - 0.77%
CARDIAC PROCEDURE COMPLICATION	2 (2, 0.19%)	0.05% - 0.77%	2 (2, 0.19%)	0.05% - 0.77%
CARDIAC TAMPONADE	2 (2, 0.19%)	0.05% - 0.77%	3 (3, 0.29%)	0.09% - 0.91%
CEREBROVASCULAR ACCIDENT	2 (2, 0.19%)	0.05% - 0.77%	2 (2, 0.19%)	0.05% - 0.77%
CHEST PAIN	1 (1, 0.10%)	0.01% - 0.68%	1 (1, 0.10%)	0.01% - 0.68%
CHRONIC OBSTRUCTIVE PULMONARY DISEASE	3 (1, 0.10%)	0.01% - 0.68%	3 (1, 0.10%)	0.01% - 0.68%
COMPLICATION OF DEVICE INSERTION	2 (2, 0.19%)	0.05% - 0.77%	2 (2, 0.19%)	0.05% - 0.77%
CONTRAST MEDIA REACTION	1 (1, 0.10%)	0.01% - 0.68%	1 (1, 0.10%)	0.01% - 0.68%
CORONARY SINUS DISSECTION	9 (9, 0.87%)	0.45% - 1.66%	9 (9, 0.87%)	0.45% - 1.66%
DECREASED SENSING	0 (0, 0%)	--	2 (2, 0.28%)	0.07% - 1.10%

Table 28: System and/or Procedure Related AEs Associated with Transvenous ICD Systems (n=1035)

	Within 30-days of Implant		Within 12-months of Implant	
MedDRA Preferred Term	**No. Events (No. Subjects, %)**	**95% CI**	**No. Events (No. Subjects, %)**	**95% CI**
DEEP VEIN THROMBOSIS	2 (2, 0.19%)	0.05% - 0.77%	4 (4, 0.40%)	0.15% - 1.05%
DEFIBRILLATION THRESHOLD INCREASED	1 (1, 0.10%)	0.01% - 0.68%	2 (2, 0.20%)	0.05% - 0.79%
DEHYDRATION	2 (2, 0.19%)	0.05% - 0.77%	2 (2, 0.19%)	0.05% - 0.77%
DEVICE ELECTRICAL FINDING	1 (1, 0.10%)	0.01% - 0.68%	1 (1, 0.10%)	0.01% - 0.68%
DEVICE LEAD DAMAGE	0 (0, 0%)	--	2 (2, 0.23%)	0.06% - 0.91%
DEVICE MALFUNCTION	0 (0, 0%)	--	1 (1, 0.10%)	0.01% - 0.74%
DEVICE MIGRATION	1 (1, 0.10%)	0.01% - 0.69%	2 (2, 0.20%)	0.05% - 0.78%
DEVICE RELATED INFECTION	1 (1, 0.10%)	0.01% - 0.69%	1 (1, 0.10%)	0.01% - 0.69%
DIZZINESS	1 (1, 0.10%)	0.01% - 0.68%	1 (1, 0.10%)	0.01% - 0.68%
DRUG HYPERSENSITIVITY	2 (2, 0.19%)	0.05% - 0.77%	2 (2, 0.19%)	0.05% - 0.77%
DYSPNOEA	3 (3, 0.29%)	0.09% - 0.90%	3 (3, 0.29%)	0.09% - 0.90%
DYSPNOEA EXERTIONAL	1 (1, 0.10%)	0.01% - 0.68%	1 (1, 0.10%)	0.01% - 0.68%
ELECTRICAL RESET OF DEVICE	0 (0, 0%)	--	2 (2, 0.21%)	0.05% - 0.82%
ELECTROMECHANICAL DISSOCIATION	1 (1, 0.10%)	0.01% - 0.68%	1 (1, 0.10%)	0.01% - 0.68%
ELEVATED PACING THRESHOLD	0 (0, 0%)	--	2 (2, 0.20%)	0.05% - 0.81%
ENTERITIS	1 (1, 0.10%)	0.01% - 0.68%	1 (1, 0.10%)	0.01% - 0.68%
EXTRASYSTOLES	1 (1, 0.10%)	0.01% - 0.69%	1 (1, 0.10%)	0.01% - 0.69%
FAILURE TO CAPTURE	0 (0, 0%)	--	1 (1, 0.10%)	0.01% - 0.73%
FLUID RETENTION	1 (1, 0.10%)	0.01% - 0.68%	1 (1, 0.10%)	0.01% - 0.68%
HAEMATOMA	1 (1, 0.10%)	0.01% - 0.68%	1 (1, 0.10%)	0.01% - 0.68%
HAEMOPNEUMOTHORAX	1 (1, 0.10%)	0.01% - 0.68%	1 (1, 0.10%)	0.01% - 0.68%
HAEMORRHAGE	1 (1, 0.10%)	0.01% - 0.68%	1 (1, 0.10%)	0.01% - 0.68%
HYPOTENSION	8 (8, 0.77%)	0.39% - 1.54%	8 (8, 0.77%)	0.39% - 1.54%
HYPOXIA	1 (1, 0.10%)	0.01% - 0.68%	1 (1, 0.10%)	0.01% - 0.68%
IMPAIRED HEALING	1 (1, 0.10%)	0.01% - 0.68%	2 (2, 0.20%)	0.05% - 0.78%
IMPLANT SITE CELLULITIS	0 (0, 0%)	--	1 (1, 0.10%)	0.01% - 0.71%
IMPLANT SITE EROSION	0 (0, 0%)	--	2 (2, 0.20%)	0.05% - 0.80%

Table 28: System and/or Procedure Related AEs Associated with Transvenous ICD Systems (n=1035)

	Within 30-days of Implant		Within 12-months of Implant	
MedDRA Preferred Term	**No. Events (No. Subjects, %)**	**95% CI**	**No. Events (No. Subjects, %)**	**95% CI**
IMPLANT SITE HAEMATOMA	21 (21, 2.03%)	1.33% - 3.10%	23 (23, 2.23%)	1.49% - 3.34%
IMPLANT SITE HAEMORRHAGE	1 (1, 0.10%)	0.01% - 0.68%	1 (1, 0.10%)	0.01% - 0.68%
IMPLANT SITE INFECTION	8 (8, 0.78%)	0.39% - 1.54%	14 (14, 1.38%)	0.82% - 2.31%
IMPLANT SITE INFLAMMATION	0 (0, 0%)	--	1 (1, 0.10%)	0.01% - 0.72%
IMPLANT SITE PAIN	10 (10, 0.97%)	0.52% - 1.79%	19 (18, 1.78%)	1.13% - 2.81%
IMPLANT SITE RASH	1 (1, 0.10%)	0.01% - 0.68%	1 (1, 0.10%)	0.01% - 0.68%
INAPPROPRIATE DEVICE STIMULATION OF TISSUE	3 (3, 0.29%)	0.09% - 0.90%	4 (4, 0.39%)	0.15% - 1.03%
INAPPROPRIATE DEVICE THERAPY	1 (1, 0.10%)	0.01% - 0.69%	6 (6, 0.61%)	0.27% - 1.35%
INCISION SITE HAEMORRHAGE	1 (1, 0.10%)	0.01% - 0.68%	1 (1, 0.10%)	0.01% - 0.68%
IODINE ALLERGY	1 (1, 0.10%)	0.01% - 0.68%	1 (1, 0.10%)	0.01% - 0.68%
JUGULAR VEIN THROMBOSIS	1 (1, 0.10%)	0.01% - 0.68%	1 (1, 0.10%)	0.01% - 0.68%
KELOID SCAR	0 (0, 0%)	--	1 (1, 0.10%)	0.01% - 0.72%
LEAD DISLODGEMENT	14 (14, 1.35%)	0.80% - 2.27%	20 (20, 1.96%)	1.27% - 3.02%
MEDICAL DEVICE CHANGE	0 (0, 0%)	--	1 (1, 0.10%)	0.01% - 0.74%
MEDICAL DEVICE COMPLICATION	0 (0, 0%)	--	1 (1, 0.10%)	0.01% - 0.72%
MEDICAL DEVICE DISCOMFORT	0 (0, 0%)	--	1 (1, 0.10%)	0.01% - 0.72%
MUSCLE SPASMS	1 (1, 0.10%)	0.01% - 0.68%	2 (2, 0.22%)	0.05% - 0.89%
MUSCLE STRAIN	1 (1, 0.10%)	0.01% - 0.68%	1 (1, 0.10%)	0.01% - 0.68%
MYOCARDIAL INFARCTION	1 (1, 0.10%)	0.01% - 0.68%	1 (1, 0.10%)	0.01% - 0.68%
OEDEMA PERIPHERAL	3 (3, 0.29%)	0.09% - 0.90%	4 (4, 0.39%)	0.15% - 1.04%
ORTHOSTATIC HYPOTENSION	2 (2, 0.19%)	0.05% - 0.77%	2 (2, 0.19%)	0.05% - 0.77%
OVERSENSING	1 (1, 0.10%)	0.01% - 0.68%	4 (4, 0.41%)	0.15% - 1.08%
OXYGEN SATURATION DECREASED	1 (1, 0.10%)	0.01% - 0.68%	1 (1, 0.10%)	0.01% - 0.68%
PAIN IN EXTREMITY	2 (2, 0.19%)	0.05% - 0.77%	2 (2, 0.19%)	0.05% - 0.77%
PERICARDIAL EFFUSION	8 (8, 0.77%)	0.39% - 1.54%	9 (9, 0.87%)	0.45% - 1.67%
PERICARDITIS	0 (0, 0%)	--	1 (1, 0.10%)	0.01% - 0.71%
PHANTOM SHOCK	1 (1, 0.10%)	0.01% - 0.69%	1 (1, 0.10%)	0.01% - 0.69%

Table 28: System and/or Procedure Related AEs Associated with Transvenous ICD Systems (n=1035)

	Within 30-days of Implant		Within 12-months of Implant	
MedDRA Preferred Term	**No. Events (No. Subjects, %)**	**95% CI**	**No. Events (No. Subjects, %)**	**95% CI**
PLEURAL EFFUSION	7 (7, 0.68%)	0.32% - 1.41%	8 (8, 0.78%)	0.39% - 1.55%
PLEURITIC PAIN	1 (1, 0.10%)	0.01% - 0.68%	1 (1, 0.10%)	0.01% - 0.68%
PNEUMONIA	3 (3, 0.29%)	0.09% - 0.90%	3 (3, 0.29%)	0.09% - 0.90%
PNEUMONIA ASPIRATION	1 (1, 0.10%)	0.01% - 0.68%	1 (1, 0.10%)	0.01% - 0.68%
PNEUMOTHORAX	4 (4, 0.39%)	0.15% - 1.03%	4 (4, 0.39%)	0.15% - 1.03%
PNEUMOTHORAX TRAUMATIC	1 (1, 0.10%)	0.01% - 0.68%	1 (1, 0.10%)	0.01% - 0.68%
PROCEDURAL HYPOTENSION	2 (2, 0.19%)	0.05% - 0.77%	2 (2, 0.19%)	0.05% - 0.77%
PROCEDURAL NAUSEA	1 (1, 0.10%)	0.01% - 0.68%	1 (1, 0.10%)	0.01% - 0.68%
PULMONARY EMBOLISM	0 (0, 0%)	--	1 (1, 0.10%)	0.01% - 0.72%
PULMONARY OEDEMA	1 (1, 0.10%)	0.01% - 0.68%	1 (1, 0.10%)	0.01% - 0.68%
PUNCTURE OF PERIOSTEUM	1 (1, 0.10%)	0.01% - 0.68%	1 (1, 0.10%)	0.01% - 0.68%
PYREXIA	1 (1, 0.10%)	0.01% - 0.68%	1 (1, 0.10%)	0.01% - 0.68%
RENAL FAILURE	3 (3, 0.29%)	0.09% - 0.90%	3 (3, 0.29%)	0.09% - 0.90%
RENAL FAILURE ACUTE	3 (3, 0.29%)	0.09% - 0.90%	3 (3, 0.29%)	0.09% - 0.90%
SHOULDER PAIN	4 (4, 0.39%)	0.15% - 1.03%	4 (4, 0.39%)	0.15% - 1.03%
SLEEP APNOEA SYNDROME	1 (1, 0.10%)	0.01% - 0.68%	1 (1, 0.10%)	0.01% - 0.68%
SUBCLAVIAN VEIN THROMBOSIS	2 (2, 0.19%)	0.05% - 0.77%	2 (2, 0.19%)	0.05% - 0.77%
SUPRAVENTRICULAR TACHYCARDIA	0 (0, 0%)	--	2 (2, 0.21%)	0.05% - 0.85%
SUTURE RELATED COMPLICATION	0 (0, 0%)	--	2 (2, 0.20%)	0.05% - 0.79%
SYNCOPE VASOVAGAL	2 (2, 0.19%)	0.05% - 0.77%	2 (2, 0.19%)	0.05% - 0.77%
THERMAL BURN	1 (1, 0.10%)	0.01% - 0.68%	1 (1, 0.10%)	0.01% - 0.68%
UNDERSENSING	1 (1, 0.10%)	0.01% - 0.68%	1 (1, 0.10%)	0.01% - 0.68%
UPPER RESPIRATORY TRACT INFECTION	1 (1, 0.10%)	0.01% - 0.69%	1 (1, 0.10%)	0.01% - 0.69%
URINARY RETENTION POSTOPERATIVE	1 (1, 0.10%)	0.01% - 0.68%	1 (1, 0.10%)	0.01% - 0.68%
VENOUS OCCLUSION	1 (1, 0.10%)	0.01% - 0.68%	2 (2, 0.20%)	0.05% - 0.79%
VENTRICULAR ASYSTOLE	1 (1, 0.10%)	0.01% - 0.68%	1 (1, 0.10%)	0.01% - 0.68%
VENTRICULAR FIBRILLATION	1 (1, 0.10%)	0.01% - 0.68%	1 (1, 0.10%)	0.01% - 0.68%

Table 28: System and/or Procedure Related AEs Associated with Transvenous ICD Systems (n=1035)				
	Within 30-days of Implant		Within 12-months of Implant	
MedDRA Preferred Term	No. Events (No. Subjects, %)	95% CI	No. Events (No. Subjects, %)	95% CI
VENTRICULAR TACHYCARDIA	2 (2, 0.19%)	0.05% - 0.77%	2 (2, 0.19%)	0.05% - 0.77%
WHEEZING	2 (2, 0.19%)	0.05% - 0.77%	2 (2, 0.19%)	0.05% - 0.77%

Procedure Related Adverse Events from Previous Clinical Studies Using a Similar Research System

Limited clinical experience relevant to the EV ICD System is available from the previously conducted Medtronic ASD, SPACE, ASD2, and the EV ICD Pilot studies that utilized similar research systems and protocol steps as those in the EV ICD Pivotal Study.

In the ASD study, in total ten adverse events were observed. Three adverse events were attributed to the ASD Procedure. The first ASD Procedure-related adverse event occurred in the patient where the ASD lead was observed implanted in the pleural cavity immediately adjacent to the mediastinum. This patient, who underwent a planned indicated surgical procedure requiring midline sternotomy after the ASD procedure, had documented decrease in oxygen saturation levels and small bilateral effusions reported by the site, diagnosed as chest infection (Note: physician classified this event as not related to the ASD Procedure). The small bilateral effusions resolved within five days after onset, and there were no further chronic sequelae to the patient.

The second ASD Procedure-related adverse event was associated with a patient scheduled for CABG surgery that had bruising along the left internal mammary artery bed following the ASD tunneling procedure, which resulted in a saphenous vein graft being used instead of left internal mammary graft in the final (planned) surgical procedure. There were no further sequelae to this patient, and it was commented that this may not have been an adverse event, if the graft location had not been changed due to the bruising.

The third ASD Procedure-related adverse event was a patient who had erythema on the back one day post-procedure, related to the defibrillation pad of the external defibrillation system (used as a safety back-up). The erythema resolved within one day after onset, and there were no further chronic sequelae to the patient.

None of the reported adverse events was classified as "related to the ASD Research System" by the AEAC.

In the SPACE study, 14 adverse events were observed, all without chronic sequelae to the patient.

Two of the adverse events were attributed to the SPACE Procedure. A pericardial effusion was noted in one patient (the first patient enrolled in the SPACE study overall) following the patient's planned sternotomy procedure, with the effusion resolved the same day and without extension of the subject's hospital stay beyond standard timeframe; there were no further planned actions deemed necessary and no further adverse effects reported for this patient. The second SPACE Procedure-related adverse event occurred in a patient whose planned procedure included sternotomy and bypass graft. This patient reported incision site pain three days post-procedure that reduced by 16 days and required no further follow-up or action.

In the ASD2 study, there were 20 adverse events (15 serious, 5 non-serious) experienced in 16 subjects. Of the 79 subjects who underwent the ASD2 implant procedure, there were seven adverse events in seven subjects adjudicated as causally (five) or possibly (two) related to the ASD2 procedure.

Three of the five adverse events adjudicated as causally related to the ASD2 procedure were classified as non-serious and included bleeding at the incision site, erythema and an episode of transient atrial fibrillation precipitated during VF induction. The other two adverse events adjudicated as causally related to the ASD2 procedure were classified as serious and included one reaction to anesthesia and one pericardial effusion with tamponade. The subject with pericardial effusion was a 62-year-old with ischemic cardiomyopathy who developed cardiac tamponade and prolonged hypotension intra-operatively. Hemodynamic stability was restored through surgical intervention, but the prolonged hypotension resulted in hypoxic cerebral injury. With no meaningful neurologic activity after 72 hours, supportive care was withdrawn at the family's request and the subject expired.

There were two adverse events adjudicated as possibly related to either the ASD2 procedure or the subject's final planned procedure/system: one pericarditis and one cardiac arrest. The subject with pericarditis received a dual-chamber ICD implant after the ASD2 procedure, but presented with a pericardial effusion on echocardiography three days later. After pericardiocentesis the subject's complaints resolved with no further sequelae. The subject with cardiac arrest was an 81-year-old with diabetes and ischemic cardiomyopathy who was admitted for decompensated heart failure, urosepsis and persistent AF. After medical management of these conditions, the subject was enrolled and underwent the ASD2 study procedure and planned dual-chamber ICD implantation without incident. The subject was then transferred in stable condition to a secondary site where asystole was detected 36 hours post-procedure. Despite cardiopulmonary resuscitation for 30 minutes, the subject expired.

In the EV ICD Pilot study, as of 11 March 2019, among 21 subjects undergoing an implant attempt of the system, there were 28 adverse events in 11 subjects. Six reported adverse events in four subjects were adjudicated to be causally related to the implant procedure and/or the EV ICD System. Five of the events (impaired healing, pleuritic pain (2), postoperative wound infection, implant site swelling) were causally related to the procedure, while one of the two pleuritic pain observations was also related to the EV ICD lead and the other subject with pleuritic pain eventually experienced a lead displacement (related to the EV ICD device and lead) leading to an inappropriate shock and system removal. Five of the six events were determined to be non-serious; the lead displacement event was classified as a major complication as it involved a system revision.

Adverse events in literature

There are limited published data available regarding the adverse events associated with the implantation of a subcutaneous ICD. A summary of adverse events and their published incidence of 2 studies are listed below:

1. Weiss R, Knight BP, Gold MR, Leon AR, Herre JM, Hood M, Rashtian M, Kremers M, Crozier I, Lee KL, Smith W, Burke MC. Safety and Efficacy of a Totally Subcutaneous Implantable Cardioverter Defibrillator. Circulation. 2013 Aug 27;128(9):944-53.

This study was a prospective, nonrandomized, multicenter trial of 314 subjects implanted with a subcutaneous ICD followed for 180 days. The following adverse events were reported in the manuscript.

Table 29: Safety and Efficacy of a Totally Subcutaneous Implantable Cardioverter Defibrillator, Reported Adverse Events

Adverse Event	Patients
Infections	
Total Number	18
System Explant	4
No System Explant	14
Inappropriate Shocks	
Total Number	41
Resulting from normal device function	16
Inappropriate Sensing	25
Cardiac Oversensing	22
Non-Cardiac Oversensing	3
Death	
Total Number	8
Non-cardiac, non-sudden and unrelated to implant	5

Adverse Event	Patients
Unwitnessed death, device interrogation showed successful treatment of a singular ventricular arrhythmia	1
Unwitnessed death, no interrogation available, diagnosed with atypical pneumonia and hypoxia before death	1
Unknown cause of death	1

2. Maass AH, de Groot JR, van Oostrom AJ, Theuns DA, Jordaens LJ, Wilde AA, Knops RE. The entirely subcutaneous implantable cardioverter-defibrillator: initial clinical experience in a large Dutch cohort. J Am Coll Cardiol. 2012 Nov 6;60(19):1933-9.

This was a retrospective study using the files of 118 consecutive patients implanted with a subcutaneous ICD system. Patient experience through 18 months post-implant was included in the dataset. Adverse events observed included the following:

Table 30: The entirely subcutaneous implantable cardioverter-defibrillator: initial clinical experience in a large Dutch cohort, Reported Adverse Events

Adverse Event	Patients	Episodes
Inappropriate Shocks		
Total Number	15	33
T-wave oversensing	9	11
Myopotentials	3	4
Double Counting	1	15
Atrial Flutter	1	2
TENS Therapy	1	1
Complications		
Total Number	16	
Lead Dislodgement	3	
Device Dislodgement	1	
Infection	7	
Premature Battery Depletion	2	
Skin Erosion	2	
Explant because of need for ATP	1	

Additional Adverse Events

The above incidences of each adverse event were reported from the collection of similar Medtronic studies. Events that have been experienced in other Medtronic studies that have the potential to be experienced by subjects, or may have been reported with different terminology also include:

Anemia, Aneurysm or pseudo-aneurysm, Angina pectoris, Aphasia, Arterio-venous fistula, Asystole, Atrial septal defect, Back pain, Blood or air embolism, Bruising, Cardiac dissection, Cardiogenic shock, Cellulitis, Constrictive pericarditis, Coronary artery constriction, Coronary artery disease, Coronary artery occlusion, Coronary vein occlusion, Device capture issue, Device connection issue, Device lead issue, Device pacing issue, Device protrusion, Device signal detection issue, Diaphoresis, Dressler's syndrome, Dysplasia, Ecchymosis, Edema, Electrical conduction disorders, Electrical shock, Electromagnetic interference, Endocarditis, Erythema, Exit block, Extravasation, Failure to terminate a ventricular tachycardia/ ventricular fibrillation, Fatigue, Fever, Headache, Heart block, Heart rate increase, Hematuria, Hyperkalemia, Hypertension, Impedance decreased, Impedance increased, Implant site abscess, Implant site complication, Implant site discomfort, Implant site drainage, Implant site seroma, Implant site swelling, Inappropriate device detection, Inappropriate device programming, Inflammation, Insomnia, Lead insertion tool delivery problem, Local swelling, Loss of consciousness, Mental status change, Musculoskeletal discomfort, Myocardial damage, Myocardial irritability, Neck pain, Necrosis, Neurological symptoms, Numbness at incision site, Numbness in hand, Panic attack, Paresthesia, Pericardial rub, Phlebitis, Poor hemodynamic recovery, Presyncope, Reduced cardiac output, Reduced perfusion, Respiratory failure, Restlessness, Retrosternal pain, Scar or scarring, Sepsis, Septic shock, Skin injuries, Skin reaction, Sleep apnea, Stroke, Subcutaneous emphysema, Sudden cardiac death, Thoracic pain, Thrombocytopenia, Thromboembolism, Thrombosis, Nerve damage, Transient ischemic attack, Urticaria, Valve damage, Vascular trauma, Vasovagal reaction, Venous insufficiency, Venous stenosis, Ventricular extrasystole, Vessel perforation or laceration, Vessel spasm, Vomiting, Weakness.

Appendix F: Participating Investigators and Institutions

A complete list of participating investigators and institutions will be provided under separate cover.

Appendix G: Ethics Committee and Competent Authority List

A complete list of participating Regulatory Bodies, Competent Authorities, and Ethics Committees and their Chairperson(s) that will be utilized as part of the study will be distributed under separate cover, upon request.

Appendix H: Previous Clinical Investigations

A complete bibliography and summary of relevant literature, summary and results of preclinical testing, and summary of results of previous clinical investigations is provided in the Investigator's Brochure.

Appendix I: Chronic Defibrillation Testing Protocol

Each subject will be induced to produce up to two episodes of SSVA and allowed two shock attempts to convert each SSVA from the EV ICD, for up to a total of 4 potential shocks from the EV ICD (see Figure 11). Starting therapy polarity is at the discretion of the physician (in the programmed setting).

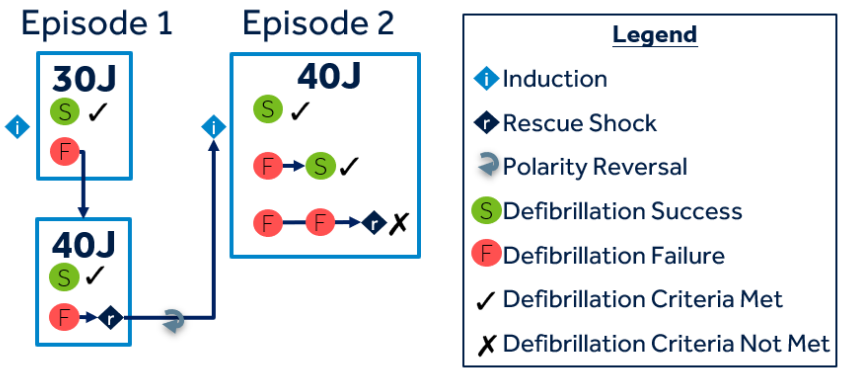


Figure 11: Diagram outlining the process of chronic SSVA induction and defibrillation testing

Episode 1

Program Rx1 and Rx2 therapies as follows:

	Rx1	Rx2
NID	30/40	NA
Redetect NID	NA	9/12
VF Therapy Status	ON	ON
Energy	30J	40J
Pathway	As programmed	As programmed

If Episode 1, Rx1 or Rx2 is successful in terminating the episode, the EV ICD System will have passed chronic defibrillation testing criteria. No additional inductions are required, and it is recommended to leave the system implanted with no changes.

Episode 2

	Rx1	Rx2
NID	9/12	NA
Redetect NID	NA	9/12
VF Therapy Status	ON	ON
Energy	40J	40J
Pathway	Opposite of programmed	Opposite of programmed

If Episode 2, Rx1 or Rx2 is successful in terminating the episode, the EV ICD System will have passed chronic defibrillation testing criteria. No additional inductions are required, and it is recommended to leave the system implanted with no changes.

If both Rx1 and Rx2 fail in Episode 2, the EV ICD System will have failed chronic defibrillation testing criteria and the next steps are at the physician's discretion. Medtronic recommends EV ICD device or lead revision (at a minimum), or system removal.

Prior to inducing and throughout the chronic defibrillation protocol, it is recommended to consider the following to improve defibrillation outcome or troubleshooting in the event of failure of first episode(s):

- Check for/resolve high impedance values
- Check for/resolve air in tunnel (e.g., fluoroscopy)
- Check for/resolve gastric bubbles (gas)
- Press on device pocket during testing
- Perform defibrillation during held end tidal expiration (end expiration apnea)

Appendix J: Applicability to CMS Beneficiaries

There is a high prevalence of ventricular tachycardia treatable by ICD therapy in the Medicare population. Medicare claims data from 2017 (the most recent currently available) shows 52,967 ICD insertion procedures (with transvenous leads) and an additional 1,657 procedures for subcutaneous ICD insertions.[xxx] As described in the background section of this CIP, subcutaneous ICD systems are currently the only available non-transvenous ICD systems. We anticipate that the EV ICD system will provide alternative option for provider consideration in cases where non-transvenous ICD systems are necessary to provide access to potentially life-saving ICD therapy in patients where vascular access is challenging or compromised.

The EV ICD trial is designed to ensure applicability of the results to the Medicare population. Of the up to 60 sites worldwide, approximately 20 will be in the US. In addition, while the EV ICD study will be open to patients aged 18 and older, the trial will aim to enroll approximately 30% of patients in the US 65 years of age or older.

xxx Medicare Physician/Supplier Procedure Summary data. Available at: https://www.cms.gov/Research-Statistics-Data-and-Systems/Statistics-Trends-and-Reports/Physician-Supplier-Procedure-Summary/index.html

Appendix K: Investigator Statement (where applicable)

Study product Name	Extravascular ICD System
Sponsor	Medtronic, Inc. 8200 Coral Sea Street NE Mounds View, MN USA 55112
Local Sponsor	**Australia** Medtronic Australasia Pty Ltd 2 Alma Road Macquarie Park NSW, 2113 Australia +61 2 9857 9000 **Canada** Medtronic of Canada, Ltd. 99 Hereford Street Brampton Ontario, L6Y 0R3 Canada +1-905-460-3800 **Europe, Middle East, Africa** Medtronic, Bakken Research Center B.V. Endepolsdomein 5 6229 GW Maastricht The Netherlands +31-43-35-66-566 **Hong Kong** Medtronic Hong Kong Medical Ltd. 1104-11, 11/F, Tower 1, The Gateway, Harbour City, Kowloon Hong Kong SAR, China +852-2919-1300 **Japan** Medtronic Japan Co., Ltd. 1-2-70 Konan, Minato-ku,

	Tokyo Japan 108-0075 Shinagawa Season Terrace 22F Phone: (+81) 3-6774-4611 Fax: (+81) 3-6774-4605 **New Zealand** Medtronic New Zealand Limited Level 3, Building 5 666 Great South Road Penrose Auckland 1051 New Zealand +64 9 634-1049
Clinical Investigation Plan Identifier	MDT16028
Version Number/Date	1.0, 02-JUL-2019
Addendum for 6-Month Defibrillation Testing Version Number/Date	*To be completed if applicable*
Addendum for Regional Reporting Requirements Version Number/Date	*To be completed if applicable*
I have read the CIP, including all appendices and applicable addenda, and I agree that it contains all necessary details for me and my staff to conduct this study as described. I will conduct this study as outlined herein and will make a reasonable effort to complete the study within the time designated. I agree to carry out all of its items in accordance with applicable regulations and in full compliance with the guidelines. I agree to ensure that the confidential information contained in this document will not be used for any purpose other than the evaluation and conduct of the clinical investigation without the prior written consent of Medtronic. I will provide all study personnel under my supervision copies of the CIP and access to all information provided by Medtronic. I will discuss this material with them to ensure that they are fully informed about the products and the study.	
Investigator's Signature:	
Investigator's Name:	
Institution:	
Date:	

17. Version History

Version	Summary of Changes	Author(s)/Title
1.0	Initial version.	Diedre Ribbens, Sr. Clinical Research Specialist