Medtronic

Clinical Investigation Plan

Clinical Investigation Plan/Study Title	ExtraVascular Implantable Cardioverter Defibrillator (EV ICD) Pilot Study
Clinical Investigation Plan Identifier	MDT17034
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: Medtronic Australasia Pty Ltd 2 Alma Road Macquarie Park NSW, 2113 Australia +61 2 9857 9000 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-MAR-2018
Lead Principal Investigator(s)	Dr Ian Crozier, MD Department of Cardiology Christchurch Hospital [redacted] New Zealand

Confidentiality Statement

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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 are contained in Table 1.

Table 1: Steering Committee (Medical Experts) contact information

Name	Contact Information
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

Full contact information for steering committee members is available 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 centers 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 2: Study sponsor contact information.

Study sponsor and contacts	
Worldwide Clinical Study Leader Samuel Liang, Sr. Clinical Research Specialist Direct Phone: +61 2 9857 9391 Email: samuel.liang@medtronic.com	*Australia / New Zealand (ANZ)* Anita van der Meer, Clinical Research Manager Direct Phone: +61 2 9857 9076 Email: anita.van.der.meer@medtronic.com
Monitoring contact	
Worldwide monitoring leader Lokesh Behal, Sr Clinical Research Monitor Direct Phone: +91 1141629020 Email: Lokesh.behal@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, there is only one CRO planned:

Cognizant Technology Solutions
500 Frank W. Burr Blvd.
Teaneck, NJ 07666
Direct Phone: (201) 801-0233
Direct Fax: (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
ADL	Activities of Daily Living
ANZ	Australia and New Zealand
AP	Anterior-Posterior view
CEC	Clinical Event Committee
CIP	Clinical Investigation Plan
CTA	Clinical Trial Agreement
CV	Curriculum Vitae
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)/Ethics Committee (EC) unless otherwise stated
E-CRF	Electronic Case Report Form
EDC	Electronic Data Capture
EGM	Electrogram
EV ICD	Extravascular Implantable Cardioverter Defibrillator
GCP	Good Clinical Practice
IB	Investigator's Brochure
IC	Informed Consent
ICD	Implantable Cardioverter Defibrillator
ICF	Informed Consent Form
INR	International Normalized Ratio
IRB	Institutional Review Board
ISF	Investigator Site File
LAT	Lateral view
NOAC	Novel Oral Anticoagulant
PSA	Pacing System Analyzer
PVT	Polymorphic Ventricular Tachycardia
SAE	Serious Adverse Event
SADE	Serious Adverse Device Effect
SC	Steering Committee
SSVA	Sustained Shockable Ventricular Arrhythmia
USADE	Unanticipated Serious Adverse Device Effect
Zone 1	Tunneling and deployment of the lead in the substernal space
Zone 2	Tunneling of the lead from the sternum to the device pocket

2. Synopsis

Title	Extravascular Implantable Cardioverter Defibrillator (EV ICD) Pilot Study
Clinical Study Type	Pilot
Product Name	System Components: • Medtronic Model DVEX2E4 EV ICD • Medtronic Model EV2401 EV ICD Lead Accessory Components: • Medtronic Model EAZ101 Sternal Tunneling Tool • Medtronic Model EAZ201 Transverse Tunneling Tool • SafeSheath II, model number SSCL9 • Medtronic 2090 CareLink Programmer with EV ICD SW041 Programmer Software Version 8.0 (or greater) installed Equipment: • DR220 Holter Recorder
Sponsor	Medtronic Inc. 8200 Coral Sea Street NE Mounds View, MN USA 55112 +1-800-328-2518
Local Sponsor	Medtronic Australasia Pty Ltd 2 Alma Road Macquarie Park NSW, 2113 Australia +61 2 9857 9000 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 to provide ventricular antitachycardia pacing and ventricular defibrillation for automated treatment of life-threatening ventricular arrhythmias in patients who do not have symptomatic bradycardia.
Investigation Purpose	The main purpose of the EV ICD Pilot study is to characterize the preliminary safety and efficacy of the EV ICD system. The use of a pilot

	study design allows characterization of the EV ICD system in a limited number of subjects before launching into a large-scale pivotal study.
Product Status	Components that are considered investigational: • Medtronic Model DVEX2E4 EV ICD • Medtronic Model EV2401 EV ICD Lead • Medtronic Model EAZ101 Sternal Tunneling Tool • Medtronic Model EAZ201 Transverse Tunneling Tool • Oscor SafeSheath II Model SSCL9 • DR220 Holter Recorder Components that are considered market-released: • Medtronic CareLink 2090 Programmer with investigational programmer Software SW041 version 8.0 (or greater)
Primary Objective(s)	Primary Safety Objective: Characterize the freedom from major complications related to the EV ICD system and/or procedure at 3-months post-implant Primary Efficacy Objective: Characterize the EV ICD defibrillation testing success rate at implant
Ancillary Objective(s)	• Characterize appropriate and inappropriate shocks • Characterize electrical performance (pacing capture thresholds, pacing impedance, sensing amplitudes) in a variety of postures and respiration cycles over time • Characterize pacing sensation • Characterize asystole pacing • Characterize lead position over time • Summarize ATP performance with spontaneous arrhythmias • Summarize adverse events
Study Design	The EV ICD Pilot Study is a prospective, multi-center, single-arm, non-randomized Study. Up to 35 subjects will be enrolled at up to 10 sites in Australia and New Zealand. Subjects indicated for single-chamber ICD therapy will be recruited and implanted with the Medtronic EV ICD system. Subjects will undergo assessments at Pre-Hospital Discharge, 2 Weeks, 4-6 Weeks and 3 Month Visits. Subjects will subsequently be followed up at 6-Months post-implant and every 6 months thereafter until study closure.
Sample Size	20-35 enrollments (worldwide) Maximum number of subjects undergoing an implant attempt will be capped at 9 per site.

Inclusion/Exclusion Criteria	Inclusion Criteria 1) Patient has a Class I or IIa indication for implantation of an ICD according to the ACC/AHA/HRS Guidelines[i] 2) Patient is willing and able to sign and date the Informed Consent Form. 3) Patient is at least 18 years of age and meets age requirements per local law 4) Patient is geographically stable and willing and able to comply with the study procedures and visits for the duration of the follow-up Exclusion Criteria 1) Patient has indications for bradycardia pacing [ii] or Cardiac Resynchronization Therapy (CRT) [iii] (Class I, IIa, or IIb indication) 2) Patient has an existing or had a prior pacemaker, ICD, or CRT device implant or leads 3) Patient has anatomical abnormality that significantly increases implant risk[iv] including: o Severe obesity [v] o Marked RV dilation o Marked sternal abnormality o Hiatus hernia that distorts mediastinal anatomy 4) Patient has prior chest radiotherapy 5) Patient had previous mediastinitis 6) Patient had previous coronary artery bypass grafting procedure 7) Patient has existing transcatheter aortic valve replacement 8) Patient has gastrostomy tube

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 2015 HRS/EHRA/APHRS/SOLAECE expert consensus statement on optimal implantable cardioverter-defibrillator programming and testing).

iii ACC/AHA/HRS guidelines for Cardiac Resynchronization Therapy

iv Per physician discretion

v BMI > 40

	9) Patient has had a prior sternotomy, prior mediastinal instrumentation, prior abdominal surgery in the epigastric region, or planned sternotomy 10) Patient has previous pericarditis that: ○ Was chronic and recurrent, or ○ Resulted in pericardial effusion [vi], or ○ Resulted in pericardial thickening or calcification [vii] 11) Patients with a medical condition that precludes them from undergoing defibrillation testing, such as: ○ known LV thrombus ○ decompensated heart failure ○ LVEF <20% [viii] ○ other physician discretion 12) Patient has persistent Atrial Fibrillation who is at high risk of a thromboembolic event with a CHA_2DS_2-VASc score ≥3, or is contraindicated for having anticoagulation interrupted for ≥72 hours 13) Patients with comorbidities which may increase surgical risk of complications[ix] including: ○ severe aortic stenosis ○ COPD and is oxygen dependent ○ Hepatosplenomegaly ○ Marked hepatomegaly 14) Patient is on renal dialysis 15) Patient with any evidence of active infection or undergoing treatment for an infection 16) Patient with current implantation of neurostimulator or any other chronically implanted device which uses current in the body. 17) Patients with a limited life expectancy of less than 12 months 18) Patient is enrolled or planning to enroll in a concurrent drug or device study that may confound the results of this

vi As documented on echo or MRI
vii As documented on CT scan or MRI
viii Most recent LVEF in the last 180 days (inclusive)
ix Per physician discretion

	study, without documented pre-approval from a Medtronic study manager 19) Patient with any exclusion criteria as required by local law (e.g., age, pregnancy, breast feeding) 20) 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 [x]
Study Procedures and Assessments	Once enrolled, a subject will be assessed at the following visits: • Baseline • Implant • Pre-Hospital Discharge • 2 Weeks • 4-6 Weeks • 3 Months • 6, 12, 18, 24… Months Study procedures are outlined in the table below.

Study procedure	B/L	IMP	PHD	2 WKS	4-6 WKS	3 MO	6, 12, 18, 24… MO	U'SCH	SYS MOD	EXT
Informed Consent	X									
Inclusion/Exclusion Assessment	X									
Physical Exam, Demographics, Cardiovascular Medical History	X									
Surface ECG	X*	X[!]							X[!^]	
Surgical history	X									
System and procedure information		X							X	
Fluoroscopy recordings during tunneling procedure		X							X^	
Fluoroscopy (AP and Lateral) of final ICD generator and lead position (cine preferred)		X							X^	
On site ECG monitoring (DR220 Holter)		X	X	X	X	X			X^	
Sensing, Impedance & Pacing Tests		X					X		X^	
Defibrillation Testing		X							X^	
Provocative testing (postures): (Sensing, Impedance and Pacing tests)			X	X	X	X				
Provocative Testing (Maneuvers)			X	X	X	X				
Provocative Testing – brisk walk				X	X					
Provocative Testing – Regular Treadmill						X				
Cardiac-gated CT	X					X (w/o contrast)				
Radiographs – Standing and Supine, AP & LAT, tidal Inhalation and Exhalation			X		X	X				
Echocardiogram	X*		X							

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

24-hour Holter Monitoring (DR220 Holter)					X	X				
Pocket/ incision photographs				X	X	X	X#	X#	X	
Save-to-media files		X	X	X	X	X	X	X	X	
Medications	X	X	X	X	X	X	X	X	X	X
Adverse Events (including AEs with fatal outcome), Device Deficiencies, Study Deviations, Other Imaging, and Subject Exits		As they occur								

* Within 30 days prior to consent is acceptable
ǂ If available, collected through EP recording system during procedure
Recommended if infection related to the EV ICD System is suspected
^ System modification where a subject leaves with an EV ICD System

Safety Assessments	All Adverse Events that are procedure related, system related, accessory related, Holter related, cardiovascular related, or serious that occur from the time of enrollment through study exit will be collected and reported to Medtronic during the study. Additionally, any device deficiency related to the EV ICD System will be collected.
Statistics	Descriptive statistics will be used to summarize all endpoints. For some endpoints such as lead position and 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 arrhythmic 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 vs. a transvenous or a subcutaneous lead. The EV ICD system will have the capability, similar to a transvenous system, to deliver ATP, post-shock pacing, and backup asystole pacing from a single device, while avoiding leads in the heart or vasculature.

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 will be of similar size and energy outputs as current transvenous systems (e.g., approximately 40 Joules and 33cc).

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. 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[17]. 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 human clinical research feasibility studies with 119 enrollments 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%). VF duration was 18.4 ± 5.6 sec. 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 should be 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. There were 79 subjects who underwent the ASD2 procedure, and 125 VF/PVT episodes were successfully collected from 68 subjects for algorithm development and validation of the current EV ICD system used in this EV ICD Pilot Study. In addition, this study highlighted the importance of training and procedure support for the chronic device implant, which is further outlined within this CIP. At the time of this report, the final report has been completed and an abstract has been submitted.

In summary, human acute feasibility data from 119 patients have contributed to the advancement of the Extravascular ICD program, and the refinement of the device and algorithm, and the implant procedure, and provide assurance for the initiation of this study with first-in-human chronic device implant of the EV ICD system.

3.2. Purpose

The purpose of the EV ICD Pilot study is to characterize the preliminary safety and efficacy of the EV ICD system: a complete extravascular ICD system with the lead implanted substernally. The use of a pilot study design allows characterization of the EV ICD system in a limited number of subjects before launching into a large-scale pivotal study.

4. Objectives and Endpoints

4.1. Objectives

4.1.1. Primary Objectives

Primary Safety Objective: Characterize the freedom from major complications related to the EV ICD system and/or procedure at 3 months post-implant.

The first primary objective is to characterize the freedom from major complications related to the EV ICD system and/or procedure at 3 months post-implant. 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 3 months (90 days) post-implant.

For an adverse event to meet the endpoint, the event must have occurred within 90 days (inclusive) of the EV ICD system implant 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
- Prolonged Hospitalization by at least 48 hours
- System revision (reposition, replacement, explant)

Primary Efficacy Objective: Characterize the EV ICD defibrillation testing success rate at implant.

The second primary objective is to characterize the defibrillation efficacy at implant of the EV ICD system. Defibrillation testing success is defined as:

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

Notes:

- In one of the two successive 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.

4.1.2. Ancillary Objectives

- Characterize appropriate and inappropriate shocks
- Characterize electrical performance (pacing capture thresholds, pacing impedance, sensing amplitudes) in a variety of postures and respiration cycles over time
- Characterize pacing sensation
- Characterize asystole pacing
- Characterize lead position over time
- Summarize ATP performance with spontaneous arrhythmias
- Summarize adverse events

5. Study Design

The EV ICD Pilot Study is a prospective, multi-center, single-arm, non-randomized study. Enrollment will include up to 35 subjects at up to 10 sites in Australia and New Zealand.

Participating sites that enroll faster than others will be allowed to do so in order to maintain an adequate enrollment rate. However, to ensure a reasonable distribution of experience and minimize center bias in study results, the maximum number of subjects undergoing an implant attempt with an EV ICD System per site will be capped at 9 subjects.

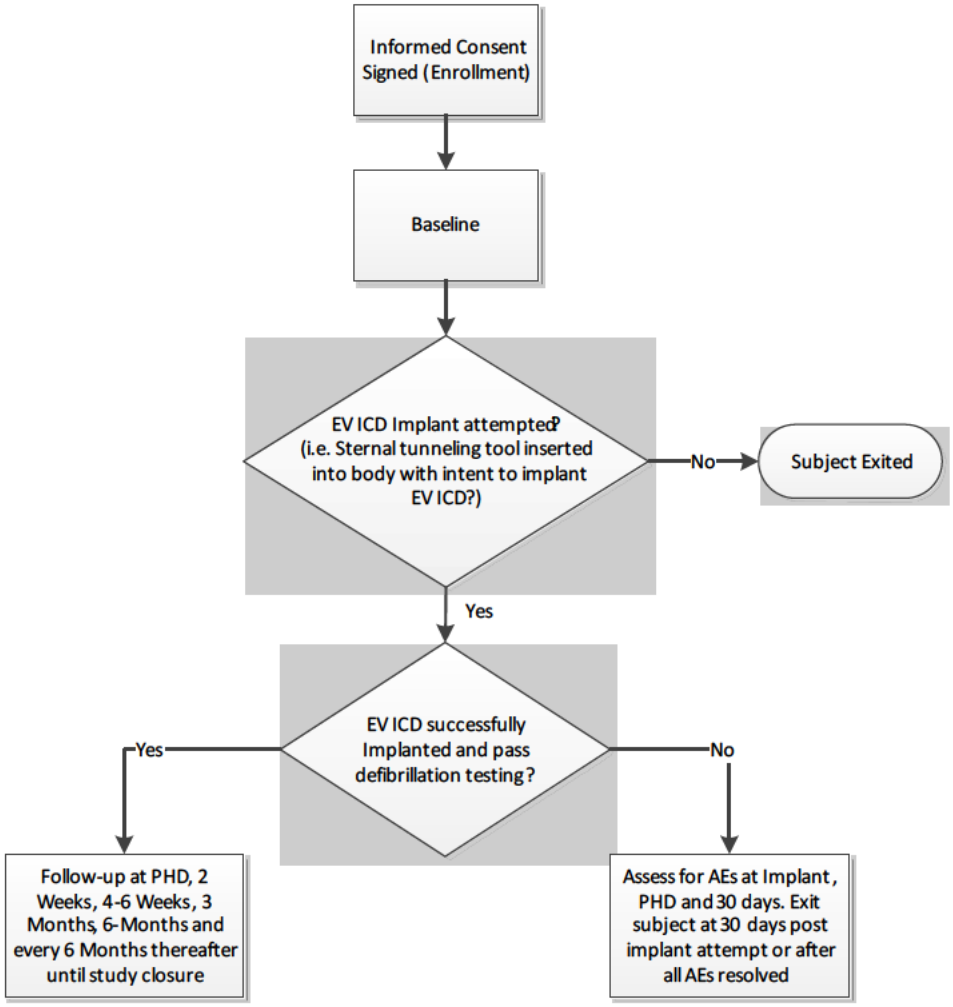

Figure 5.1: Overview of the EV ICD Pilot Study.

5.1. Duration

Subjects indicated for single-chamber ICD therapy will be recruited and implanted with the Medtronic EV ICD system. The study is expected to enroll over a period of 5 months. Subjects will undergo assessments at Pre-Hospital Discharge, 2 Weeks, 4-6 Weeks and 3 Month Visits, with follow-up for the primary safety objective at 3 months. Subjects will subsequently be followed up at 6-Months post-implant and every 6 months thereafter until study closure. Study closure is expected to occur after the EV ICD system is market-released [redacted] Each subject's participation is expected to be approximately 4 years.

5.2. Rationale

The rationale for conducting the EV ICD Pilot study is to collect first-in-human ambulatory data with a fully implanted EV ICD System in a limited number of subjects. The main purpose of the EV ICD Pilot study is to characterize the preliminary safety and efficacy of the EV ICD system. The use of a pilot study design allows characterization of the EV ICD system in a limited number of subjects before launching into a large-scale pivotal study.

The main benefits of executing a pilot study are threefold. Firstly, early human data collected in this pilot study will facilitate optimization of chronic device settings to achieve the best performance of the EV ICD system. To date, three acute human feasibility studies have been performed. Features have been designed and developed using data collected from these studies, and supplemented with animal and bench evaluations. Data from the pilot study will provide guidance for programming in the pivotal study to maximize patient safety.

Secondly, a new procedure is required to implant the EV ICD system. Given the novelty of the techniques used in this procedure, experience from the pilot study may provide additional recommendations and best practices for overcoming the learning curve for the implant procedure, the slope of which is yet to be defined.

Finally, a smaller pilot study with extensive data collection is a prudent first step to characterizing a new system leading up to a larger pivotal clinical trial where intense data collection may not be necessary, or be as practical.

Taken together, these benefits along with the inherent risk minimization, justify a small initial pilot study to gain early experience with the EV ICD system that will maximize benefit of the system to patients.

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):

- Subjects will undergo screening to confirm eligibility for enrollment with defined inclusion/exclusion criteria prior to enrollment.
- Subject demographics and comorbidities will be collected at baseline to later assess possible characteristics that may influence endpoints
- To ensure a reasonable distribution of data among sites, sites will be encouraged to enroll at least 3 subjects, and the maximum number of subjects per site undergoing an implant attempt with the EV ICD system will be capped at 9 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 and Medtronic personnel will be trained on their respective aspects of the study using standardized training materials
- All study clinicians will be trained on and required to follow the Clinical Investigation Plan
- 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
- All sites will use the same version of the Clinical Investigation Plan and standardized case report forms.

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. In addition, the Model DR220 Holter Recorder will be used during the procedure and follow-up visits, and is considered investigational in the participating geographies.

Table 3: EV ICD System Components

Model Number	Component	Investigational or Commercially Available at study start
System Components		
DVEX2E4	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
2090	Medtronic CareLink Programmer	Commercially available in all geographies. Investigational EV ICD SW041 software is downloaded onto programmer.

6.2. EV ICD (Model DVEX2E4)

The Medtronic Model DVEX2E4 is an investigational single-chamber extravascular implantable cardioverter defibrillator (EV ICD). It consists of a titanium generator can 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, ventricular tachyarrhythmia detection and therapy, including antitachycardia pacing, and post-shock pacing. The EV ICD also provides diagnostic and monitoring features to assist with system evaluation and patient care.

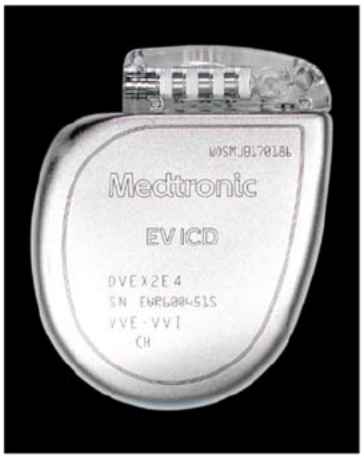

Figure 6.1: The Medtronic EV ICD Model DVEX2E4.

The DVEX2E4 ICD contains an EV4 connector, which is compatible with an EV4-LLHH quadripolar lead.

6.3. EV ICD Lead (Model EV2401)

The Medtronic Model EV2401 extravascular lead is an investigational lead with shaped passive fixation, designed for sensing, cardioversion, defibrillation and pacing therapies. 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 (lower ring), Coil 2 (lower coil), Ring 1 (middle ring), Coil 1 (upper coil). The configuration of these electrodes is shown in Figure 6.2. 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.

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

6.4. 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 in the implant procedure recommendations as Zone 1.

The sternal tunneling tool, shown in Figure 6.3 below, consists of the following components:

- A handle.
- A tunneling rod that delivers a introducer to the anterior mediastinum. The tunneling rod is malleable to accommodate patient anatomy.
- An 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.
- A thumb tab used to raise and lower the external guide.

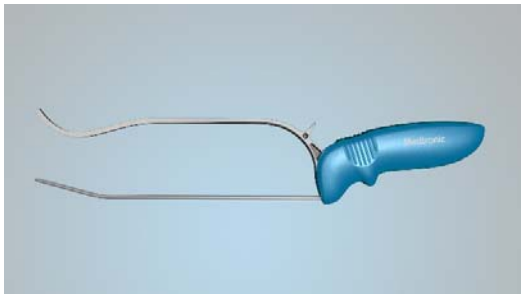

Figure 6.3: EAZ101 sternal tunneling tool.

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

6.5. Transverse Tunneling tool (Model EAZ201)

The Medtronic Model EAZ201 transverse tunneling tool, shown in Figure 6.4, 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 in the implant procedure recommendations as Zone 2.

Figure 6.4: EAZ201 transverse tunneling tool.

[redacted]

If additional tunneling tools are used to tunnel the lead subcutaneously, this should be discussed with Medtronic clinical study personnel prior to use and the tools used will be documented. This will not be considered a study deviation.

6.6. Oscor SafeSheath II Model SSCL9

The investigational Oscor SafeSheath® II Model SSCL9 introducer is a hemostatic tear-away introducer. [redacted] A 10cc plastic syringe will be packaged with the introducer 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.

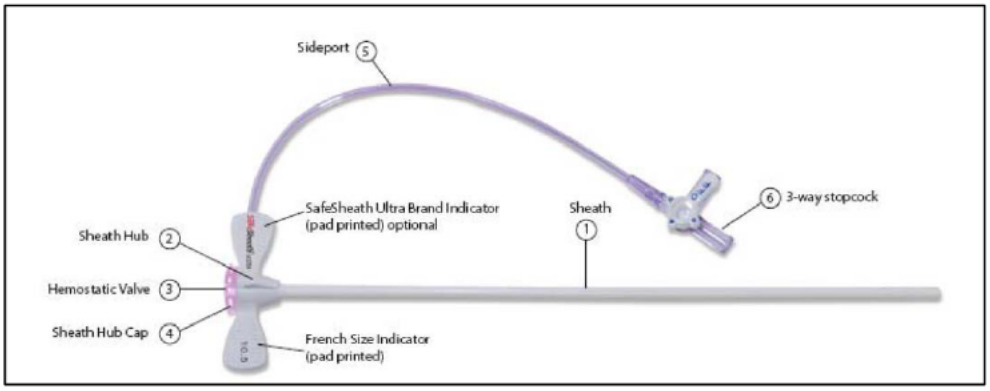

Figure 6.5: The Oscor SafeSheath II Model SSCL9

The Oscor SafeSheath® II Model SSCL9 may become commercially available during the course of the study.

6.7. EV ICD Programmer Software (Model SW041) and Medtronic Carelink 2090 Programmer

The investigational Medtronic Model SW041 programmer software, Version 8.0 (or greater) runs on the commercially available Medtronic CareLink 2090 Programmer and communicates with an implanted EV ICD Model DVEX2E4 device to program settings and view stored data. The SW041 software adjusts programmable parameters and evaluates the performance of the implanted EV ICD system.

In this study, the programmer software will be used to provide a user interface with which the user can control induction, shocking and pacing features and their parameters, and display diagnostics for each shock delivered.

The commercially available Medtronic CareLink 2090 Programmer with Conexus telemetry communicates with the EV ICD Model DVEX2E4 device.

In this study, the programmer will be used within its intended use to initiate and terminate defibrillation, pacing, and sensing, as well as adjust the programmable settings on the DVEX2E4 EV ICD.

The SW041 programmer software will be downloaded on the 2090 programmer via USB or via the Software Distribution Network (SDN).

6.8. Manufacturer

All of the EV ICD System and accessory components are manufactured by Medtronic, with the exception of the DR220 Holter Recorder, manufactured by NorthEast Monitoring Inc., and the SSCL9 introducer sheath, manufactured by Oscor, Inc.

6.9. Packaging

For investigational products in ANZ, the language of labeling and clinical manuals will be in English. The Clinical Manuals or Instructions for Use will accompany each investigational component, including the DR220 Holter Recorder. Investigational products will be clearly labeled, e.g., “Exclusively for clinical investigations” and with the study identifier “Protocol #: MDT17034”.

The investigational Medtronic Model SW041 programmer software application may use the Software Distribution Network for installation onto the Medtronic Carelink 2090 programmer; thus media packaging requirements are not applicable for distribution via the SDN. Labeling of USB drives containing SW041, if used, 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 Medtronic Programmer, the Medtronic Programmer will be labeled to indicate that it contains investigational software.

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, the labeling is in the appropriate local language.

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

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

6.10. Intended Population

The Medtronic EV ICD system is indicated to provide ventricular antitachycardia pacing and ventricular defibrillation for automated treatment of life-threatening ventricular arrhythmias in patients who do not have symptomatic bradycardia. The intended population of the EV ICD System includes patients who are indicated for implantation of a single chamber ICD according to current ACC/AHA/HRS guidelines, and who do not have a bradycardia pacing or cardiac resynchronization therapy indication.

A complete SureScan system is required for use in the MRI environment. Before performing an MRI scan, refer to the SureScan MRI technical manual for MRI-specific warnings and precautions.

6.11. Equipment

The equipment necessary for the assessment for the study include the Medtronic 2090 programmer and DR220 Holter Recorder. The maintenance and calibration of the DR220 Northeast Monitoring Holter Recorder and Medtronic CareLink 2090 programmer used for this study will be assessed outside of this clinical study. Sites are responsible for maintaining and calibrating site equipment used in the course of this study as applicable in accordance with established site practice or local regulation. Records should be kept and be able to be provided upon request by the Sponsor or regulatory agency.

6.11.1. NorthEast Monitoring Model DR220 Digital Holter Recorder

The NorthEast Monitoring Inc. Model DR220 Digital Holter Recorder is a portable ECG device able to collect telemetry signals and marker channel information from any Medtronic device for up to 48 hours. The DR220 Holter Recorder measures 12.5cm in length, 7.0cm wide and 2.5cm depth. For the purposes of this study, the investigational Holter Recorder will be used within its intended use to acutely collect continuous ECG, EGM, and marker data to ensure the EV ICD sensing algorithms are operating as expected.

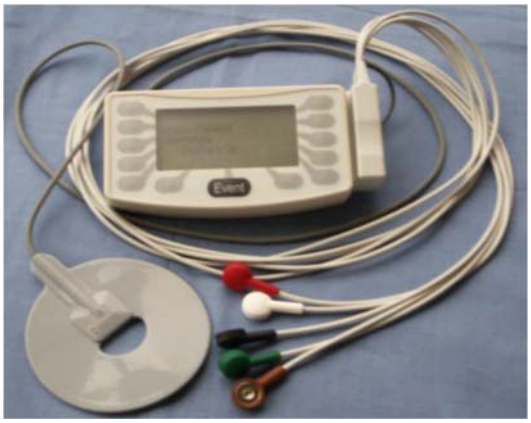

Figure 6.6: NorthEast Monitoring DR220 Holter Recorder.

6.12.Product Use

Detailed instructions for use of the EV ICD System, accessory components and required equipment are provided in the Investigator's Brochure (IB). Additionally, trained and experienced Medtronic support will be provided for every implant.

6.13. Product Training Requirements

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

- access into the anterior mediastinum,
- substernal tunneling (Zone 1),
- transverse tunneling to the device pocket (Zone 2),
- device pocket creation, and
- implant device testing, as approved by Medtronic.

This training needs to 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 safe methods are utilized to safely access the anterior mediastinum via a sub-xiphoid approach. As cardiothoracic surgeons routinely perform midline sternotomy procedures, 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). A Cardiac Surgeon/Cardiothoracic Surgeon will scrub-in and attend, at minimum, the first five implant procedures for each Implanting Physician, proctor on safe blunt dissection technique for tunneling into the anterior mediastinum and support the duration of the implant procedure. It is required that the Cardiac Surgeon/Cardiothoracic Surgeon will also provide emergency support during all clinical study implant procedures.

6.14. Product Receipt, Tracking, and Accountability

The EV ICD system components (EV ICD, lead), accessory components (sternal tunneling tool, and transverse tunneling tool and Safesheath introducer) and the DR220 Holter Recorder will be considered investigational in geographies in which the product is not available commercially and will be labeled for exclusive use in clinical investigations. This includes Australia and New Zealand. Investigational system components will be distributed to a site only when Medtronic has received all required documentation (not limited to, Ethic Committee 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 in the Device Disposition Log electronic Case Report Forms (e-CRFs), which will be maintained in the Electronic Data Capture (EDC) system.

The e-CRF 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 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 Clinical Study Management Plan requirements, or applicable study-specific document 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.

6.15. Product Storage

All investigational products must be stored in a secure location at the site with access limited only to authorized study personnel. It is the responsibility of the investigator to correctly handle, store, and track the investigational products. Further details may be found in the Investigator's Brochure (IB). Storage areas of the DR220 Holter Recorders should be locked/secure with access limited only to approved study staff.

The programmer installed with the software can be used for commercial use and there are no special storage requirements.

6.16. Product Return

All explanted, open but unused, and 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 case report form(s) or disposition log(s) (note that this is not considered a study deviation). The Device Disposition Log must be updated in the event of an explant. To receive a Return Mailer Kit, please contact your local Medtronic field personnel or representative. Holter Recorders and all unused investigational products must be returned to Medtronic upon study closure at the site.

In addition, the following components should be returned to Medtronic after use:

- EAZ101 Sternal Tunneling Tool
- EAZ201 Transverse Tunneling Tool

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 installed 2090 programmers manually.

7. Selection of Subjects

7.1. Study Population

The study population will consist of patients who have class I or IIa indication for implantation of a single chamber Implantable Cardioverter Defibrillator (ICD) according to current ACC/AHA/HRS guidelines and who do not have a bradycardia pacing or cardiac resynchronization therapy indication. Only patients who intend to undergo a *de novo* implant procedure for the EV ICD system will be included in the study.

7.2. Subject Enrollment

Patients will be screened to ensure they meet all of 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

1) Patient has a Class I or IIa indication for implantation of an ICD according to the ACC/AHA/HRS Guidelines[xi]
2) Patient is willing and able to sign and date the Informed Consent Form
3) Patient is at least 18 years of age and meets age requirements per local law
4) Patient is geographically stable and willing and able to comply with the study procedures and visits for the duration of the follow-up

xi 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

7.4. Exclusion Criteria

1) Patient has indications for bradycardia pacing [xii] or Cardiac Resynchronization Therapy (CRT) [xiii] (Class I, IIa, or IIb indication)
2) Patient has an existing or had a prior pacemaker, ICD, or CRT device implant or leads
3) Patient has anatomical abnormality that significantly increases implant risk[xiv] including:
   - Severe obesity [xv]
   - Marked RV dilation
   - Marked sternal abnormality
   - Hiatus hernia that distorts mediastinal anatomy
4) Patient has prior chest radiotherapy
5) Patient had previous mediastinitis
6) Patient had previous coronary artery bypass grafting procedure
7) Patient has existing transcatheter aortic valve replacement
8) Patient has gastrostomy tube
9) Patient has had a prior sternotomy, prior mediastinal instrumentation, prior abdominal surgery in the epigastric region, or planned sternotomy
10) Patient has previous pericarditis that:
    - Was chronic and recurrent, or
    - Resulted in pericardial effusion [xvi], or
    - Resulted in pericardial thickening or calcification [xvii]
11) Patients with a medical condition that precludes them from undergoing defibrillation testing, such as:
    - known LV thrombus
    - decompensated heart failure
    - LVEF <20% [xviii]
    - other physician discretion
12) Patient has persistent Atrial Fibrillation who is at high risk of a thromboembolic event with a CHA_2DS_2-VASc score ≥3, or is contraindicated for having anticoagulation interrupted for ≥72 hours
13) Patients with comorbidities which may increase surgical risk of complications[xix] including:

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xii 2015 HRS/EHRA/APHRS/SOLAECE expert consensus statement on optimal implantable cardioverter-defibrillator programming and testing).
xiii ACC/AHA/HRS guidelines for Cardiac Resynchronization Therapy
xiv Per physician discretion
xv BMI > 40
xvi As documented on echo or MRI
xvii As documented on CT scan or MRI
xviii Most recent LVEF in the last 180 days (inclusive)
xix Per physician discretion

- severe aortic stenosis
- COPD and is oxygen dependent
- Hepatosplenomegaly
- Marked hepatomegaly

14) Patient is on renal dialysis
15) Patient with any evidence of active infection or undergoing treatment for an infection
16) Patient with current implantation of neurostimulator or any other chronically implanted device which uses current in the body.
17) Patients with a limited life expectancy of less than 12 months
18) Patient is enrolled or planning to enroll in a concurrent drug or device study that may confound the results of this study, without documented pre-approval from a Medtronic study manager
19) Patient with any exclusion criteria as required by local law (e.g., age, pregnancy, breast feeding)
20) 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 [xx]

8. Study Procedures

During the activation process (prior to subject enrollment), Medtronic will train site personnel on, but not limited to, the clinical investigation plan, relevant standards and regulations, informed consent, written clinical investigation agreements and on data collection and reporting tools. If new members join the investigational 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.

In addition, all participating site staff must be trained on the current version of the CIP and must be delegated by the principal investigator to perform study related activities. Medtronic will provide each study site with written documentation of study site/investigator readiness.

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 4.

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

Table 4: EV ICD Pilot Study schedule of events.

Study procedure	Baseline	Implant	PHD	2 Weeks	4-6 Weeks	3 Months	6, 12, 18, 24… Months	Unsched.	Sys. Mod.	Exit
Informed Consent	X									
Inclusion/Exclusion Assessment	X									
Physical Exam, Demographics, Cardiovascular Medical History	X									
Surface ECG	X*	X[†]							X[†^]	
Surgical history	X									
System and procedure information		X							X	
Fluoroscopy recordings during tunneling procedure		X							X^	
Fluoroscopy (AP and Lateral) of final ICD generator and lead position (cine preferred)		X							X^	
On site ECG monitoring (DR220 Holter)		X	X	X	X	X			X^	
Sensing, Impedance & Pacing Tests		X					X		X^	
Defibrillation Testing		X							X^	
Provocative testing (postures): (Sensing, Impedance and Pacing tests)			X	X	X	X				
Provocative Testing (Maneuvers)			X	X	X	X				
Provocative Testing – brisk walk				X	X					
Provocative Testing – Regular Treadmill						X				
Cardiac-gated CT	X					X (w/o contrast)				
Radiographs – Standing and Supine, AP & LAT, tidal Inhalation and Exhalation			X		X	X				
Echocardiogram	X*		X							
24-hour Holter Monitoring (DR220 Holter)					X	X				
Pocket/ incision photographs				X	X	X	X[#]	X[#]	X	
Save-to-media files		X	X	X	X	X	X	X	X	
Medications	X	X	X	X	X	X	X	X	X	X
Adverse Events (including AEs with fatal outcome), Device Deficiencies, Study Deviations, Other Imaging, and Subject Exits		As they occur								

* Within 30 days prior to consent is acceptable

[†]If available, collected through EP recording system during procedure

[#] Recommended if infection related to the EV ICD System is suspected

^ System modification where a subject leaves with an EV ICD system.

8.2. Subject Screening

It is recommended to 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.

8.3. Prior and Concomitant Medications

There are no restrictions regarding prior or concomitant medications. If subject is on anticoagulation, he/she must not be contraindicated for having their anticoagulation medication interrupted for ≥72 hours.

Document all oral and intravenous medications prescribed to the subject at the time of the Baseline visit on the electronic case report forms (eCRFs). Any oral or intravenous medications commenced or ceased during participation in the study should be documented on the eCRFs.

8.4. 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 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 other privacy language as required by law that has been approved by Medtronic and the study site's Ethics Committee (EC) and signed and personally dated by the subject and the Principal Investigator. A subject may only consent after information has been given to the subject on all aspects of the clinical investigation that are relevant to the subject's decision to participate.

Prior to enrolling subjects, each site's Ethics Committee will be required to approve the ICF and other privacy language as required by law. The document(s) must be controlled (i.e., versioned and dated) to ensure it is clear which version(s) were approved by the Ethics Committee. Any adaptation of the sample ICF must be reviewed and approved by Medtronic and the Ethics Committee reviewing the application 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, approval may be requested from subjects to confirm their continued participation. ICF templates will be provided under a separate cover.

Prior to initiation of any study-specific procedures, IC must be obtained from the subject. Likewise, privacy or health information protection regulation may require subjects to sign additional forms to authorize sites to submit subject information to the study sponsor. The IC process must be conducted by the Principal Investigator or an authorized designee, and the ICF and other privacy language as required by law must be given to the subject in a language he/she is able to read and understand.

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 Pilot 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 data protection authorization, 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 by 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 signed and dated ICF, the data protection authorization, as required by law, and any other written information, signed and dated if required by local law.
- Ensure subject are 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 should 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 shall sign and personally date the ICF attesting

that the information was accurately explained and that IC was freely given. The source documentation should 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 of the signed ICF must be filed in the hospital/clinical chart and/or with the subject's study documents.

A copy of the ICF and other privacy language as required by law, signed and dated if required by local law, must be provided to the subject.

The ICF and other privacy language if required by law must be available for monitoring and auditing. Any Medtronic Field 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 Field personnel identify 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.

8.5. 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 should 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
- Demographics
- Physical exam: A basic physical exam will be performed, including height, weight and chest circumference
- Relevant medication and relevant cardiovascular medical history
- Primary indication for EV ICD implant
- Surface ECG if not already completed per standard of care
- Echocardiograms within the last 30 days

If available as part of routine standard practice, it is recommended to submit the following data to Medtronic:

- Results of EP testing within the last 180 days

- Any recent imaging of the chest within the last year (e.g., MRI, CT-scan, X-ray).

8.5.1. CT Imaging Assessment

Cardiac-gated CT scan (respiratory cycle for CT: tidal inhalation only) is to be performed during the Baseline visit. It is recommended that the baseline CT scan be performed with the use of contrast, unless contrast is contraindicated for the subject. It is further recommended that prospective gating (best diastole phase of the cardiac cycle) be used to reduce radiation dose to the subject.

- The CT image should include the thorax from the collarbone to the inferior aspect of the ribcage and include the entire width of the torso, i.e. side-to-side.
- The slice thickness should be ≤ 1.2 mm (≤ 0.8 mm preferred).
- The in-plane resolution should be ≤ 0.7 mm (≤ 0.5 mm preferred)

It is recommended to evaluate the subject's pre-operative CT-scan prior to implant procedure, to assess sternal-heart distance, sternal curvature, xiphoid shape and other anatomical characteristics. If the physician does not feel the patient is a good candidate based on the CT-scan assessment, the subject should be exited from the study.

CT images should be transferred in DICOM format.

8.6. Implant Visit

It is strongly recommended that the implant visit occur within 30 days of study enrollment. The substernal tunneling procedure must be performed by an Investigator that successfully completed hands-on training on the EV ICD implant procedure, as approved by Medtronic. This training needs to be documented in the Investigator Site File (ISF). It is required that a Cardiac Surgeon/Cardiothoracic Surgeon trained on relevant components of the study procedure will scrub-in and attend, at minimum, the first five implant procedures for each Implanting Physician, proctor on safe blunt dissection technique for tunneling into anterior mediastinum and support the duration of the implant procedure. It is required that a Cardiac Surgeon/Cardiothoracic Surgeon will also provide emergency support during all clinical study implant procedures.

8.6.1. Antibiotic and Infection Control Strategies

Standard hospital procedures should be followed regarding antibiotic therapy for implantable cardioverter defibrillator implantation, and prophylactic antibiotic use is required and should be administered per standard of care to avoid risk of infection[23]. Strategies to minimize the risk of infection utilized during the implant procedure include recommendations to:

- Ensure that the subject does not have any clinical signs of infection prior to the EV ICD implant (i.e., show absence of fever for 48 hours prior to the procedure).
- Administer prophylactic parenteral antibiotics prior to the device implant per guidelines[24].
- Perform pre-operative antiseptic preparation of the surgical site.

- Avoid shaving the operative site: clip if necessary.
- Maintain proper sterile technique throughout the procedure.
- Utilize separate tables for instruments and gowns/gloves.
- Prevent or minimize hematoma formation by meticulous cautery of bleeding sites.

Details regarding antibiotic usage will be collected.

8.6.2. Anticoagulation

Subjects on anticoagulants will have oral and/or systemic anticoagulants withheld peri- and post-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 ≥24 hours pre-procedure

Post-procedure:

- Withhold oral and/or systemic anticoagulants for approximately 72 hours post-procedure.

8.6.3. Procedure Steps

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

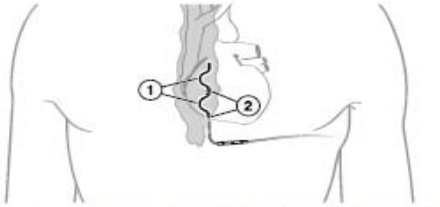
It is strongly recommended to use General Anesthesia with cardiac monitoring for the implant procedure.

Table 5: Outline of the study-specific implant procedure steps.

Implant Step	Recommended Procedure + Imaging
1. Patient Assessment	• Review pre-op CT-Scan. • 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 patient 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.
2. Patient Prep and Drape	• Prep chest for implant per Standard of Care. • Placement of 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 just posterior of the left mid-axillary line, using fluoroscopy (AP & Lateral views) as guidance and the cardiac silhouette. • Place skin button electrode near this location for alternate vector sensing measurements with the Pacing System Analyzer (PSA). • Draw surface landmarks on chest. **Recommended**: Identify sternal midline, left sternal border, xiphoid process, costal margins, top of cardiac silhouette and incision location and device pocket location. • Sterile prep 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	Recommended 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 must 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. • Pre-procedural fluoroscopy should be performed in both Lateral and AP views to assess the angle of insertion into the substernal space prior to starting the implant procedure to assist in determining sub-xiphoid incision location for the patient anatomy and tunneling tool insertion.
4. Sub-Xiphoid Access	• Make an incision below the xiphoid process and left of sternal midline. Anatomical variation adjustments may be necessary: ○ 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. ○ Consider the margins of the left Costal Rib and Xiphoid Process; the incision should be along the base of the isosceles triangle.
5. Blunt Dissection of Diaphragmatic Attachments	• Cardiac/Cardiothoracic Surgeon proctorship on safe access techniques and blunt dissection are required for, at minimum, the first 5 implant procedures for each Implanting Physician. Use of curved Kelly hemostat + Lateral fluoroscopy and fingertip confirmation of tissue plane to dissect through diaphragmatic attachments. Bovie may also be used, if trained by surgeon on tissue dissection in subxiphoid space.

Implant Step	Recommended Procedure + Imaging
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 to top of cardiac silhouette, as determined by AP Fluoroscopy. 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 suspect lungs crossing midline, consider tunneling during 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 EAZ101 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. • Deploy the lead by withdrawing the sheath out of the incision to expose the electrodes. • **Required Lead Orientation:** Defibrillation Coils toward patient's right chest; Pace/Sense Rings toward patient left chest. Target Ring 1 at the level of RV center (heart silhouette). Ring 2 should be in substernal tissue above the diaphragmatic crossing, not subcutaneous tissue. • 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 recommended orientation prior to acute testing.

Implant Step	Recommended Procedure + Imaging
	• It is recommended to not reinsert the lead through the introducer valve more than three times during the procedure. If this occurs, recommended to 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.
8. Assessment of EV ICD Lead	• Evaluate R-wave signal amplitude for Ring 1-Ring 2 configuration using Medtronic CareLink Programmer Model 2090 Analyzer. Evaluate alternate sensing vectors (Ring 1 to Skin Button Electrode, Ring 2 to Skin Button Electrode, Coil 1 to Coil 2) as necessary. ○ Set up the 2090 PSA to new R-wave filter, ODO mode, RV sensing vector to Ring1 to Ring2. ○ Record the measured sensing values. ○ Repeat process on alternate vectors (Coil 1 to Coil 2 or Ring1 to Sterile Skin Button Electrode) if Ring1-Ring2 R-wave amplitude is less than 1mV. ○ If R-wave amplitude is < 1mV for all possible sensing vectors, attempt the following troubleshooting recommendations: ▪ Repositioning allowed by moving lead caudal ▪ Repositioning by re-advancement of the sheath + EAZ101 tunneling tool to achieve more cranial position if necessary, then redeploy the lead ▪ Re-tunneling is allowed if the lead is not over the RV in AP view, lead dislodgement or a kink in sheath ○ If R-wave amplitude is < 1mV after the troubleshooting attempts have been exhausted and all sensing vectors have been evaluated, the implant should be abandoned, and the implant of an alternative ICD system should be considered.

Implant Step	Recommended Procedure + Imaging
	• Remove introducer sheath prior to sub-xiphoid suture sleeve fixation.
9. Sub-Xiphoid Suture Sleeve and Lead Fixation	• **Required:** Use 3 non-absorbable sutures with high tension force to fixate suture sleeve to lead body in sub-xiphoid incision using each of the 3 grooves.
10. Create EV ICD device pocket	• Use fluoroscopy to confirm defibrillation vector based on lead placement and cardiac silhouette for EV ICD device location. • Create device pocket incision and pocket in the sub-latissimus plane just posterior to the left mid-axillary line.
11. Transverse Subcutaneous Tunneling Procedure (Zone 2)	• Insert distal tip of zone 2 tunneling rod in sub-xiphoid incision, above/anterior 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 zone 2 tunneling rod.
12. Device Pocket and Sub-Xiphoid Incision Closure	• Fixate device header against fascial plane using non-absorbable suture in the holes provided. • Use of the TYRX™ Envelope is not permitted in the Pilot Study. • Close the pocket and sub-xiphoid incisions prior to device testing and remove air from incisions prior to closure. • Final closure of incisions should be in 3 layers, and wound dressings should 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.

Implant Step	Recommended Procedure + Imaging
14. EV ICD Device Testing	• Using sterile sleeve(s) provided, attach the Holter Model DR220 antenna and Model 2090 programmer head against skin of closed (at least one layer) device pocket. • Interrogate the EV ICD device and perform electrical testing (sensing, pacing, impedance). • Perform defibrillation testing protocol, as described in section 8.6.7. • Reconfirm lead position after each defibrillation attempt from the implanted system.

8.6.4. Fluoroscopy and Photography

Prior to inserting the EAZ101 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. This 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 recordings during the substernal tunneling with the Model EAZ101 tunneling tool and introducer as well as during Model EV2401 lead placement.
- Two fluoroscopy cine images (AP and LAT) are required of the final Model EV2401 lead placement following substernal insertion of the lead for one full respiration cycle without panning the camera. Static fluoroscopic images of the final EV ICD Model DVEX2E4 in AP and LAT views are to be collected to document final position relative to the heart.

Fluoroscopy (or cine) recordings will be retained for the subject file, and copies will be sent to Medtronic.

Photography/ Videography

If allowed per local regulations and accepted by the subject in the Informed Consent, Medtronic personnel attending the Implant Visit may take pictures of and/or videotape the implant procedure for training, education, and/or research purposes. These photos and/or video recordings will not display any identifiable features of the subject.

8.6.5. ECG Holter Monitoring

Set up DR220 Holter as shown in Figure 8.1 prior to testing of the EV ICD System. Ensure the antenna is placed inside a sterile sleeve prior to placing over the subject's implanted ICD.

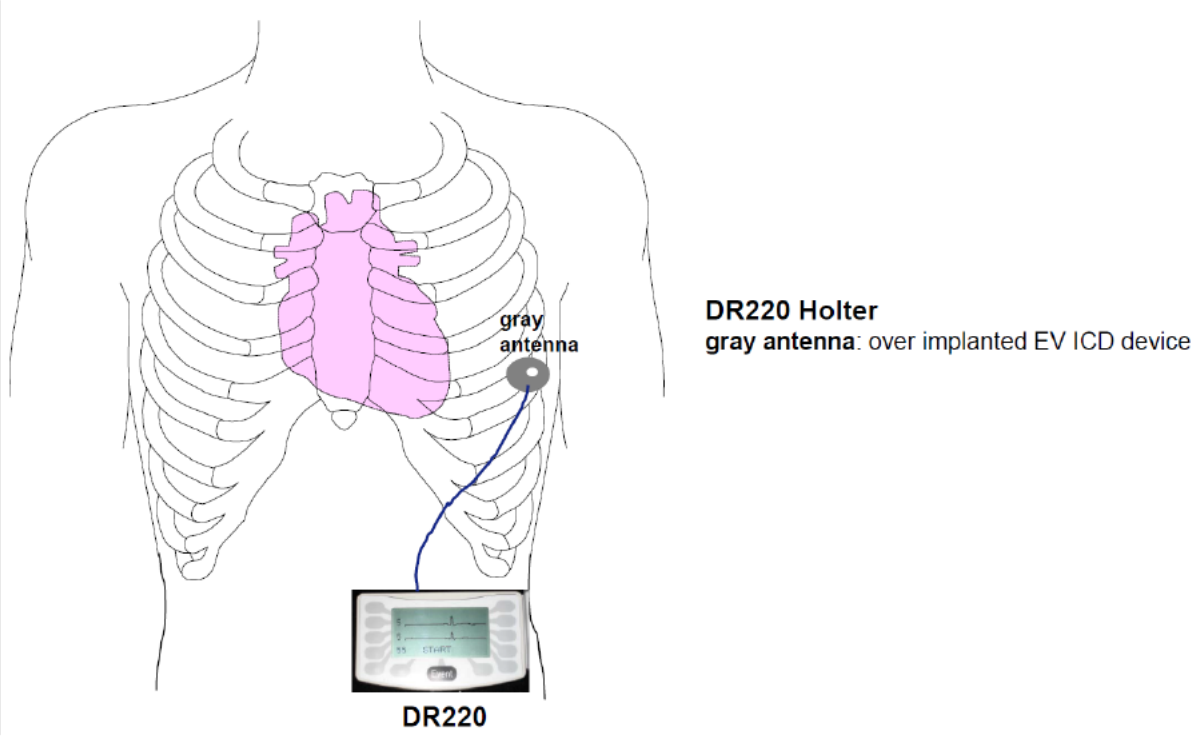


Figure 8.1: Example of DR 220 Holter system set-up for continuously collecting device ECG data during Implant visit, and pre-Hospital Discharge Visit.

8.6.6. 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. The programmer head will be placed inside a sterile sleeve for implant testing.

If available, obtain a copy of the surface ECG recording from the EP recording system during the implant procedure.

8.6.6.1. Sensing Testing

Set ICD RV sensing vector to Ring1-Ring2. Adjust sensing parameters to avoid T-wave oversensing, P-wave oversensing or other oversensing. Once configured, execute the Sensing Test while running the live strip. Ensure a copy of the live strip is sent to Medtronic (e.g., a scan). Print the Sensing Test Report on the 2090 Programmer and store at site. Evaluate alternate sensing vectors as necessary. Program determined sensing settings.

R-wave amplitude for sensing should be greater than or equal to 1mV for the programmed sensing vector.

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

8.6.6.2. 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 on the 2090 Programmer and store at site.

8.6.6.3. Pacing Testing

Using a Pulse Width Search, conduct pacing capture threshold (PCT) test until lowest voltage pacing threshold is found. Continue pacing testing (up to 30V) to determine extracardiac muscle stimulation threshold. The clinician will be asked to evaluate the presence of extracardiac muscle stimulation. The following configurations may be evaluated: Ring1-Coil2, Ring1-Ring2, Coil2-Coil1.

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

Note: If post pace oversensing is observed, sensing parameters should be adjusted to eliminate or minimize oversensing.

Print final capture threshold report and final parameters, and send to Medtronic.

8.6.7. VF induction and Defibrillation Testing

8.6.7.1. General Requirements

In order to ensure subject safety in an ambulatory setting, VF induction and defibrillation testing is required at implant. Adjust device programming to ensure adequate safety margins for sensing and defibrillation during VF induction testing.

Ensure a Wavelet template is collected prior to induction. Induction of VT/VF will be achieved using one of the following methods:

a. Burst Induction (Coil2-Coil1, 40V).

b. T-shock (up to 20J).

Follow the defibrillation testing as outlined in Figure 8.2, beginning at Episode 1 (20J). The testing protocol may require up to five (5) sustained shockable ventricular arrhythmia (SSVA) episodes induced and up to seven (7) EV ICD shocks delivered (Figure 8.2).

Ensure EV ICD VF detection is enabled prior to performing induction. If the subject's health is at risk, defibrillation testing should be suspended or terminated.

Defibrillation testing success is defined as:

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

Notes:

- In one of the two successive SSVA episodes, up to two 30J shocks are permitted
- To achieve final system configuration, changing the position of the can 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 day of implant.

Ensure an external transthoracic defibrillation system is present and ready to deliver rescue shocks during defibrillation testing.

The NID for EV ICD initial detection should be programmed as 30/40 for the first induction in order to capture sufficient length of recorded SSVA. Subsequent inductions will be performed using NID for initial detection = 18/24.

The NID for Redetection (where applicable) should be programmed as NID 9/12.

It is recommended to wait 5 minutes between the end of an SSVA episode and subsequent induction. Waiting period after failed induction attempts is at the investigator's discretion.

Reminder: Print live strip for the duration of each SSVA episode. Ensure a copy of the live strip is sent to Medtronic (e.g. a scan). Print the VT/VF episode report 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.

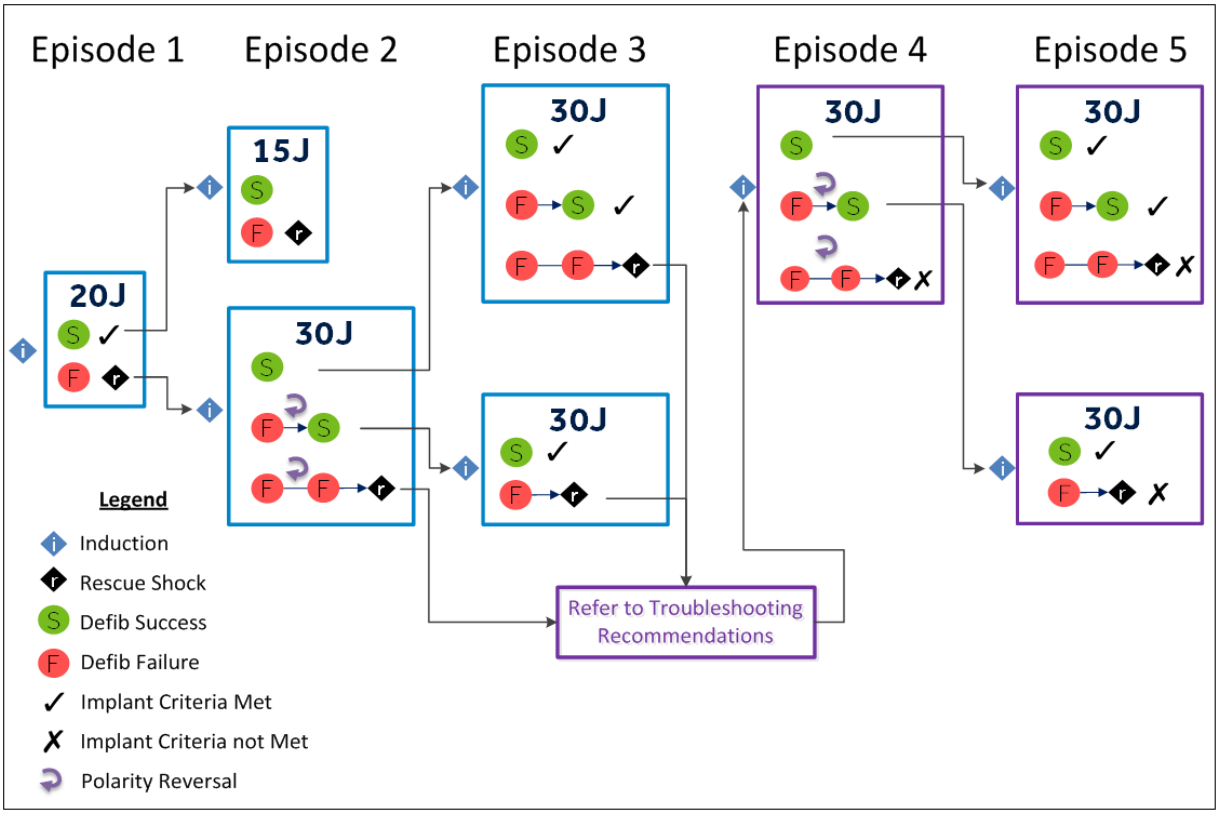


Figure 8.2: Diagram outlining the process of SSVA induction and defibrillation testing.

8.6.7.2. Episode 1

Program Rx1 and Rx2 therapies as follows:

	Rx1	Rx2- Rx6
NID	30/40	NA
Redetect NID	NA	NA
VF Therapy Status	ON	OFF
Energy	20J	NA
Pathway	STD	NA

If Episode 1, Rx1 is successful in terminating the episode, the EV ICD System will have passed Implant Criteria. Proceed with Section 8.6.7.3, Episode 2 testing at 15J for better characterization of defibrillation threshold in the subject.

If Episode 1 shock was not successful, an external defibrillator should be used to deliver the rescue shock. Proceed to Section 8.6.7.3, Episode 2.

8.6.7.3. Episode 2

If Episode 1 was Successful, test at 15 J

	Rx1	Rx2 – Rx6
NID	18/24	NA
Redetect NID	NA	NA
VF Therapy Status	ON	OFF
Energy	15J	NA
Pathway	STD	NA

Record whether 15J was successful in terminating SSVA Episode.

If shock fails to terminate the SSVA episode, an external defibrillator should be used to deliver the rescue shock. The EV ICD System is still considered to have met Implant Criteria via a single 20J shock in Episode 1.

If Episode 1 was Unsuccessful, test at 30J

	Rx1	Rx2	Rx3 – Rx6
NID	18/24	NA	NA
Redetect NID	NA	9/12	NA
VF Therapy Status	ON	ON	OFF
Energy	30J	30J	NA
Pathway	STD	REV	NA

If Rx1 or Rx2 is successful in Episode 2, continue to Episode 3.

If both Rx1 and Rx2 fail in Episode 2, consider taking one or more recommended steps at improving the chance of shock success as outlined in Section 8.6.7.5 and continue to Episode 4.

8.6.7.4. Episode 3

If Episode 2, Rx1 was successful

	Rx1	Rx2	Rx3-Rx6
NID	18/24	NA	NA
Redetect NID	NA	9/12	NA
VF Therapy Status	ON	ON	OFF
Energy	30J	30J	NA
Pathway	STD	STD	NA

If either Rx1 or Rx2 is successful in terminating Episode 3, the EV ICD System will have passed Implant Criteria.

If Episode 2, Rx2 was successful

	Rx1	Rx2	Rx3-Rx6
NID	18/24	**NA**	**NA**
Redetect NID	NA	NA	NA
VF Therapy Status	ON	OFF	OFF
Energy	30J	NA	NA
Pathway	REV	NA	NA

Note that Rx1 is programmed to the polarity that gave success in Episode 2.

If Rx1 is successful in terminating Episode 3, the EV ICD System will have passed Implant Criteria.

If the Episode 3 shock was unsuccessful, consider taking one or more recommended steps at improving chance of shock success as outlined in Section 8.6.7.5 Troubleshooting Recommendations and continue to Episode 4.

8.6.7.5. Troubleshooting Recommendations

Prior to inducing Episode 4, it is recommended to consider the following when troubleshooting to improve defibrillation outcome:

- Check for pneumothorax
- Check for high impedance values
- Check for air in tunnel (e.g., fluoroscopy)
- Check for air in pocket
- Consider changing default shock polarity
- Allow time (e.g., next day or during the admission) to minimize transient factors affecting defibrillation success
- If all of the above measures are exhausted, evaluate the position of the EV ICD generator and the EV ICD Lead. If required, consider repositioning of EV ICD generator or EV ICD lead.

8.6.7.6. Episode 4 - Post-Troubleshooting

	Rx1	Rx2	Rx3 – Rx6
NID	18/24	NA	NA
Redetect NID	NA	9/12	NA
VF Therapy Status	ON	ON	OFF
Energy	30J	30J	NA
Pathway	STD Or REV	REV Or STD	NA

Note that Rx1 and Rx2 therapies should be programmed in opposite polarities.

If Episode 4, Rx1 or Rx2 is successful, continue to Episode 5. If both Rx1 and Rx2 fail in Episode 4, the EV ICD System will have failed Implant Criteria and implantation of an alternative system should be considered.

8.6.7.7. Episode 5 - Post-troubleshooting

If Episode 4, Rx1 was successful:

Program Rx1 and Rx2 per Rx1 in Episode 4.

	Rx1	Rx2	Rx3 – Rx6
NID	18/24	NA	NA
Redetect NID	NA	9/12	NA
VF Therapy Status	ON	ON	OFF
Energy	30J	30J	NA
Pathway	STD Or REV	STD Or REV	NA

If either Rx1 or Rx2 is successful in terminating Episode 5, the EV ICD System will have passed Implant Criteria.

If both Rx1 and Rx2 fail in Episode 5, the EV ICD System will have failed Implant Criteria, and implantation of an alternative system should be considered.

If Episode 4, Rx1 was Unsuccessful (Rx2 successful):

Program Rx1 per Rx2 in Episode 4.

Program Rx2 therapy OFF.

Note that Rx1 in Episode 5 is programmed to the polarity that gave success in Episode 4.

	Rx1	Rx2	Rx3 – Rx6
NID	18/24	NA	NA
Redetect NID	NA	NA	NA
VF Therapy Status	ON	OFF	OFF
Energy	30J	NA	NA
Pathway	REV Or STD	NA	NA

If Rx1 is successful in terminating the episode, the EV ICD System will have passed Implant Criteria.

If the Episode 5 Rx1 shock was not successful, the EV ICD System will have failed Implant Criteria, and implantation of an alternative system should be considered.

8.6.7.8. Programming Recommendations at End of Implant Procedure

At the end of the procedure, VF Detection is required to be ON and VF Therapies and Pacing therapies are required to 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 is required to have cardiac monitoring.

8.6.7.9. Unsuccessful Implant Definition

Implant procedure/testing is considered unsuccessful if any of the following occur:

- EV ICD System is not fully implanted
- Defibrillation testing does not meet criteria for success
- R-wave < 1mV for all possible sensing vectors after troubleshooting methods are exhausted

If the subject completes the initial implant procedure without completing the defibrillation testing, the subject may be brought back prior to pre-hospital discharge to complete the defibrillation testing, as outlined in Figure 8.2.

If the EV ICD system is explanted or repositioned after initial implant procedure but prior to pre-hospital discharge, this should be captured on a system modification eCRF. In the event of the EV ICD being permanently explanted, these subjects should be followed and assessed for AEs through 30 days or until procedure or system related AEs have been resolved, at which point subjects can be exited.

An unsuccessful implant procedure, and unsuccessful or incomplete 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. Subjects with an unsuccessful EV ICD attempt will be followed up through 30 days or until procedure or system related AEs have been resolved, at which point they can be exited.

8.7. Pre-Hospital Discharge

Perform the following tests of the EV ICD System at the pre-hospital discharge. Prior to the subject being discharged, VF Therapies are required to be programmed ON and pacing therapies, as appropriate, should be programmed ON.

8.7.1. ECG Holter Monitoring

Set up DR220 Holter as described in section 8.6.5 prior to testing of the EV ICD System. Ensure the antenna is placed over the dressing of the device.

8.7.2. Electrical Testing

Perform Electrical Testing (Sensing, Impedance and Pacing Tests) as outlined in Section 8.8.3.

8.7.3. Provocative Testing

Perform the following elements of provocative testing as the subject is able:

- Electrical testing in different postures per Section 8.8.4.1
- Sinus rhythm in different postures per Section 8.8.4.2
- Maneuvers per Section 8.8.4.3

8.7.4. Imaging

Collect the radiographs at pre-hospital discharge per Table 6. Additional radiographs may be collected at the discretion of the physician in additional postures (i.e. prone, left decubitus, right decubitus) at any post-implant time point if electrical testing at follow-up reveals deterioration in sensing or pacing performance. Additional imaging at different postures is recommended if:

- Pacing output changes by 3V in magnitude in either direction (pacing testing performed in 1V increments); or
- R-wave amplitude falls by 50% or falls below 1mV.

Table 6: Image collection during Pre-Hospital Discharge Visit.

Visit	Image Collection
Pre-hospital Discharge Visit	• Supine AP → Tidal Inhalation and Tidal Exhalation • Supine LAT → Tidal Inhalation and Tidal Exhalation • Standing AP → Tidal Inhalation only • Standing LAT → Tidal Inhalation only

All images should be transferred in DICOM format.

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.

8.7.5. Medications

Changes to oral or intravenous medications will be recorded.

8.8. Scheduled Follow-up Visits

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

- Electrical Testing per section 8.8.3 (electrical stability and acceptability of pacing threshold and pacing at safety margin)
- Provocative testing per section 8.8.4 (Ensure adequate sensing in ambulatory setting)
- Collection of imaging per section 8.8.5 – (mechanical stability)
- Holter monitoring per section 8.8.2 (on site) and 8.8.6 (24 Hour) – (electrical stability)

Medtronic will provide the target dates and window for each follow-up visit to the implanting center. Follow-up visit windows open on the Window Start date and remain open as defined in Table 7. It is recommended that subjects are scheduled as close as possible to the target date for a given follow-up visit.

Table 7: 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 Weeks	10	14	21
4-6 Weeks	28	30	49
3 Month	90	90	120
6 Month	180	180	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.

8.8.1. Wound Inspection (2 Weeks, 4-6 Weeks, 3 Months)

Visually inspect the device Pocket Incision and the Lead Incision for appropriate recovery. Obtain photographs of the pocket area and the Lead Incision area per section 8.8.5.2.

8.8.2. On Site ECG Holter Monitoring (2 Weeks, 4-6 Weeks, 3 Months)

A DR220 Holter monitor will be used to continuously monitor device ECG during all in-office follow-up visits up through the 3-Month visit.

2 Weeks, 4-6 Weeks, 3 Month Visits: Set up Holter according to Figure 8.3 prior to testing of the EV ICD System.

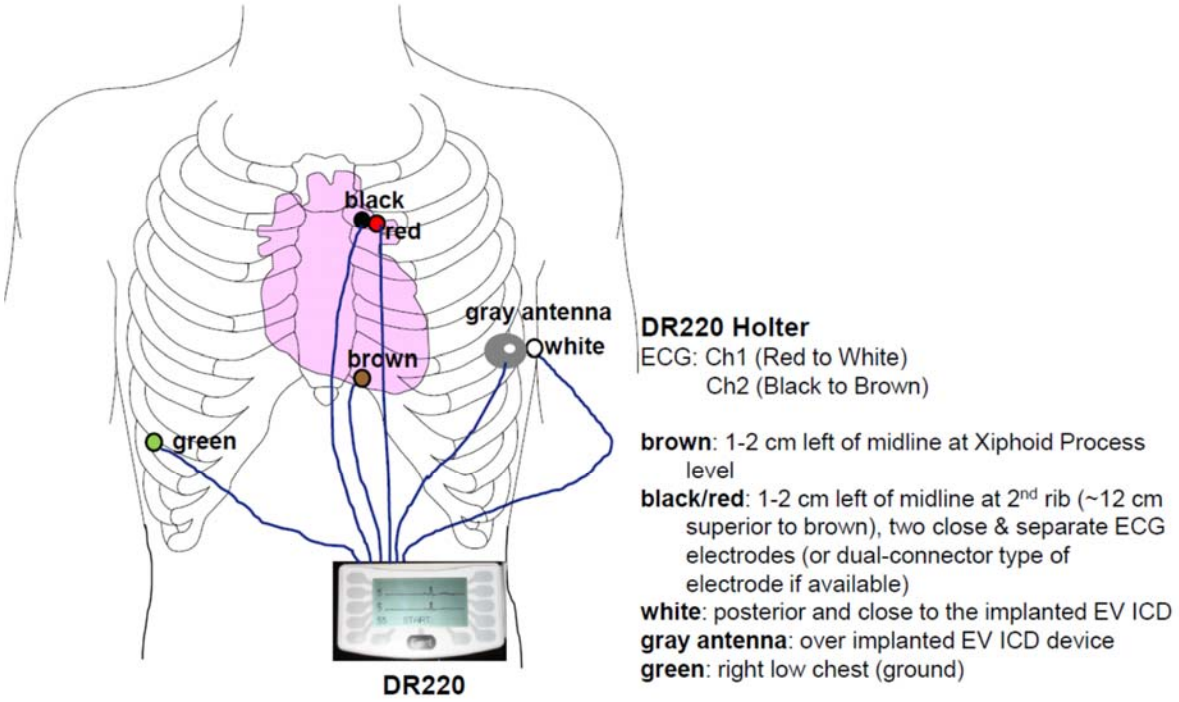


Figure 8.3: Example of DR 220 Holter system set-up for continuously collecting device ECG data and body-surface ECG data during in-office follow-ups (2 Weeks, 4-6 Weeks, and 3 Month visits) and 24-hour Holter (at 4-6 Weeks and 3 Month follow-ups).

8.8.3. Electrical Testing (2 Weeks, 4-6 Weeks, 3 Months)

Subjects' medical records should be made available prior to performing electrical testing. Interrogate the device by selecting "Interrogate ALL" on the 2090 programmer at the beginning of the visit. Save the data via a Save-to-media file.

Perform the following tests while the subject is in the postures described in section 8.8.4.1.

8.8.3.1. Sensing Testing

Adjust sensing parameters to avoid T-wave oversensing, P-wave oversensing or other oversensing. Once configured, execute the Sensing Test while running the 2090 strip chart recorder. Print the Sensing Test Report on the 2090 Programmer, and send a copy of live strips and report to Medtronic.

If R-wave has deteriorated (<1mV), evaluate alternate sensing vectors and program sensing settings as desired. Ensure R-wave in selected sensing vector is ≥1mV in all postures. If R-wave ≥1mV cannot be maintained in any of the vectors, consider assessment of lead movement via imaging and system modification if necessary.

8.8.3.2. Impedance Testing

Subthreshold impedance will be measured for the following electrode pairs:

- Ring1-Ring2
- Ring1-Coil2
- High Voltage

Print the Lead Impedance Test Report on the 2090 Programmer and submit a copy to Medtronic.

8.8.3.3. Pacing Testing

Using a Pulse Width Search, conduct pacing capture threshold (PCT) test until lowest voltage pacing threshold is found. Continue pacing testing up to 30V to determine extracardiac muscle stimulation threshold. The following configurations may be evaluated: Ring 1-Coil2, Ring1-Ring2, Coil2-Coil1.

At the conclusion of pacing capture threshold testing, the subject's device should be programmed after confirming extracardiac stimulation threshold while awake to allow for an assessment of the margin between pacing capture threshold and extracardiac stimulation. If post pace oversensing is observed, sensing parameters should be adjusted to eliminate or minimize oversensing.

Print final capture threshold report and final parameters and send a copy to Medtronic.

8.8.4. Provocative Testing (2 Weeks, 4-6 Weeks, 3 Months)

All subjects are encouraged to perform all postures and maneuvers. If the subject is physically unable to complete or perform a posture or maneuver, this should be documented, however, a study deviation will not be required.

8.8.4.1. Electrical Testing in Different Postures

Conduct electrical tests described in section 8.8.3 whilst the subject is in each of the following postures:

- Sitting in the upright position (standing is also allowed)

- Bent over from sitting in chair with both hands touching or reaching for the ground
- Supine
- Prone (or simulated prone during PHD visit)
- Lying on left side (if possible)
- Lying on right side

8.8.4.2. Sinus Rhythm in Different Postures

Collect sinus rhythm data (for approximately one minute) whilst the subject is in each of the following postures:

- Sitting in the upright position (standing is also allowed)
- Bent over from sitting in chair with both hands touching or reaching for the ground
- Supine
- Prone (or simulated prone during PHD visit)
- Lying on left side (if possible)
- Lying on right side

8.8.4.3. Maneuvers

Request the subject to perform each of the following maneuvers to determine the effect(s) on sensing (if any):

- Heavy coughing (approximately 10 times), while sitting or standing
- Valsalva maneuver (2 times)

For approximately 1 minute:

- Sawing action (left-hand, roughly 3 times per second) while sitting or standing
- Deep breathing while sitting or standing
- Simulate brisk walking, e.g., marching in place
- Pressing hands together and harder to create muscle noise
- Star jumps (i.e., jumping jacks)
- 4-6 Weeks and 3 Month visits only: manipulate device (e.g., gently wiggling the device repeatedly) to look for changes in sensing due to mechanical movement

Subjects will be allowed to have recovery time after each maneuver as needed.

8.8.4.4. Brisk Walk and Treadmill (2 Weeks, 4-6 Weeks and 3 Months)

Subjects will perform a brisk walk or treadmill test, and are allowed recovery time after as needed.

2 Week and 4-6 Weeks: Brisk walk - Have the subject walk as briskly for 3-5 minutes as the patient finds tolerable to increase heart rate for approximately three minutes in an open hallway

3-Months: Treadmill – Have the subject run at speed on a treadmill for 3 to 6 minutes, as tolerated

Interrogate the device by selecting "Interrogate ALL" on the 2090 programmer at the end of the visit. Save the data via a Save-to-media file.

8.8.5. Imaging (4-6 Weeks, 3 Months)

8.8.5.1. Radiographs and CT Scans

Cardiac-gated CT scan (respiratory cycle for CT: tidal inhalation only) is to be performed during the 3 Month follow-up visit. Contrast is not required. It is recommended that prospective gating (best diastole phase of the cardiac cycle) be used to reduce radiation dose to the subject.

- The CT image should include the thorax from the collarbone to the inferior aspect of the ribcage and include the entire width of the torso, i.e., side-to-side, and the implanted ICD device.
- The slice thickness should be ≤ 1.2 mm (≤ 0.8 mm preferred).
- The in-plane resolution should be ≤ 0.7 mm (≤ 0.5 mm preferred).

All radiographs will be collected in the anterior-posterior (AP) and lateral (LAT) configurations as specified in Table 8.

Additional radiographs may be collected at the discretion of the physician in additional postures (i.e. prone, left decubitus, right decubitus) at any post-implant time point if electrical testing at follow-up reveals deterioration in sensing or pacing performance. Additional imaging at different postures is recommended if:

- Pacing output changes by 3V in magnitude in either direction (pacing testing performed in 1V increments); or
- R-wave amplitude falls below 1mV, or falls by 50% of previous measurement.

Table 8: Image collection during follow-up period.

Visit	Image Collection
4-6 Weeks	• Supine AP → Tidal Inhalation and Tidal Exhalation • Supine LAT → Tidal Inhalation and Tidal Exhalation • Standing AP → Tidal Inhalation only • Standing LAT → Tidal Inhalation only
3 Months	Cardiac-gated CT (no contrast) (Respiratory cycle for CT: tidal inhalation only)
	• Supine AP → Tidal Inhalation and Tidal Exhalation • Supine LAT → Tidal Inhalation and Tidal Exhalation • Standing AP → Tidal Inhalation only • Standing LAT → Tidal Inhalation only

All images should be transferred in DICOM format.

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.

8.8.5.2. Photographs (2 Weeks, 4-6 Weeks, 3 Months)

If allowed per local regulations and accepted by the subject in the Informed Consent, photographs of the sternal incision site and the device pocket using a supplied camera will be requested for training, education, and/or research purposes. These photographs will not display any identifiable features of the subject.

Additionally, photographs of the device pocket and sternal incision are recommended at any subsequent scheduled visits in which infection related to the EV ICD System is suspected or previously diagnosed. Report any adverse events per Section 10.

8.8.6.24 Hour Holter Monitoring (4-6 Weeks, 3 Months)

The DR220 Holter monitor will be set up according to Figure 8.3 for 24-hour Holter monitoring at the 4-6 Week and 3 Month Visits.

During the 24-hour Holter Monitoring assessment, the subject may leave the study site (e.g. return home) and should go about their activities of daily living (ADL). Each subject will receive a subject activity log and be instructed to document the time of day and a variety of pre-populated ADLs including, but not limited to, ‘exercise’ or ‘sleep’. The subject will be instructed to return the activity log, Holter monitor leads, recorder and memory card at the end of the 24-hour assessment period. The Holter data should be transmitted to Medtronic.

8.8.7. Medications (2 Weeks, 4-6 Weeks, 3 Months)

Changes to oral or intravenous medications will be recorded.

8.9. Long-term Follow-up (6 monthly)

Subjects will be followed up at 6 Months post-implant and 6 monthly until the study is closed. The following data will be collected during these visits:

- Electrical Testing (Sensing, Impedance, and Pacing tests (see section 8.8.3)
- Save-to-media file
- Medications (see section 8.8.7)
- Photographs of device pocket and sternal incision (see section 8.8.5.2) are recommended if an infection related to the EV ICD System is suspected or previously diagnosed
- Adverse Event assessment

8.10. Unscheduled Visits

An unscheduled follow-up visit is defined as any unplanned visit by the subject to the investigative study site due to the EV ICD system between protocol required visits. Routine visits such as planned visits are not collected.

Emergency department visits are not required to be reported as Unscheduled Follow-up visits as they are not considered investigative study sites.

If an unscheduled visit occurs:

- Document any adverse events and device deficiencies on their associated eCRFs, as applicable.
- Where possible, device interrogation data should be collected via a save-to-media file for subjects at the beginning and end of the visit (initial and final interrogation). Device interrogation data should be sent to Medtronic, with a copy being maintained at the site in the subject's file.
- If electrical testing is conducted, it is recommended that programmer strips are obtained. It is preferred that full programmer strips are obtained real-time while the test is running. A copy of the entire programmer strips will be stored at the site and one full copy will be sent to Medtronic.
- Photographs as recommended (see section 8.8.5.2)

8.11. System Modification

A System Modification will be reported in the event the EV ICD system requires an invasive modification after the initial implant (e.g., explant, replacement, repositioning).

If the system modification involves replacing or repositioning the lead or EV ICD, then all testing and data collection required at Implant and the Pre-Hospital Discharge visit should be repeated, with the following caveat:

- If system modification occurs after initial pre-hospital discharge visit -
  - ECG Holter monitoring is not required
  - Defibrillation testing will be completed per physician discretion. It is recommended that the device is programmed with a 10J safety margin

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 from the study provided any procedure, system or accessory related adverse events are resolved.

8.12. 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 relevant and pertinent to the involvement of personnel conducting study activities and investigator responsibilities, 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 the eCRF shall be performed by Medtronic personnel or their representatives at sites
- A Medtronic Procedure Expert will support a study investigator at the Implant Visit by proactively providing advice and feedback during the implant procedure, but no tunneling shall be performed by Medtronic personnel or their representatives.

Sponsor representatives may conduct monitoring and auditing activities for this study.

8.13. 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. In addition, efficacy of antitachycardia pacing (ATP) and asystole pacing will be characterized as part of the ancillary objectives.

8.14. Assessment of Safety

All Adverse Events that are procedure related, system related, accessory related, Holter related, cardiovascular related or serious will be collected throughout the study duration, starting at the time of signing the consent form. Additionally, any device deficiencies related to the EV ICD System will be collected. In addition, an ancillary objective will summarize reported Adverse Events. Further information on the collection of Adverse Events is discussed in Section10.

8.15. Recording Data

This study will be conducted using the Oracle Clinical Remote Data Capture system (OC RDC). The OC RDC system, which allows the study centers 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 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. The following eCRFs may be considered as source:

- Protocol Deviation
- Device Tracking

Save-to-media files will be collected and stored on USB flash drives at the site. A copy will be submitted to Medtronic via secure and compliant electronic file transfer services (e.g., Clinical Transfer, Kiteworks) and/or mailed via USB.

Programmer printouts will be collected in hard or electronic copy and stored at the site. A copy will be submitted to Medtronic via secure and compliant electronic file transfer services (e.g., Clinical Transfer, Kiteworks) and/or mailed via USB.

Fluoro /radiograph/ CT images are to be stored on a CD/DVD or USB flash drive at the site. A copy will be submitted to Medtronic via secure and compliant electronic file transfer services (e.g., Clinical Transfer, Kiteworks) and/or mailed via USB.

Photographs are to be copied from the camera SD card and saved onto a USB flash drive at the site. A copy will be submitted to Medtronic via secure and compliant electronic file transfer services (e.g., Clinical Transfer, Kiteworks) and/or mailed via USB.

ECG recordings from DR220 are to be copied from the SD card and saved onto the USB flash drive at the site. A copy will be submitted to Medtronic via secure and compliant electronic file transfer services (e.g., Clinical Transfer, Kiteworks) and/or mailed via USB.

8.16.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 end point analysis). However, prior approval from Medtronic is required for such situations.

All study deviations must be reported on the Case Report Form 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 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 center-specific reports to investigators summarizing information on deviations that occurred at the 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, echocardiograms)
- Inclusion/exclusion criteria not met
- Missing required save-to-media files
- Missing Holter data

8.17. Subject Withdrawal or Discontinuation

Subjects are urged to remain in the study as long as possible but 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/exclusion criteria
- 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 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.

Subjects who had undergone an implant attempt and 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 once all system and procedure-related AEs are resolved.

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

- Reason for exit (this should be documented in the Study Exit eCRF and in the subject's medical record)

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 or 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 (Medical Device Risk Management).

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 patient 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 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 investigator's decision to assess whether or not to continue the study at the respective site, should safety-related concerns arise.

Risk control strategies for the EV ICD Pilot study risks were developed by a cross-functional team and in accordance with the Risk Management process. Potential risks associated with this study are minimized by selecting qualified investigators and training site personnel on the Clinical Investigation Plan and hands-on training program.

Medtronic is further minimizing the possibility of risks by performing pre-clinical testing prior to the EV ICD Pilot study, providing guidelines for subject selection and evaluation, and providing adequate training, instructions and labeling.

A summary of potential risks and risk reduction strategies associated with the EV ICD Pilot study is presented in the table below.

Table 9: 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 protocol ii. The protocol requires that the EV ICD implant procedure is to be performed by an investigator who has received hands-on training on all aspects of the implant procedure iii. Medtronic intends to use a proctorship strategy during

Risks	Mitigation Strategies
	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 patient	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 neurostimulator or any other chronically implanted device which uses 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 shock therapy	i. Exclusion of subjects with current implantation of a 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 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 patient	i. Exclusion of subjects with current implantation of a 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. Pacing therapy configuration instructions provided in the protocol which help avoid oversensing and resulting failure to deliver pacing therapy when needed (e.g., post-shock)

Risks	Mitigation Strategies
	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 which help avoid ineffective shock therapy and resulting arrhythmia acceleration ii. EV ICD system design verification and end-to-end system design validation ensuring defibrillation therapy as specified
Extracardiac stimulation	i. Clinician training and protocol 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 protocol 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 patient tissues	i. EV ICD system reliability analysis ensuring freedom from failures as specified
Patient exposure to toxic materials	i. EV ICD system design utilizes materials that have sufficient biological compatibility and performance as demonstrated by a biocompatibility assessment
Patient 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 bioinstability	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	i. EV ICD system design verification and end-to-end system design validation ensuring data corruption monitoring as

Risks	Mitigation Strategies
is presented to user	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 patient against unnecessary radiation exposure during diagnostic imaging.
During travel, patients 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.

Possible additional risks for participating in this study include the following, and 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 electrodes used with the Holter recorder might cause mild skin discomfort or irritation or some skin discomfort following electrode removal.
- Patients who are pregnant or of child bearing potential and not on a reliable form of birth regulation method or abstinence are excluded from study enrollment. 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.

9.2. Potential Adverse Events from Risk Assessment

The potential adverse events identified from the risk assessment are outlined in Table 10.

Table 10: EV ICD System related and study related adverse events.

EVICD System-Related Adverse Events	EVICD Pilot Study-Related Adverse Events
Return of cardiac symptoms	Tachyarrhythmia
Cardiac arrest	Cardiac arrest
Syncope	Syncope
Dizziness	Dizziness
Lethargy	Palpitations
Palpitations	Dyspnea
Dyspnea	Hiccups
Tachyarrhythmia	Skeletal muscle twitching

EVICD System-Related Adverse Events	EVICD Pilot Study-Related Adverse Events
Bradyarrhythmia	Pain
Pain	Discomfort
Discomfort	Mental anguish
Mental anguish	Infection
Infection	Allergic reaction
Acute tissue trauma	Radiation sickness
Seroma	Acute tissue trauma
Pneumothorax	Chronic tissue trauma
Hemothorax	Organ damage
Cardiac perforation	
Pericardial effusion	
Cardiac tamponade	
Hematoma	
Hemorrhage	
Organ damage (liver, mammary arteries, diaphragmatic arteries)	
Pericarditis	
Hospitalization	
Toxic reaction to implant	
Allergic reaction to implant	
Allergic reaction of local tissues	
Wound dehiscence	
Erosion	
Discomfort associated with product migration	
Discomfort associated with fibrotic growth	
Electrical/thermal tissue damage	
Hiccups	
Skeletal muscle twitching	
Death	
Lead abrasion	
Lead fracture	
Lead insulation failure	
Lead migration	
Device migration	
Twiddler's syndrome	

EVICD System-Related Adverse Events	EVICD Pilot Study-Related Adverse Events
Extracardiac stimulation	
Inappropriate shocks	
Failure to provide necessary therapy	
Patients 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)	

9.3. Potential Benefits

The potential benefits of the EV ICD System are consistent with the lifesaving ICD therapy provided by currently approved single chamber ICDs. ICD therapy is the treatment of choice for patients who are at risk for sudden cardiac death due to life-threatening ventricular arrhythmias. Furthermore, the EV ICD System 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.

In addition to the standard benefits of ICD therapy, there may be additional benefits specific to the EV ICD system due to its novel design. As compared to a transvenous system, the EV ICD system is expected to have lower risk of procedural 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. Furthermore, the EV ICD System introduces additional potential benefits as compared to the subcutaneous ICD systems currently on the market.

These potential benefits include:

- 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
- Brady support pacing for asystole
- 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.

It is possible the EV ICD System may offer no benefit.

9.4. Risk-Benefit Rationale

The majority of the risks associated with the EV ICD system are similar to the risks associated with existing ICD systems on the market. These risks include: complications during implant/explant, failure to provide high voltage therapy (i.e., shock) or low voltage therapy (i.e., pacing), unnecessary therapy delivery (i.e., inappropriate shocks), extracardiac stimulation, biological reaction to implanted product, missing or misleading diagnostic information, risks associated with defibrillation testing, and catastrophic failure of the implanted product that could necessitate procedural system revision. The unique risks potentially introduced by the EV ICD system include: unique harms associated with procedural complications (e.g., liver laceration), 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. Yet, this collection of potential risks are sufficiently justified by the foreseeable benefits, which include: increased patient access to life-saving ICD therapies, 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), additional bradyarrhythmia therapy capabilities as compared to subcutaneous systems (i.e., brady support pacing for asystole), and improved patient comfort and acceptance due to smaller size of device as compared to subcutaneous systems. The EV ICD System hazard analysis establishes a systematic evaluation of all foreseeable risks associated with use of the EV ICD System. Furthermore, the hazard analysis provides the means to ensure that risk controls are applied to all identified risks such that the risks are reduced as far as possible. Finally, the hazard analysis captures an estimate of the remaining residual risks after the risk controls are incorporated. The results of the hazard analysis confirm that the patient risks are reduced as far as possible, and the residual risks are deemed acceptable per the risk benefit justification described above.

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

The following AEs will be collected throughout the study duration, starting at the time the informed consent form is signed:

- All procedure related AEs
- All system related AEs
- All accessory related AEs
- All Holter related AEs
- All cardiovascular related AEs
- All Serious Adverse Events (SAEs), regardless of relatedness

Reporting of these events to Medtronic will occur on an Adverse Event (AE) 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. In all geographies, Unavoidable Adverse Events, listed in Table 11 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 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. See the Device Deficiency eCRF for the information to be reported 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 Adverse Event 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 .

10.2. Processing Updates and Resolution

For any changes in status of a previously reported adverse event (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 adverse events must be followed until the adverse event 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 adverse events 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 adverse event 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 the DR220 Holter.

Table 11: 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 a 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) 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.
Holter Related	Holter Related: An adverse event that results from the presence or performance (intended or otherwise) of the Holter
Cardiovascular Related	An adverse event relating to the heart and the blood vessels or the circulation (e.g. atrial fibrillation, myocardial infarction, stroke, peripheral vascular disease)
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 were 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 1: 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 Device Effect (SADE)	An ADE that has resulted in any of the consequences characteristic of a SAE. (ISO 14155:2011 section 3.36)
Unanticipated Serious Adverse Device Effect (USADE)	A 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, 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.

<table>
<tr><td>Major complication</td><td>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
Prolonged 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.</td></tr>
<tr><td>Minor complication</td><td>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.</td></tr>
<tr><td>Observation</td><td>Any adverse event that is not a complication.

Note: Only system or procedure related AEs will be classified as complication (major, minor) or observation.</td></tr>
<tr><td colspan="2">Timing</td></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><td colspan="2">Other</td></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 (<100°F or 37.8°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>
</table>

Hospitalization	A therapeutic inpatient hospitalization (excludes observation unit, emergency room and outpatient visits) lasting greater than or equal to 24 hours.

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.

Upon receipt of adverse events 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 adverse event based on the information provided by the investigator.

Regulatory reporting of AEs and device deficiencies that could have led to an SADE will be completed according to local regulatory requirements. Refer to for a list of 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 (FAL), please see Appendix E: Foreseeable Adverse Event List. The FAL 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 12: 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, Implant tool, Software, Programmer, Cardiovascular
	Sponsor	Procedure, Device, Lead, Implant tool, Software, Programmer
Severity	Investigator	SAE, Device Deficiency with SADE potential
	Sponsor	SAE, 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 the TGA.

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.

Refer to for a list of 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, 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 13: Reporting requirements

Serious Adverse Events (SAEs) / Serious Adverse Device Effects (SADEs)	
Investigator submit to:	
Medtronic	Submit to the sponsor per local reporting requirements.
Ethics Committee	Submit per local reporting requirements.
Institution	Submit to Institution per local reporting requirements.
Regulatory authorities	Submit per local reporting requirements.
Sponsor submit to:	
Investigators	Submit to investigator per local reporting requirements.
Regulatory authorities	Submit to regulatory authority per local reporting requirements.
Ethics Committee	Submit to EC per local reporting requirements.
Unanticipated Serious Adverse Device Effects (USADEs)	
Investigator submit to:	
Medtronic	Submit to the sponsor per local reporting requirements.
Regulatory Authority	Submit to regulatory authority per local reporting requirements.
Ethics Committee	Submit to EC per local reporting requirements.
Institution	Submit to Institution per local reporting requirements.
Sponsor submit to:	
Investigator	Submit to the investigator per local reporting requirements.
Regulatory authorities	Submit to regulatory authority per local reporting requirements.
Ethics Committee	Submit to EC per local reporting requirements.
Significant Safety Issue (SSI)	
Investigator submit to:	

Medtronic	Submit to the sponsor per local reporting requirements.
Regulatory Authority	Submit to regulatory authority per local reporting requirements.
Ethics Committee	Submit to EC per local reporting requirements.
Institution	Submit to Institution per local reporting requirements.
Sponsor submit to:	
Investigator	Submit to the investigator per local reporting requirements.
Regulatory authorities	Submit to regulatory authority per local reporting requirements.
Ethics Committee	Submit to EC per local reporting requirements.
Institution	Submit to Institution per local reporting requirements.
Urgent Safety Measure (USM)	
Investigator submit to:	
Medtronic	Submit to the sponsor per local reporting requirements.
Regulatory Authority	Submit to regulatory authority per local reporting requirements.
Ethics Committee	Submit to EC per local reporting requirements.
Institution	Submit to Institution per local reporting requirements.
Sponsor submit to:	
Investigator	Submit to the investigator per local reporting requirements.
Regulatory authorities	Submit to regulatory authority per local reporting requirements.
Ethics Committee	Submit to EC per local reporting requirements.
All other reportable Adverse Events (System, Procedure and Cardiovascular-Related)	
Investigator submit to:	
Medtronic	Submit to the sponsor per local reporting requirements.

Regulatory Authorities	Submit to regulatory authority per local reporting requirements.
Ethics Committee	Submit to EC per local reporting requirements.
Sponsor submit to:	
Regulatory authorities	Submit to regulatory authority per local reporting requirements.
Ethics Committee	Submit to EC per local reporting requirements.
Device Deficiencies with SADE potential	
Investigator submit to:	
Medtronic	Submit to the sponsor per local reporting requirements.
Regulatory authorities	Submit to regulatory authority per local reporting requirements.
Ethics Committee	Submit to EC per local reporting requirements.
Sponsor submit to:	
Regulatory authorities	Submit to regulatory authority per local reporting requirements.
Ethics Committee	Submit to EC per local reporting requirements.
All other Device Deficiencies	
Investigator submit to:	
Medtronic	Submit to the sponsor per local reporting requirements.
Regulatory Authorities	Submit to regulatory authority per local reporting requirements.
Ethics Committee	Submit to EC per local reporting requirements.
New information that may adversely affect safety of the subjects or the conduct of the study	
Investigator submit to:	
Medtronic	Submit to the sponsor per local reporting requirements.
Ethics Committee	Submit to EC per local reporting requirements.

Sponsor submit to:	
Investigator	Submit to investigators per local reporting requirements.
Regulatory authorities	Submit to regulatory authority per local reporting requirements.
Ethics Committee	Submit to EC per local reporting requirements.

10.6. Subject Death

All subject deaths must be reported by the investigator to Medtronic on an AE form (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 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 the Medtronic clinical study team, if available. If an autopsy is conducted, the autopsy report should also be sent to the Medtronic clinical study team if available and allowed by state/local law. When the death occurs at a remote site, it is the investigative center'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 review all deaths and provide a final adjudication of the death classification.

10.8. Product Complaint Reporting

The reporting of product complaints is not part of the EV ICD Pilot Study and should be done in addition to the AE 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 a 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 that are not participating investigators for 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 classification and supportive documentation (when available). The CEC is responsible

for reviewing the Investigator's assessment 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 CRF 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. 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. 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. At the time of the EV ICD Pilot Clinical Investigation Plan Version 1 completion, committee members had not been identified. The ERC Member list will be under a separate cover when available upon request.

12. Statistical Design and Methods

12.1. General Considerations

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

All analyses will be performed on an "As Treated" basis.

The cohort will include all enrolled subjects who undergo the study procedures, 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 (SAP) 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 for. Any change to the data analysis methods described in the protocol will require an amendment only if it changes a principal feature of the protocol. Any other change to the data analysis methods described in the protocol, and the justification for making the change, will be described in the clinical study report.

12.2. Sample Size

At least 20 and up to 35 subjects will be implanted with the investigational EV ICD system. This is to gather early data with regard to patient safety and device efficacy. The sample size is not pre-specified to satisfy hypothesis testing statistical requirements, but rather to allow for multiple investigational sites enrolling patients and implanting the EV ICD system.

12.3. Primary Objective #1

Characterize the freedom from major complications related to the EV ICD system and/or procedure at 3 months post-implant.

12.3.1. Hypothesis

This trial is for the purposes of gathering preliminary data on the investigational product, and so there are no hypotheses for this objective.

12.3.2. Performance Requirements

Performance requirements are not pre-specified for this objective. 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 3-months (90-days) post-implant.

For an adverse event to meet the endpoint, the event must have occurred within 90 days (inclusive) of the EV ICD system implant 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

- Prolonged Hospitalization by at least 48 hours
- System revision (reposition, replacement, explant)

12.3.3. Rationale for Performance Criteria

This is an observational study, and this objective is for the purpose of gathering data pertaining to device safety over the first 3 months post-implant. There are no pre-specified performance criteria.

12.3.4. Analysis Methods

Results will be summarized in aggregate using descriptive statistics. The 90-day freedom from major complication rate will be generated using the Kaplan-Meier method, and the total number of major complications experienced by subjects for whom an implant is attempted will be summarized.

12.3.5. Determination of Patients/Data for Analysis

All subjects for whom an implant of the investigational product is attempted will be included in the analysis.

12.4. Primary Objective #2

Characterize the EV ICD defibrillation testing success rate at implant.

12.4.1. Hypothesis

This trial is for the purposes of gathering preliminary data on the investigational product, and so there are no hypotheses for this objective.

12.4.2. Performance Requirements

Performance requirements are not pre-specified for this objective. 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.

Notes:

- In one of the two successive 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.

12.4.3. Rationale for Performance Criteria

This is an observational study, and this objective is for the purpose of gathering data pertaining to defibrillation efficacy at implant. There are no pre-specified performance criteria.

12.4.4. 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.

12.4.5. Determination of Patients/Data for Analysis

All subjects for whom defibrillation testing is attempted with the investigational device will be included in the analysis.

12.5. Ancillary Objective #1

Characterize appropriate and inappropriate shocks.

12.5.1. Hypothesis

This trial is for the purposes of gathering preliminary data on the investigational product, and so there are no hypotheses for this objective.

12.5.2. 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.

12.5.3. Rationale for Performance Criteria

This is an observational study, and this objective is intended to 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.

12.5.4. 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.

12.5.5. Determination of Patients/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 3 months post-implant will be included.

12.6. Ancillary Objective #2

Characterize electrical performance (pacing capture thresholds, pacing impedance, sensing amplitudes) in a variety of postures and respiration cycles over time.

12.6.1. Hypothesis

This trial is for the purposes of gathering preliminary data on the investigational product, and so there are no hypotheses for this objective.

12.6.2. 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, 4-6 weeks, and 3 months post-implant.

12.6.3. Rationale for Performance Criteria

This is an observational study, and this objective is for the purpose of characterizing device performance with regard to achieving pacing capture and determining sensing performance over time and at different postures. There are no pre-specified performance criteria.

12.6.4. Analysis Methods

Results will be summarized in aggregate using descriptive statistics. Pacing testing will be done at the postures provided in section 8.8.4.1. For each posture, and each follow-up visit, the proportion of subjects undergoing pacing testing will be reported, as well as the proportion for whom capture is obtained.

12.6.5. Determination of Patients/Data for Analysis

All subjects successfully implanted with an EV ICD having pacing tests for at least one posture will be included in the analysis.

12.7. Ancillary Objective #3

Characterize extracardiac pacing sensation.

12.7.1. Hypothesis

This trial is for the purposes of gathering preliminary data on the investigational product, and so there are no hypotheses for this objective.

12.7.2. Performance Requirements

Performance requirements are not pre-specified for this objective. The endpoint with regard to extracardiac pacing will be defined as:

- the presence of extracardiac muscle stimulation during pacing at implant as determined by the clinician
- the degree of pacing sensation as determined by the subject at follow-up testing

12.7.3. Rationale for Performance Criteria

This is an observational study, and this objective is characterizing extracardiac muscle stimulation and patient experience with pacing. There are no pre-specified performance criteria.

12.7.4. Analysis Methods

Results will be summarized in aggregate using descriptive statistics. Clinicians will be asked to assess presence of extracardiac muscle stimulation at implant, and subjects will be asked during follow-ups the degree of experienced extracardiac muscle stimulation for each pacing vector collected. Descriptive statistics will be used to summarize distribution among the subjects who underwent pacing. This objective will be analyzed using data from the implant, pre-hospital discharge, 2-week visit, 4-6 week visit, and 3 month visit.

12.7.5. Determination of Patients/Data for Analysis

All subjects successfully implanted with an EV ICD undergoing pacing testing or reporting symptoms attributed to being paced will be included in the analysis.

12.8. Ancillary Objective #4

Characterize asystole pacing.

12.8.1. Hypothesis

This trial is for the purposes of gathering preliminary data on the investigational product, and so there are no hypotheses for this objective.

12.8.2. Performance Requirements

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

12.8.3. Rationale for Performance Criteria

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

12.8.4. Analysis Methods

Subjects receiving asystole pacing will be listed individually, with the amount of such pacing that each subject received.

12.8.5. Determination of Patients/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 3 months post-implant will be included.

12.9. Ancillary Objective #5

Characterize lead position over time.

12.9.1. Hypothesis

This trial is for the purposes of gathering preliminary data on the investigational product, and so there are no hypotheses for this objective.

12.9.2. Performance Requirements

Performance requirements are not pre-specified for this objective. The endpoint is whether a subject's lead changed position over time (from implant to 3 months), and degree that it changed.

12.9.3. Rationale for Performance Criteria

This is an observational study, and this objective is for the purpose of characterizing degree of change in the EV ICD lead position. There are no pre-specified performance criteria.

12.9.4. Analysis Methods

Imaging (radiographs) will be performed at pre-hospital discharge, as well as visits at 4-6 weeks and 3 months. Lead position will be assessed and degree of movement will be summarized for each subject.

12.9.5. Determination of Patients/Data for Analysis

All subjects successfully implanted with an EV ICD will be eligible for the analysis.

12.10. Ancillary Objective #6

Summarize ATP performance with spontaneous arrhythmias.

12.10.1. Hypothesis

This trial is for the purposes of gathering preliminary data on the investigational product, and so there are no hypotheses for this objective.

12.10.2. Performance Requirements

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

12.10.3. Rationale for Performance Criteria

This is an observational study, and this objective is for the purpose of characterizing device ATP performance with regard to terminating monomorphic and polymorphic ventricular arrhythmias. 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, whether it successfully terminated as a result, and by the specific rhythm of the episode (monomorphic vs. polymorphic VT). Both the number of episodes and the number of subjects experiencing such episodes will be reported.

12.10.5. Determination of Patients/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 3 months post-implant will be included in the analysis.

12.11. Ancillary Objective #7

Summarize adverse events.

12.11.1. Hypothesis

This trial is for the purposes of gathering preliminary data on the investigational product, and so there are no hypotheses for this objective.

12.11.2. Performance Requirements

Performance requirements are not pre-specified for this objective. The endpoint is an adverse event (see Table 11 for definition of adverse event) experienced by a subject post-enrollment and prior to exit. All 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 is an observational study, and this objective is for the purpose of gathering data pertaining to device safety over at least the first three 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.

12.11.5. Determination of Patients/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 3 months post-implant will be included.

13. Ethics

13.1. Statement(s) of Compliance

The study will be conducted according to the Declaration of Helsinki, Clinical Investigation Plan, 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 Pilot 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 Pilot 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 Pilot Study is ISO 14155:2011 compliant for all participating geographies with the exception that only those AEs that are system related, procedure

related, cardiovascular related, or serious, will be collected. Therefore, only a subset of AEs will be collected in this study, including any that could be potentially relevant.

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

- Principles of Declaration of Helsinki
- 21 CFR Part 11 (Electronic Records, Electronic Signatures)
- The Clinical Trial Agreement
- The procedures described within this CIP
- Local Ethics Committee Requirements

In addition to the regulatory 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, the study will be conducted in compliance with:

- ISO14155:2011
- Declaration of Helsinki and all of its subsequent amendments, including the latest version 2013
- CPMP/ICH/135/95

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 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 Committee

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

14. Study Administration

14.1. Monitoring

Procedures in the CIP require source documentation. Source documentation will be maintained at the site. Source documents, which may include worksheets, patient medical records, programmer printouts, and interrogation files, must be created and maintained by the investigational site team.

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 center in order to ensure that the study is conducted in accordance with the CIP, the Clinical Trial Agreement, and applicable regulatory and local requirements. Medtronic, or delegates, must therefore be allowed access to the subjects' case histories (clinic and hospital records, and other source data/ documentation) upon request as per the Subject Informed Consent, Research Authorization (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 qualification visits, 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 subject 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 center.

14.2. Data Management

Data will be collected using an electronic data management system for clinical studies. Electronic CRF data will be stored in a secure, password-protected database which will be backed up nightly. The OC RDC system, which is 21CFR§11 Part E compliant, controls user access, and ensures data integrity. The OC RDC system is validated and maintains an audit trail of entries, changes or corrections in eCRFs.

User access will be granted to each individual based on his or her delegation of authority and completion of required training. Data will be reviewed using programmed and manual data checks. Data queries will be made available to centers 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 indefinitely by Medtronic.

The data reported on the eCRFs shall be derived from source documents and be consistent with these source documents, and any discrepancies shall be explained in writing.

Device data from transmissions will be uploaded to secure servers. Save-to-media data collected at office visits will be sent to Medtronic. Upon receipt, device data will be maintained with databases 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 center 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 by providing direct access to source data/documents.

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.

14.6.CIP Amendments

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

- 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 (i.e., 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 for a period of 10 years (New Zealand) or 15 years (Australia) after product approval or the date on which the investigation is terminated.

- All correspondence between the Ethics Committee, sponsor, monitor, FDA or 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 protocol
- Subject identification log (if applicable)
- 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.
- Investigational device accountability logs.
- Equipment maintenance records, if applicable.
- Any other records that FDA or local regulatory agencies require to be maintained.
- Final Study Report including the statistical analysis.

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, adverse events and adverse device effects (reported per the country-specific collection requirements), device deficiencies, deaths, and any deviations from the Clinical Investigation Plan. 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 . The investigator shall prepare and submit in a complete, accurate and timely manner the reports listed in this section.

Table 14: Investigator reports applicable per Medtronic requirements

Report	Submit to	Description/Constraints
Withdrawal of Ethics Committee approval	Sponsor and Relevant Authorities	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 center 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.
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.

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 Investigator Trial Agreements, financial disclosure and current signed and dated (Europe 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

- 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
- Case Report Forms, including AE and DD forms and CRF 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, regulatory agency or FDA, provide accurate, complete and current information about any aspect of the investigation. Safety data Medtronic reporting requirements are listed in section .

Table 15: 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, 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 investigation. Site specific study deviations will be submitted to investigators periodically.

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 indefinitely.

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 center. 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 center.

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/Center Suspension or Early Termination

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

- Failure to obtain initial Ethics Committee approval or annual renewal of the study
- Persistent non-compliance to the clinical study (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 center
- 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/IRB/Head of Medical Institution approval lapse, the investigator will promptly inform the EC/IRB/Head of Medical Institution. 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/IRB/Head of Medical Institution, 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/IRB/Head of Medical Institution 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

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16. Appendices

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

Draft Case Report Forms for the EV ICD Pilot 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 Pilot 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) execute 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 center 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 all objectives and analysis, will be distributed to all investigators, Ethic Committees and Competent 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 (IFUs) for the components of the EV ICD System and accessories, and equipment are provided with each component under separate cover.

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 16 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 Pilot 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 16 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 16: 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 16: 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 16: 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 16: 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 16: 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, and ASD2 studies that utilized similar research systems and protocol steps as those in the EV ICD Pilot 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 center where asystole was detected 36 hours post-procedure. Despite cardiopulmonary resuscitation for 30 minutes, the subject expired.

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 17: 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
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 18: 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, 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

The complete list of participating investigators and institutions will be provided under separate cover upon request.

Appendix G: Ethics Committee and Competent Authority List

A complete list of participating Ethics Committees and their Chairperson(s) will be distributed under separate cover when available, upon request.

Competent Authorities include the following:

In Australia:

Therapeutic Goods Administration

PO Box 100

Woden, ACT 2606

Australia

In New Zealand:

Medsafe
New Zealand Medicines and Medical Devices Safety Authority
PO Box 5013
Wellington 6140

New Zealand

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: Investigator Statement

Study product Name	Extravascular ICD system
Sponsor	Medtronic Inc. 8200 Coral Sea Street NE Mounds View, MN USA 55112
Local Sponsor	Medtronic Australasia Pty Ltd 2 Alma Road Macquarie Park NSW, 2113 Australia
Local Sponsor	Medtronic New Zealand Limited Level 3, Building 5 666 Great South Road Penrose Auckland 1051 New Zealand
Clinical Investigation Plan Identifier	MDT17034
Version Number/Date	1.0, 02-MAR-2018
I have read the protocol, including all appendices, 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 protocol 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	Not Applicable, New Document	Samuel Liang, Sr Clinical Research Specialist