Medtronic **Statistical Analysis Plan**	
Clinical Investigation Plan Title	ExtraVascular Implantable Cardioverter Defibrillator (EV ICD) Pilot Study
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1. Version History

Version	Summary of Changes	Author(s)/Title
1.0	• Not Applicable, New Document	Lou Sherfesee, Sr. Principal Statistician
2.0	• Make document ISO 14155:2020 compliant. Updated from the previous ISO 14155:2011 compliant version 1.0	Rahul Kanwar, Sr. Statistician
2.1	• There were several comments in version 2.0 that were left in the document and had not yet been resolved. Those comments were addressed and removed. The changes made included ○ Removed redundant and unnecessary methodological comments in Section 7.9 ○ Removed extra spaces around hyphens throughout document ○ Added the SAP version date and am now using the 'C' template for the document	Jeff Lande, Sr. Principal Statistician

2. List of Abbreviations and Definitions of Terms

Abbreviation	Definition
ATP	Antitachycardia pacing
EV	Extravascular
ICD	Implantable cardioverter defibrillator

3. Introduction

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. 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.

Medtronic has developed an extravascular ICD system which uses a substernal lead vs. a transvenous or a subcutaneous lead. The Extravascular (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.

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.

This Statistical Analysis Plan has been designed to document, the EV ICD Pilot Study design and the planned analyses to be included in interim and final reports.

4. Study Objectives

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 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 Antitachycardia Pacing (ATP) performance with spontaneous arrhythmias
- Summarize adverse events

5. Investigation Plan

The EV ICD Pilot Study is a prospective, multi-center, single-arm, nonrandomized study. Up to 35 subjects will be enrolled at up to 10 sites in Australia and New Zealand. Subjects with a class I or IIa indication for single-chamber ICD therapy will be recruited and implanted with the Medtronic EV ICD system, which features defibrillation capability, as well as ATP and bradycardic pacing capability. Patients with a bradycardia pacing or cardiac resynchronization therapy indication are excluded. Subjects will undergo defibrillation testing at implant, as well as pacing threshold 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. For further details regarding the investigational plan, see the EV ICD Pilot Clinical Investigation Plan.

6. Determination of 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.

7. Statistical Methods

7.1 Study Subjects

7.1.1 Disposition of Subjects

This is a single-arm study. Subjects who are consented will undergo implant of the EV ICD system, with required defibrillation, sensing, and pacing testing. At enrollment, subjects consent to have the EV ICD system implanted. Subjects will then return for 2 week, 4-6 weeks, 3 and 6 month visits, as well as every 6 months thereafter. A STROBE diagram will show each of these stages of follow-up through 30 months or beyond if needed, with categories for missed visit, death and exit. Screening log is not used in this study given the poor compliance to the use of it in the past.

7.1.2 Clinical Investigation Plan (CIP) Deviations

Study deviations will result in corresponding Study Deviation eCRFs being completed. These deviations will be summarized with descriptive statistics including, for each type of deviation, how many occurrences there were in the study, and the number of subjects experiencing each type of deviation. Inclusion/exclusion violations will not result in subjects being excluded from analysis of objectives. Of particular importance will be required testing not completed at implant or follow-up.

7.1.3 Analysis Sets

All enrolled subjects who undergo an EV ICD implant attempt will be included in the evaluation of the safety objective, and all subjects who undergo implant defibrillation testing will be included in the evaluation of the primary efficacy objective. Descriptive statistics will be used to summarize results.

7.2 General Methodology

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 prespecified 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.

7.3 Center Pooling

Due to the feasibility nature of this study and reduced sample size, statistical comparisons of sites’ performance will not be performed.

7.4 Handling of Missing, Unused, and Spurious Data and Dropouts

All available data will be included in the data listings and tabulations. Imputation of values for missing data for primary and secondary efficacy analyses will not be performed. With regard to the safety primary objective, subjects who exit the study prior to experiencing a major system or procedure-related complication will be censored at the date of their exit (in the case of the subject being lost to

follow-up, the subject will be censored at the date of last contact with the subject) in the calculation of any Kaplan-Meier freedom from complication rates.

7.5 Adjustments for Multiple Comparisons

No adjustments will be made for multiple comparisons, as descriptive statistics will primarily be used.

7.6 Demographic and Other Baseline Characteristics

Descriptive statistics will be used to summarize all implant procedure information collected, including

- Lead insertion
- Sensing testing
- Closure
- Operative Time: Time of First Incision to Time at final suture/procedure stop

7.7 Treatment Characteristics

Descriptive statistics will be used to summarize all implant procedure information collected, including

- Lead insertion
- Sensing testing
- Closure
- Operative Time: Time of First Incision to Time at final suture/procedure stop

7.8 Interim Analyses

Once all enrolled subjects have had the opportunity to undergo implant defibrillation testing, the data at implant will be assessed for submission to one or more regulatory agencies. It will accompany data acquired through the point at which all subjects have had the opportunity to be followed to a 3-month visit, the accumulated data will be summarized for possible external dissemination. Descriptive statistics will be used to summarize the data.

7.9 Evaluation of Objectives

7.9.1 Primary Objective #1

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

7.9.1.1 Hypothesis

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

7.9.1.2 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)

7.9.1.3 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.

7.9.1.4 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.

7.9.1.5 Determination of Patients/Data for Analysis

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

7.9.2 Primary Objective #2

Characterize the EV ICD defibrillation testing success rate at implant.

7.9.2.1 Hypothesis

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

7.9.2.2 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.

7.9.2.3 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.

7.9.2.4 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.

7.9.2.5 Determination of Patients/Data for Analysis

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

7.9.3 Ancillary Objective #1

Characterize appropriate and inappropriate shocks.

7.9.3.1 Hypothesis

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

7.9.3.2 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.

7.9.3.3 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.

7.9.3.4 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.

7.9.3.5 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.

7.9.4 Ancillary Objective #2

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

7.9.4.1 Hypothesis

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

7.9.4.2 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.

7.9.4.3 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.

7.9.4.4 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.

7.9.4.5 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.

7.9.5 Ancillary Objective #3

Characterize extracardiac pacing sensation.

7.9.5.1 Hypothesis

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

7.9.5.2 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

7.9.5.3 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.

7.9.5.4 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.

7.9.5.5 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.

7.9.6 Ancillary Objective #4

Characterize asystole pacing.

7.9.6.1 Hypothesis

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

7.9.6.2 Performance Requirements

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

7.9.6.3 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.

7.9.6.4 Analysis Methods

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

7.9.6.5 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.

7.9.7 Ancillary Objective #5

Characterize lead position over time.

7.9.7.1 Hypothesis

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

7.9.7.2 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.

7.9.7.3 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.

7.9.7.4 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.

7.9.7.5 Determination of Patients/Data for Analysis

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

7.9.8 Ancillary Objective #6

Summarize ATP performance with spontaneous arrhythmias.

7.9.8.1 Hypothesis

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

7.9.8.2 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.

7.9.8.3 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.

7.9.8.4 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.

7.9.8.5 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.

7.9.9 Ancillary Objective #7

Summarize adverse events.

7.9.9.1 Hypothesis

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

7.9.9.2 Performance Requirements

Performance requirements are not pre-specified for this objective. The endpoint is an adverse event (see Table 11 in the CIP 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.

7.9.9.3 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.

7.9.9.4 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.

7.9.9.5 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.

7.10 Safety Evaluation

Ancillary objective #7 is to summarize adverse events. See Section 7.9.9 for details.

7.11 Health Outcomes Analyses

A health outcomes analysis will not be performed beyond summarizing adverse events.

7.12 Changes to Planned Analysis

None

8. Validation Requirements

Level I validation will be performed on programs related to the primary objectives, while level II validation will be performed for programs related to all other objectives, as well as for programs summarizing baseline demographics, study deviations, follow-up compliance, and study exits.

9. References

None.