ExtraVascular Implantable Cardioverter Defibrillator (EV ICD) Pivotal Study

NCT04060680

Statistical Analysis Plan, 17-DEC-2020

Medtronic **Statistical Analysis Plan**	
Clinical Investigation Plan Title	ExtraVascular Implantable Cardioverter Defibrillator (EV ICD) Pivotal Study
Clinical Investigation Plan Identifier	MDT16028
Clinical Investigation Plan Version	1.0
Clinicaltrials.gov Identifier	NCT04060680
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Document Version	2.0
Document Date	17-DEC-2020

Table of Contents

1. Version History 5

2. List of Abbreviations and Definitions of Terms 6

3. Introduction 6

4. Study Objectives 7

4.1 Primary Objectives 7

4.2 Ancillary Objectives 8

5. Investigation Plan 8

6. Determination of Sample Size 10

6.1 Primary Objective #1: Safety 11

6.2 Primary Objective #2: Efficacy 12

7. Statistical Methods 14

7.1 Study Subjects 14

7.1.1 Disposition of Subjects 14

7.1.2 Clinical Investigation Plan (CIP) Deviations 14

7.1.3 Analysis Sets 14

7.2 General Methodology 15

7.3 Poolability 15

7.4 Handling of Missing, Unused, and Spurious Data and Dropouts 15

7.5 Adjustments for Multiple Comparisons 16

7.6 Demographic and Other Baseline Characteristics 16

7.7 Treatment Characteristics 16

7.8 Interim Analyses 16

7.9 Evaluation of Objectives 17

7.9.1 Primary Objective #1: Safety 17

7.9.2 Primary Objective #2: Efficacy 20

7.9.3 Ancillary Objective #1: Appropriate and Inappropriate Shocks 25

7.9.4 Ancillary Objective #2: Electrical Performance 25

7.9.5 Ancillary Objective #3: Extracardiac Pacing Sensation 26

7.9.6 Ancillary Objective #4: Asystole Pacing 27

7.9.7 Ancillary Objective #5: ATP Performance 28
7.9.8 Ancillary Objective #6: Adverse Events 28
7.9.9 Ancillary Objective #7: Chronic Defibrillation Testing 29
7.9.10 Supplemental Analysis 30
7.10 Safety Evaluation 31
7.11 Managing COVID-19 Impact 31
7.12 Changes to Planned Analysis 32
8. Validation Requirements 32
9. Appendix 33
9.1 Analysis for Market Approval Outside the US 33

1. Version History

Version	Summary of Changes	Author(s)/Title
1.0	• Not Applicable, New Document	Yan Zhang, Prin Statistician
2.0	• Cover page, Clinicaltrials.gov identifier is added • Section 6.2, PASS output of sample size calculation for primary efficacy endpoint is added • Section 7, 7.1.1, 7.4, 7.9.8.4 and 7.10 are updated per ISO 14155:2020 requirements • Section 7.1.3, analysis sets for primary and sensitivity analyses are clarified • Section 7.5, hierarchical testing order is removed • Section 7.8, timepoints of DMC meetings are added and the availability of DMC closed report is clarified • Section 7.9.1.4, confirmatory and sensitivity analyses for primary safety objective are documented • Section 7.9.2.4, details of confirmatory and sensitivity analyses for primary efficacy objective are provided • Section 7.9.2.5, subjects who complete the defibrillation protocol are defined • Section 7.9.6.4, programming parameter for asystole pacing is clarified • Section 7.9.9.2, clarification on the endpoint analysis for chronic defibrillation testing is added • Section 7.9.9.5, analysis for chronic defibrillation testing per physician discretion is replaced with original CIP language • Section 7.9.10, supplemental analysis of post shock pacing effectiveness is added • Section 7.11, how to manage COVID-19 impact is added • Section 7.12, changes to planned analysis are updated	Yan Zhang, Prin Statistician

Version	Summary of Changes	Author(s)/Title
	• Analysis of market approval outside the US is moved to section 9.1 in the appendix) which is new, and details of the analysis are clarified	

2. List of Abbreviations and Definitions of Terms

Abbreviation	Definition
AE	Adverse Event
ANZ	Australia and New Zealand
ATP	Antitachycardia pacing
CEC	Clinical Events Committee
CIP	Clinical Investigation Plan
DMC	Data Monitoring Committee
EMEA	Europe, Middle East, and Africa
EV ICD	ExtraVascular Implantable Cardioverter Defibrillator
GEE	Generalized Estimating Equations
ICD	Implantable Cardioverter Defibrillator
OPC	Objective Performance Criterion
PHD	Pre-hospital Discharge Visit
PMA	Pre-Market Application
SAP	Statistical Analysis Plan
S-ICD	Subcutaneous Implantable Cardioverter Defibrillator
SSVA	Sustained shockable ventricular arrhythmia

3. Introduction

This Statistical Analysis Plan (SAP) has been designed to document, before data are analyzed, the rationale for the study design, and the planned analyses that will be included in study reports. This SAP does not limit the analysis in reports. Additional analysis of the study data beyond this plan may be needed. This SAP is developed for the EV ICD Pivotal study, based on the Clinical Investigation Plan (CIP) version 1 dated July 02, 2019.

Today, implantable cardioverter defibrillator (ICD) therapy is the treatment of choice for subjects who are at risk for sudden cardiac death due to life-threatening ventricular arrhythmias. Traditional ICD systems with transvenous leads are considered standard of care for primary or secondary prevention of

tachyarrhythmic death. However, these systems have limitations. Short- and long-term complications arising from ICD systems with transvenous leads, such as infection, pneumothorax, venous thrombosis, lead dislodgement, lead malfunction, and lead perforation, have persisted for decades as impediments to ICD usage. 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 rather than a transvenous or a subcutaneous lead. The EV ICD System has similar capabilities to a single-chamber transvenous system while avoiding leads in the heart or vasculature. Compared to current market-released non-transvenous subcutaneous ICDs, the EV ICD System includes a smaller device that uses less defibrillation energy which may result in longer battery life and has the additional capabilities to deliver pacing therapies such as antitachycardia pacing (ATP) and backup asystole pacing from a single device.

In order to develop and evaluate a newly designed system for the substernal space, Medtronic completed pre-clinical research evaluations of substernal defibrillation, pacing, and sensing, and subsequently initiated three acute human clinical research feasibility studies to explore the potential development of a future chronic implantable extravascular defibrillation system with a lead implanted in the substernal space. Later, a first-in-human chronic pilot study was initiated based on the assurance from acute feasibility data. The acute feasibility and pilot studies contributed to the advancement of the EV ICD program, including refinement of the device, algorithm and implant procedure.

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

4. Study Objectives

4.1 Primary Objectives

The first primary objective is to demonstrate the freedom from major complications related to the EV ICD System and/or procedure at 6 months post-implant exceeds 79% Objective Performance Criterion (OPC). The endpoint is defined as a subject's first occurrence of a major complication related to the EV ICD System and/or procedure, as determined by an independent Clinical Events Committee (CEC), that occurs on or prior to 6 months (182 days) post-implant.

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

- Death

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

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

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

Notes:

- In one of the two consecutive SSVA episodes, up to two 30J shocks are permitted.
- To achieve final system configuration, changing the position of the ICD generator and/or the lead, or changing shock polarity is permitted.
- Subjects can return for testing on another day if testing is not fully completed on the day of implant.
- If SSVA cannot be induced, the EV ICD System must be removed (refer to CIP section 8.5.8).
- For more information on the rationale behind these objectives, refer to section 7.9 (i.e., CIP section 12).

4.2 Ancillary Objectives

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

5. Investigation Plan

The EV ICD Pivotal Study is a prospective, multi-center, single-arm, non-randomized, pre-market clinical study. Enrollment will include up to 400 subjects at up to 60 sites worldwide. Subject inclusion/exclusion criteria can be found in CIP section 7.

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

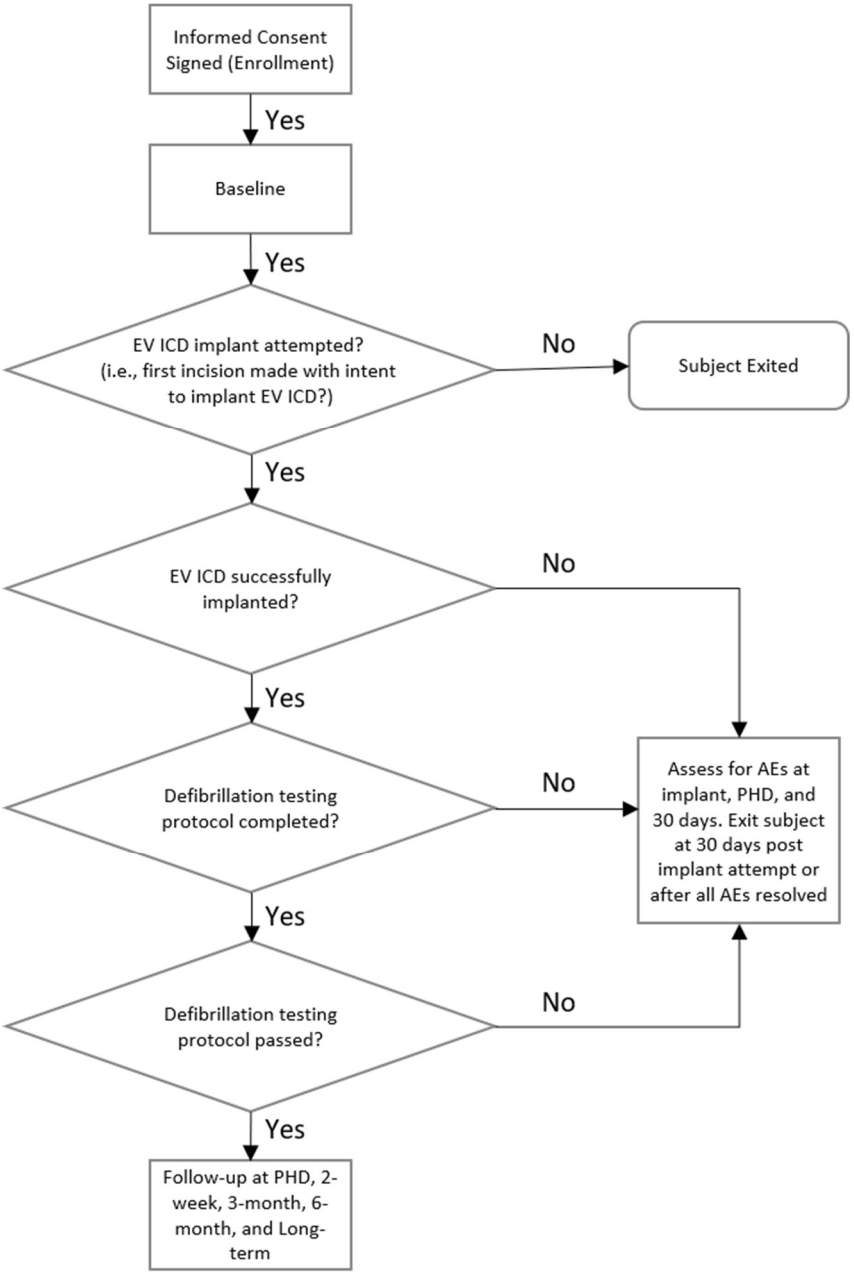
Participating sites that enroll faster than others will be allowed to do so to maintain an adequate enrollment rate. However, to ensure a reasonable distribution of experience and minimize site bias in

study results, the maximum number of subjects enrolled at each site will be capped at 35 (approximately 10% of total enrollments).

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

The following diagram provides an overview of the EV ICD Pivotal Study. This can also be found in CIP section 5.

Figure 1: Overview of the EV ICD Pivotal Study



6. Determination of Sample Size

As stated in the CIP, there are two primary objectives (safety and efficacy), and each objective requires 292 subjects to, in the case of the safety objective, undergo an implant attempt of the EV ICD System,

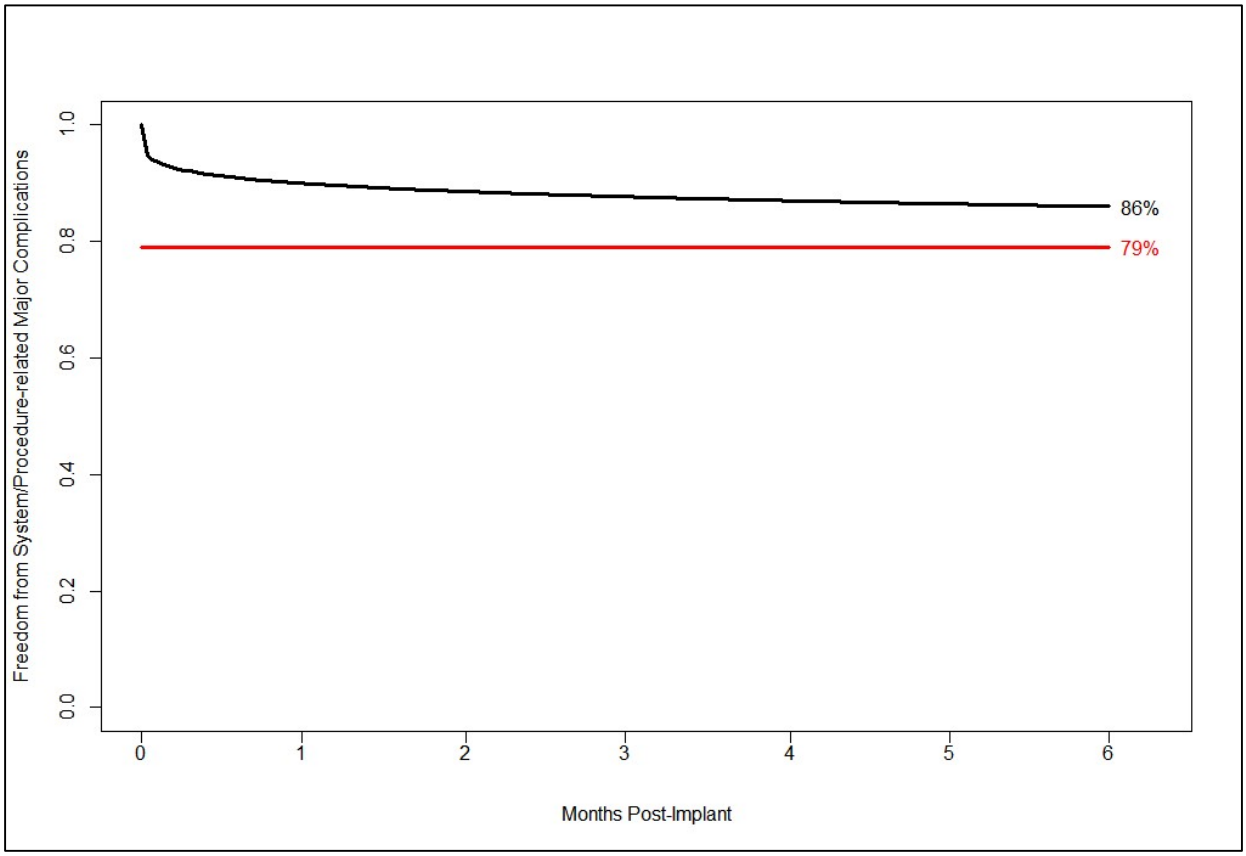
and in the case of the efficacy objective, complete the pre-specified defibrillation testing protocol (see CIP section 8.5.7 for details). Since the defibrillation protocol may not be initiated until an implant attempt occurs, the overall sample size requirement will be derived from the efficacy objective;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

6.1 Primary Objective #1: Safety

An Objective Performance Criterion (OPC) of 79% was chosen based on prior precedent to evaluate the primary safety objective metric of the EV ICD System/procedure-related major complication-free rate at 6 months. The estimated EV ICD System/procedure-related major complication-free rates through 6 months are provided in Figure 2 (i.e., CIP Figure 9). They are modeled using a Weibull distribution assuming a rate of 90% at one month and 86% at 6 months. A solid line denoting the Objective Performance criterion of 79% is also provided. It is also assumed that attrition (exit or death) will follow a Weibull distribution, with an attrition rate of 9% at one month (allowing for unsuccessful implants) and 16% through one-year post-implant.

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

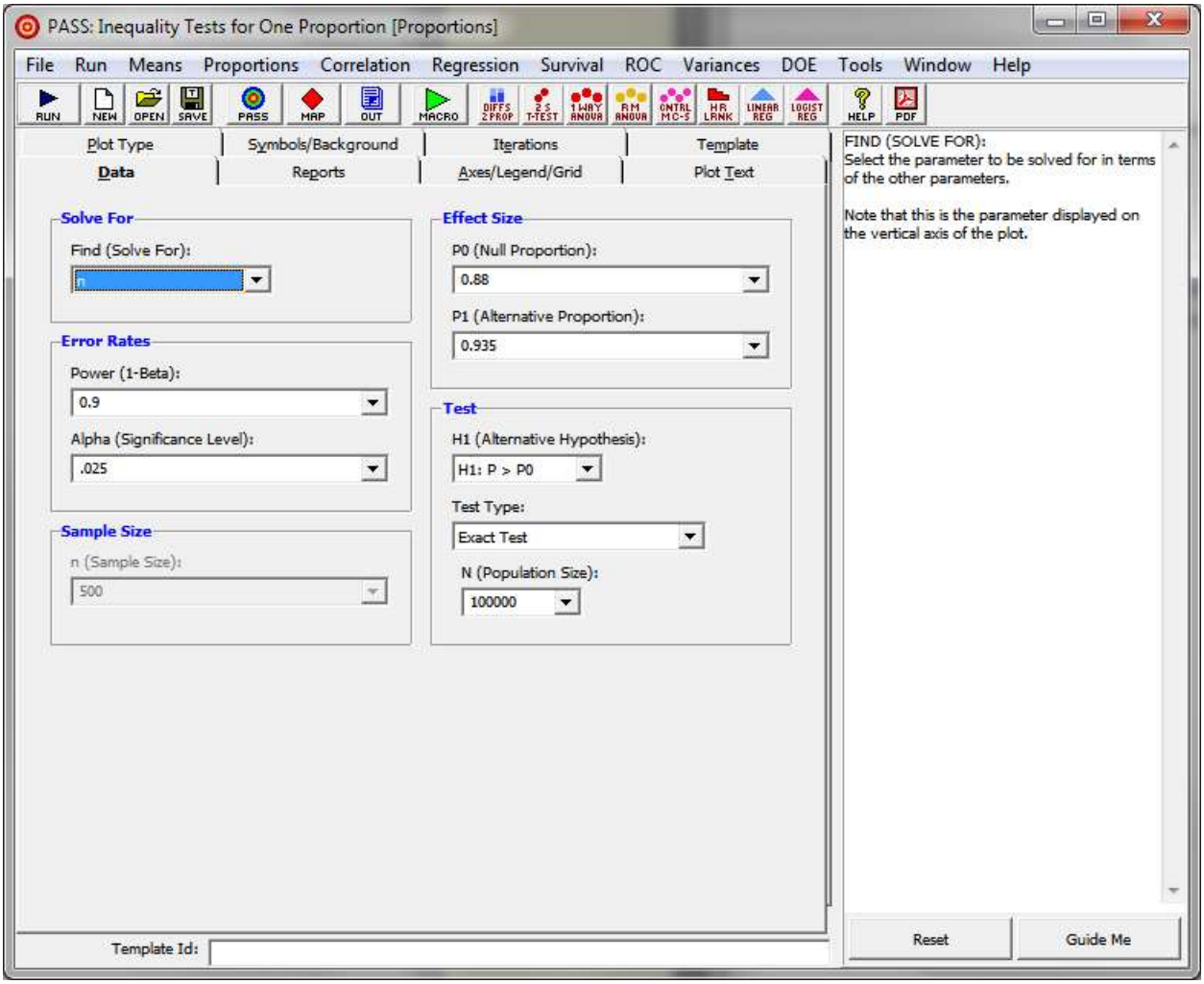
Figure 2: Estimated Freedom from System/Procedure-related Major Complications



6.2 Primary Objective #2: Efficacy

An OPC of 88% was chosen to evaluate the primary efficacy objective metric of implant testing success defined as successfully terminating one or more induced ventricular fibrillation episodes (see CIP sections 8.5.7 and 12.5.2 for more details). Each subject who completes the defibrillation protocol will be counted as a success or failure; it is assumed the true success rate is 93.5%. The required sample size to evaluate this objective using the lower confidence bound of a two-sided exact binomial 95% confidence interval and OPC of 88% with 90% power is 292 subjects completing the defibrillation protocol. This was calculated using the statistical software package PASS 2008; see the screenshot and output below from PASS.

Figure 3: Sample Size Estimation for Primary Efficacy Objective Using PASS 2008



Power Analysis of One Proportion

Numeric Results for testing H0: P = P0 versus H1: P > P0. N = 100000.
Test Statistic: Exact Test

Power	N	Proportion Given H0 (P0)	Proportion Given H1 (P1)	Target Alpha	Actual Alpha	Beta	Reject H0 If R>=This
0.9019	292	0.8800	0.9350	0.0250	0.0243	0.0981	268

Report Definitions
Power is the probability of rejecting a false null hypothesis. It should be close to one.
N is the size of the sample drawn from the population. To conserve resources, it should be small.
Alpha is the probability of rejecting a true null hypothesis. It should be small.
Beta is the probability of accepting a false null hypothesis. It should be small.
P0 is the value of the population proportion under the null hypothesis.
P1 is the value of the population proportion under the alternative hypothesis.

Summary Statements
A sample size of 292 from a population of 100000 achieves 90% power to detect a difference (P1-P0) of 0.0550 using a one-sided binomial test. The target significance level is 0.0250. The actual significance level achieved by this test is 0.0243. These results assume that the population proportion under the null hypothesis is 0.8800.

7. Statistical Methods

The CIP version 1 dated July 02, 2019 is the only version as of the approval date of this document. Should there be a CIP update, the impacts of it on the integrity of the study will be evaluated; if such impacts are confirmed, the data collected before and after the amendment will be analyzed statistically per ISO 14155:2020 to assess the effect of the amendment on the safety and efficacy analysis.

7.1 Study Subjects

7.1.1 Disposition of Subjects

This is a single-arm study. After subjects sign the informed consent form, they are enrolled in the study. Screening logs are not used in this study as historically they have typically been found to have poor compliance. Extensive inclusion/exclusion criteria have been chosen in this study to restrict the target population to those thought to be best served by this EV ICD system and mitigate the risk of selection bias. Enrollment can be a stand-alone visit or can occur on the same day as the baseline visit. After that subjects will undergo implant of the EV ICD system, with required defibrillation, sensing, impedance and pacing testing. Subjects will then return for follow-up visits at 2 Weeks, 3 Months, 6 Months, and every 6 months thereafter. Subject disposition will be presented using a flow diagram where completed visits, missed visits, and attrition due to exit and death will be indicated.

7.1.2 Clinical Investigation Plan (CIP) Deviations

A study deviation is an event within a study that did not occur according to the CIP or the Clinical Trial Agreement. 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. If it is discovered there were subjects not meeting the inclusion/exclusion criteria who underwent an implant attempt and possibly defibrillation testing, additional analyses may be performed with these subjects excluded.

7.1.3 Analysis Sets

All subjects with an implant attempt of the investigational product will be included in the primary analysis for the primary safety objective. All subjects who complete the defibrillation protocol will be included in the primary analysis for the primary efficacy objective. Results from the primary analyses will determine if the primary safety and efficacy objectives are met. In addition, sensitivity analyses may be

considered to assess the robustness of the results when there is missing data. For example, patients who begin the defibrillation testing at implant but do not complete it may be included in the sensitivity analysis for the primary efficacy objective.

7.2 General Methodology

Data analysis will be performed by Medtronic statisticians or designees.

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

7.3 Poolability

This study plans to enroll up to 400 subjects at up to 60 sites worldwide. Poolability analysis may be performed to compare the results between different geographic regions such as ANZ, EMEA, Japan,Hong Kong, and United States/Canada. Consistency between the regions for the primary safety endpoint will be evaluated using a log-rank test, that for the primary efficacy endpoint will be evaluated using Fisher's exact test. If these tests indicate that the homogeneity of study results across regions may be a concern, further analyses will be performed to determine potential explanations for the possible heterogeneity.

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

All available data will be included in the data listings and tabulations.

Only subjects who complete the defibrillation protocol at implant will be included in the primary analysis that determines if the primary efficacy objective is met. Subjects who do begin the defibrillation testing at implant but do not complete it may be included in a sensitivity analysis. Specifically, a tipping point analysis may be performed based on all subjects that have begun the defibrillation testing at implant to determine the robustness of this analysis to missing data.

With regard to the primary safety 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 or death of unknown classification, 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. In the situation where the attrition rate is much higher than expected or there appears to be a systematic reason for attrition, the assumption of noninformative censoring may no longer be valid and a sensitivity analysis may be considered.

7.5 Adjustments for Multiple Comparisons

There is no adjustment for multiple comparisons. However, both the primary safety and efficacy objectives will be evaluated at a one-sided significance level of 0.025. Because a subject may be included in the analysis for the primary safety objective but not the efficacy objective if the subject does not complete the defibrillation protocol, the primary safety and efficacy objectives are not independent.

7.6 Demographic and Other Baseline Characteristics

Descriptive statistics will be used to summarize baseline and demographic characteristics. For categorical data, counts and percentages will be employed, while for continuous variables, means, standard deviation, quartiles, minimum, and maximum will be provided. These statistics will be provided both for all enrolled subjects and for the subset of subjects who undergo implant of the EV ICD system.

7.7 Treatment Characteristics

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

- Pre-procedure and substernal tunnel characteristics
- Sensing testing via analyzer and lead insertion
- Closure characteristics
- Operative time: Time of first incision to time of final device pocket suture

7.8 Interim Analyses

Medtronic plans to analyze the accumulated data once 60 subjects undergoing implant of the EV ICD System have completed their 3-month follow-up visit. This analysis is for CE Mark approval. Details of this analysis are available in section 9.1.

A Data Monitoring Committee (DMC) has been formed for this study. The details on DMC responsibilities and process can be found in the DMC Charter. The DMC will be evaluating, at minimum, the rates of EV ICD system/procedure-related major complications on an ongoing basis, though not for the purpose of early stoppage of the trial for success. Thus, alpha-spending will not be employed. The trial is planned to continue until all subjects have at least reached their 6-month follow-up visit and both primary objectives may be assessed with the pre-specified cohort.

According to the DMC Charter, a DMC meeting is planned for three study timepoints: (1) after 60 subjects underwent an implant attempt, (2) prior to the submission of interim report for CE Mark, and (3) prior to the Pre-Market Application (PMA) submission to FDA. The Committee may meet more or less frequently if requested by Medtronic or the DMC Chair, or agree with DMC. A DMC closed report will be generated through the first timepoint at minimum. In the DMC closed report, the conditional power of the primary safety objective ultimately being met given the observed results at the time will be calculated. The DMC may assess futility based on the conditional power and other information.

7.9 Evaluation of Objectives

7.9.1 Primary Objective #1: Safety

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

7.9.1.1 Hypothesis

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

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

7.9.1.2 Performance Requirements and Endpoint Definition

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

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

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

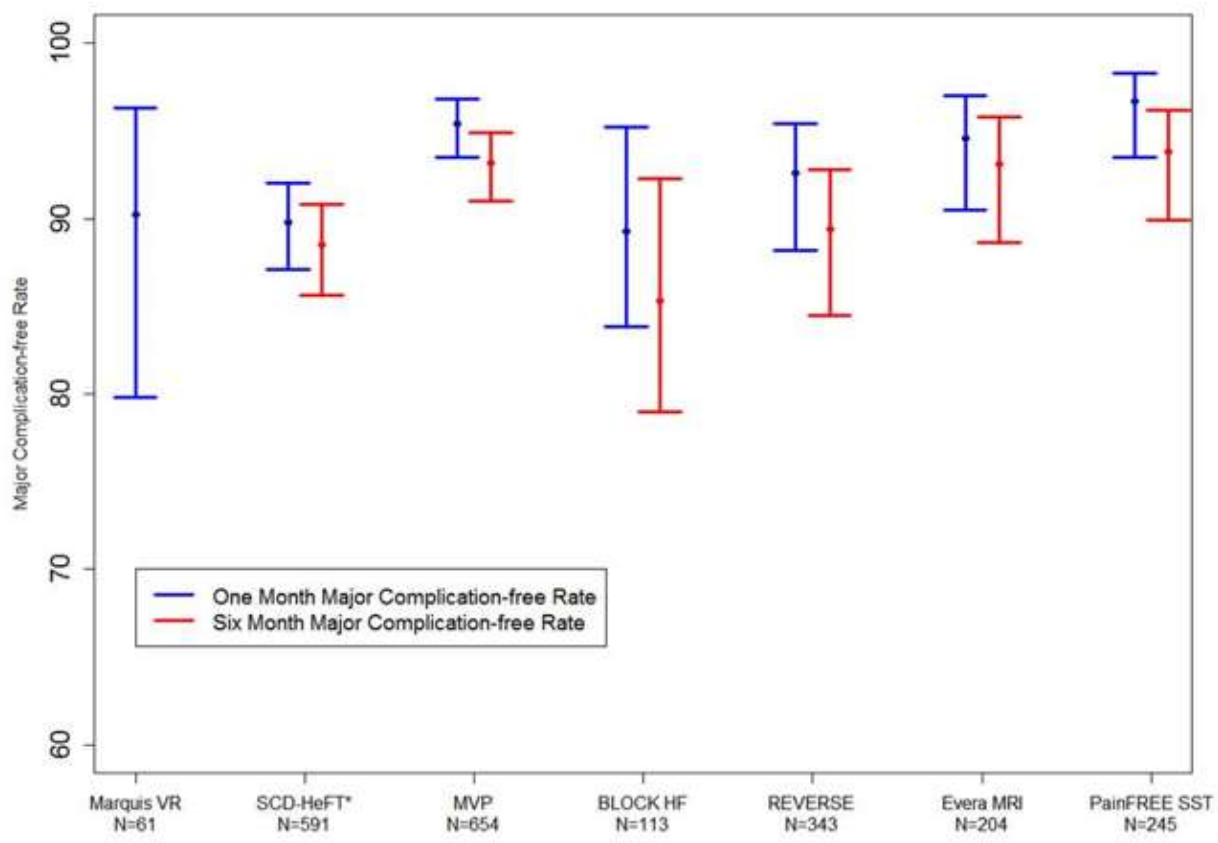
The pre-specified OPC for the major complication free rate at 6 months is 0.79, meaning the lower confidence bound of two-sided 95% confidence interval for the freedom from EV ICD major complication incidence rate must exceed 0.79.

7.9.1.3 Rationale for Performance Criteria

The determination of the pre-specified OPC (79%) for the major complication objective was based on review of internal Medtronic transvenous ICD trial data as well as literature involving alternative devices. An assessment of comparable major complication-free rates at 6 months for Medtronic transvenous devices showed observed rates as low as 85% (Figure 4, i.e. CIP Figure 10). In each such

study, only ICD subjects with no history of CABG or valve surgery were analyzed, as that subset of subjects was considered representative of the possible EV ICD population.

Figure 4: Historical ICD Generator/RV Lead/Procedure-related Major Complication-free Rates



*SCD-HeFT rates may include major and minor complications

The following table provides further detail regarding these trials.

Table 1: Historical Medtronic Transvenous ICD Trial Major System/Procedure Complication-free Rates

Study	Study Description	30-day Freedom Rate (95% CI)	6-Month Freedom Rate (95% CI)
Marquis VR[1]	Medtronic Market Release Study Evaluating Marquis VR ICD	90.2% (79.8%, 96.3%)	N/A, subjects not followed to 6 months
SCD-HeFT[2]	Randomized study comparing ICD therapy to placebo	89.8%* (87.1%, 92.0%)	88.5%* (85.6%, 90.8%)
MVP[3]	Post-market study comparing MVP to VVI pacing in ICD population without pacing indication	95.4% (93.5%, 96.8%)	93.2% (91.0%, 94.9%)
BLOCK HF[4]	IDE (G030156) study comparing efficacy of CRT to RV pacing in AV block patients	89.3% (83.8%, 95.2%)	85.3% (79.0%, 92.3%)
REVERSE[5]	IDE (G040004) study comparing efficacy of CRT to ICD/OMT therapy in NYHA II patients	92.6% (88.2%, 95.4%)	89.4% (84.5%, 92.8%)
Evera MRI[6]	IDE (G140039) study evaluating safety and efficacy of the Medtronic Evera MRI ICD System	94.6% (90.5%, 97.0%)	93.1% (88.6%, 95.8%)
PainFREE SST[7]	Randomized study to evaluate the Medtronic Protecta ICD System	96.7% (93.5%, 98.3%)	93.8% (89.9%, 96.2%)

*Included both major and minor complications

Additionally, the OPC threshold of 79% has been used to evaluate only system-related complications in a pivotal trial for an alternative subcutaneous defibrillation device[8], and so there is precedent for 79% being considered an acceptable criterion for evaluating safety at 6 months for defibrillation products. In that S-ICD study the observed 6-month freedom from system-related or procedure-related complications was 92.1% with a lower confidence limit of 88.9%. A pooled analysis of the S-ICD IDE and

1 Data on file.
2 Bardy G, et al. Amiodarone or an Implantable Cardioverter-Defibrillator for Congestive Heart Failure. *NEJM*. 2005; 352:3: 225-237.
3 Sweeney M, et al. Atrial pacing or ventricular backup-only pacing in implantable cardioverter-defibrillator patients. *Heart Rhythm*. 2010; 7(11); 1552-1560.
4 Curtis A, et al. Biventricular Pacing for Atrioventricular Block and Systolic Dysfunction. *NEJM*. 2013; 368:17: 1585-1593.
5 Linde C, et al. Randomized trial of cardiac resynchronization in mildly symptomatic heart failure patients and in asymptomatic patients with left ventricular dysfunction and previous heart failure symptoms. *JACC*. 2008; 52(23): 1834-1843.
6 Gold MR, et al. Full-Body MRI in Patients With an Implantable Cardioverter-Defibrillator: Primary Results of the Randomized Study. *JACC*. 2015; 65(24):2581-2588.
7 Auricchio A, et al. Low inappropriate shock rates in patients with single- and dual/triple-chamber implantable cardioverter-defibrillators using a novel suite of detection algorithms; PainFree SST trial primary results. *Heart Rhythm.* 2015; 12(5):926-936.
8 Weiss R, et al. Safety and Efficacy of a Totally Subcutaneous Implantable-Cardioverter Defibrillator. *Circulation*. 2013; 128: 944-953.

EFFORTLESS Post Market S-ICD Registry[9] reported that 92.3% of subjects were free of a system or procedure-related complication through 6 months. Since Medtronic is evaluating both EV ICD System and procedure-related complications, an OPC of 0.79 at 6 months for establishing freedom from such complications is appropriate.

7.9.1.4 Analysis Methods

Results will be summarized in aggregate using descriptive statistics. The total number of major complications experienced by subjects for whom an implant is attempted will be summarized. The primary analysis for primary safety endpoint will be based on the endpoint definition described in section 7.9.1.2. Subjects not experiencing an event will be censored at their last point of contact. The 182-day freedom from major complication rate will be generated using the Kaplan-Meier method, along with a two-sided 95% confidence band based on a log-log transformation. If the lower bound is at least 0.79 (79%), the objective will be considered met.

If any adverse events that occurred within 182 days (inclusive) of the EV ICD System implant attempt were adjudicated by the CEC as being major complications and the relatedness to the EV ICD System and/or procedure was determined by the CEC as "probable", a sensitivity analysis will be conducted with such adverse events included as having met the primary safety endpoint. An additional sensitivity analysis may be performed including major complications with a system or procedure-relatedness classification of "possible", should there be any such major complications.

Comparison against the pre-specified OPC with the full cohort of subjects that have undergone an implant attempt is considered a confirmatory analysis of this objective.

Noninformative censoring is assumed in the primary analysis. In the situation where the attrition rate is higher than expected or there appears to be a systematic reason for attrition that may bias the results, the assumption of noninformative censoring may no longer hold and a sensitivity analysis such as a tipping point analysis may be considered.

7.9.1.5 Determination of Subjects/Data for Analysis

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

7.9.2 Primary Objective #2: Efficacy

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

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

7.9.2.1 Hypothesis

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

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

7.9.2.2 Performance Requirements and Endpoint Definition

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

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

Notes:

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

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

7.9.2.3 Rationale for Performance Criteria

Defibrillation implant success for transvenous devices, though no longer routinely performed, has historically been shown to be as low as 88% (Table 2, i.e. CIP Table 16). A literature search combined with prior Medtronic trial data showed transvenous defibrillation testing rates commonly in the 90-93% range, which is in line with the hypothesized defibrillation efficacy of EV ICD.

Table 2: Historical Transvenous ICD Defibrillation Testing Success Rates

Reference	Sample Size	Defibrillation Implant Success
Medtronic 6932 Lead Study (MDL #13520, Data on file)	N=165 Model 6932 leads N=166 Model 6936 leads	87.7% 83.5%
Medtronic 6944 Lead Study (MDL #24416, Data on file)	N=112 Model 6944 leads N=122 Model 6942 leads	91.1% 91.8%

Reference	Sample Size	Defibrillation Implant Success
Leong-Sit AMJ: 2006; 152:1104-8	N=168	90.5%
Pires JCE 2006; 17:1-6	DFT at implant (N=129) Safety Margin Testing at Implant (N=503) No Testing at Implant (N=203)	77% 93% N/A
Michowitz Europace 2011; 13:683-88	N=204	91.7%
SIMPLE Study Lancet 2015; 385:785-91	Safety Margin Testing at Implant (N=1218) No Testing at Implant (N=1227)	91.8% N/A

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

Defibrillation results in the post market setting support the belief of S-ICD efficacy being 91-94%. The first results from the EFFORTLESS Study[10] provided a report on the full subject cohort and study endpoint with follow-up ≥1 year. The pre-defined endpoints of this registry are 30- and 360-day complications, and shocks for atrial fibrillation or supraventricular tachycardia. These results provide more data on the efficacy of the S-ICD over time, during both induced and spontaneous arrhythmias. In the first 30 days following implantation, 861 subjects had at least 1 evaluable acute conversion test, with 777 of these tests (91.6%) using a defibrillation energy of ≤65 J, which allows for a safety margin.

In a retrospective analysis, Friedman et al[11] reported on trends and in-hospital outcomes associated with early adoption of the S-ICD compared to single- and dual-chamber transvenous ICD implants. Table 3 (i.e. CIP Table 17) provides in-hospital outcomes associated with the S-ICD implants. Among 2791 subjects with S-ICD who underwent DFT testing, 2588 (92.7%), 2629 (94.2%), 2635 (94.4%), and 2784 (99.7%) were successfully defibrillated (≤65, ≤70, ≤75, and ≤80 J, respectively). The 92.7% defibrillation efficacy at 65J is the best comparator, as it offers a 15J safety margin.

Additionally, there have been other studies and sub-analyses that have reported on the defibrillation threshold testing performance of the S-ICD device. Frankel DS et al[12] evaluated 65J first shock success in

10 Boersma L, et al. Implant and Midterm Outcomes of the Subcutaneous Implantable Cardioverter-Defibrillator Registry – The EFFORTLESS Study. JACC (August 2017); 70(7): 830-841.
11 Friedman D, et al. Trends and In-Hospital Outcomes Associated with Adoption of the Subcutaneous Implantable Defibrillator in the United States. JAMA Cardiol (November 2016); 1(8): 900-911.
12 Frankel DS et al. Impact of Body Mass Index on Safety and Efficacy of the Subcutaneous Implantable Cardioverter-Defibrillator. JACC: Clinical Electrophysiology (May 2018): 4(5): 652-659.

acute DFT testing in the S-ICD IDE trial among subgroups define by BMI, while Peddareddy L et al[13] reported acute DFT testing results at their site only. These studies show evidence of defibrillation testing performance of less than the OPC of 88% in subgroups of subjects, further justifying the clinical relevance of such a threshold.

Table 3: S-ICD EFFORTLESS Defibrillation Testing Results

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

7.9.2.4 Analysis Methods

The primary efficacy objective will be evaluated using a one-proportion binomial exact test along with a two-sided 95% Clopper-Pearson confidence bound. Each subject who completes the defibrillation protocol will be determined to either have successfully met the defibrillation endpoint or not met the endpoint. The proportion of subjects having EV ICD defibrillation success at implant will be calculated: the denominator is the number of subjects who complete the defibrillation protocol, and the numerator is the number of subjects who have defibrillation success at implant. Subjects who do not complete the defibrillation protocol will not be included in this primary analysis.

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

The analysis will be performed with SAS code similar to:

```
proc freq data=DefibImplant;
   exact binomial;
   tables DefibSuccess / binomial(p=0.88) alpha=0.05;
run;
```

where 'DefibSuccess' is a variable coding whether a patient has defibrillation success at implant; 'exact' statement requests both one- and two-sided exact tests for the binomial proportion of DefibSuccess; 'p = 0.88' in the binomial option specifies the null hypothesis proportion for the binomial test; the 'alpha=0.05' option sets the confidence level of two-sided confidence interval (CI) for the binomial proportion as 95%, hence the lower confidence limit of this 95% CI is the one-sided 97.5% confidence boundary. If it is greater than 88%, we reject the null hypothesis at a significance level of 0.025. The primary analysis is considered a confirmatory analysis of this objective.

If there is missing data or subjects begin the defibrillation testing at implant but do not complete it, a sensitivity analysis may be performed. Specifically, a tipping point analysis[14, 15] may be performed based on all subjects that have begun the defibrillation testing at implant to determine the robustness of this analysis to missing data.

Let $n_{mis\sin g}$ be the number of subjects who are not included in the denominator for the primary analysis mentioned above. Starting at 0 and ending at $n_{mis\sin g}$, the defibrillation success rate is changed by adding 1 failure at a time and a two-sided 95% CI will be produced each time. If at any point the lower confidence limit is less than or equal to 88%, then the number of failures in the missing subjects that results the study fails to reject the null hypothesis of this objective is a tipping point.

The percentage of defibrillation successes among the missing subjects needed to meet the objective would be compared to the observed success rate, which would be used to assess if the study conclusion is robust in regard to the missing data.

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 Subjects/Data for Analysis

All subjects who complete the defibrillation protocol will be included in the analysis. The CIP Figure 7 is a diagram that outlines the steps of defibrillation testing at implant. Subjects who complete the

14 Yan X, Lee S, Li N. Missing data handling methods in medical device clinical trials. Journal of Biopharmaceutical Statistics. 2009,19:1085-1098.
15 Campbell G, Pennello G, Yue L. Missing data in the regulation of medical devices. *J Biopharm Stat*. 2011 Mar; 21(2): 180-95.

defibrillation protocol are those who ended with a checkmark (denoting 'defibrillation criteria met') or a cross sign (denoting 'defibrillation criteria not met') in their defibrillation testing based on this diagram.

7.9.3 Ancillary Objective #1: Appropriate and Inappropriate Shocks

Characterize appropriate and inappropriate shocks.

7.9.3.1 Hypothesis

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

7.9.3.2 Performance Requirements and Endpoint Definition

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

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

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. Kaplan-Meier curves for time to first appropriate shock and time to first inappropriate shock may be provided to demonstrate shock incidence. Any instances of VT/VF terminated by ATP but also receiving a shock following ATP delivery will be reported.

7.9.3.5 Determination of Subjects/Data for Analysis

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

7.9.4 Ancillary Objective #2: Electrical Performance

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

7.9.4.1 Hypothesis

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

7.9.4.2 Performance Requirements and Endpoint Definition

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

7.9.4.3 Rationale for Performance Criteria

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

7.9.4.4 Analysis Methods

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

7.9.4.5 Determination of Subjects/Data for Analysis

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

7.9.5 Ancillary Objective #3: Extracardiac Pacing Sensation

Characterize extracardiac pacing sensation.

7.9.5.1 Hypothesis

There are no hypotheses for this objective.

7.9.5.2 Performance Requirements and Endpoint Definition

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

7.9.5.3 Rationale for Performance Criteria

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

7.9.5.4 Analysis Methods

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

7.9.5.5 Determination of Subjects/Data for Analysis

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

7.9.6 Ancillary Objective #4: Asystole Pacing

Characterize asystole pacing.

7.9.6.1 Hypothesis

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

7.9.6.2 Performance Requirements and Endpoint Definition

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

7.9.6.3 Rationale for Performance Criteria

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

7.9.6.4 Analysis Methods

The CIP Section 8.6 specifies the programming requirements and recommendation at the pre-hospital discharge visit, where the requirements on pause prevention is for asystole pacing. Descriptive statistics will be used to summarize the number of subjects and amount of asystole pacing experienced during follow-up.

7.9.6.5 Determination of Subjects/Data for Analysis

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

7.9.7 Ancillary Objective #5: ATP Performance

Summarize ATP performance with spontaneous arrhythmias.

7.9.7.1 Hypothesis

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

7.9.7.2 Performance Requirements and Endpoint Definition

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

7.9.7.3 Rationale for Performance Criteria

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

7.9.7.4 Analysis Methods

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

7.9.7.5 Determination of Subjects/Data for Analysis

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

7.9.8 Ancillary Objective #6: Adverse Events

Summarize adverse events.

7.9.8.1 Hypothesis

There are no hypotheses for this objective, as safety of the EV ICD System is being evaluated by Primary Objective #1 (see section 7.9.1). This objective is to provide a comprehensive summary of adverse events experienced during follow-up.

7.9.8.2 Performance Requirements and Endpoint Definition

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

7.9.8.3 Rationale for Performance Criteria

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

7.9.8.4 Analysis Methods

Results will be summarized in aggregate using descriptive statistics. Counts and percentages of subjects experiencing system and/or procedure-related adverse events will be reported, as well as, in the case of system-related events, the specific component of the system to which the event was related. Adverse Events will be broken out by MedDRA keyterm, with both counts of events and counts of subjects experiencing each type of event reported. The seriousness of adverse events and adverse device effects will also be summarized. Details of individual adverse events including MedDRA key term, center diagnosis, description, actions, outcome, relatedness and seriousness will be listed. When deemed necessary, individual adverse events where center investigator classification on relatedness differs from the CEC adjudication and/or center investigator assessment on seriousness differs from the Medtronic Safety assessment will be identified for reporting. Determination of Subjects/Data for Analysis

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

7.9.9 Ancillary Objective #7: Chronic Defibrillation Testing

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

7.9.9.1 Hypothesis

No statistical hypotheses will be tested for this objective.

7.9.9.2 Performance Requirements and Endpoint Definition

The performance requirement for this objective is that the observed proportion of subjects, among those with an induced VF episode at their 6-month visit, for whom the episode is successfully terminated with a shock is at least 0.88. The endpoint, defibrillation testing success, is defined as successful completion of the chronic defibrillation testing protocol at the 6-month visit. Subjects included in this analysis should have consented to the chronic defibrillation testing. If a consented chronic defibrillation testing is conducted after the 6-month visit, it will also be included in the analysis.

7.9.9.3 Sample Size

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

7.9.9.4 Rationale for Performance Criteria

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

7.9.9.5 Analysis Methods

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

7.9.9.6 Determination of Subjects/Data for Analysis

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

7.9.10 Supplemental Analysis

Quality of Life/subject acceptance will also be measured through the SF-12 qualify of life survey at baseline and 6 months and Florida Subject Acceptance Survey (FPAS) at 6 months. These tools will be

administered so that subject response in this study may be compared to response to such tools in other ICD studies. Data collected through these questionnaires will be summarized using descriptive statistics. For the SF-12, the version 2 of the questionnaire (SF-12v2) will be used and the data handling will be based on the instructions provided by Ware et al.[16]

Supplemental analysis will also be performed to characterize the effectiveness of post shock pacing. As indicated in the CIP Section 8.6, enabling post shock pacing is per physician recommendation. For patients that receive shocks on spontaneous episodes during follow-up, descriptive statistics will be used to summarize: (1) the number of subjects that experienced post shock pacing, (2) the percentage of shocked episodes with post shock pacing, and (3) the percentage of post shock pacing episodes that demonstrated capture.

7.10 Safety Evaluation

Ancillary objective #6 is to summarize adverse events, see section 7.9.8 for details. In addition, the term and center description of individual device deficiencies and whether they could have led to a serious adverse device effect will be reported. Individual deaths including death classification per center investigator and per CEC adjudication will also be listed.

7.11 Managing COVID-19 Impact

The study enrollment period started from September 13, 2019 when the first site was activated. The first study subject was enrolled on September 16, 2019. On March 20, 2020, all study centers were informed of a pause in new enrollments, and that implant procedures for enrolled subjects were to be postponed or cancelled. The decision to temporarily pause enrollments was made after consultation with the EV ICD Pivotal Steering Committee in consideration of the safety of study subjects, investigational site staff, and Medtronic employees during the global COVID-19 pandemic. Medtronic made FDA aware of this pause on 29MAR2020. Additional Regulatory Authorities were subsequently notified, as applicable per local regulations. According to the DMC May 2020 report, 36 subjects were enrolled and 25 of them underwent an implant attempt as the visit cutoff date of March 27, 2020. Since the study needs at least 292 subjects completing the defibrillation testing protocol for the primary efficacy objective (see Section 6), data that had been collected before enrollment pause due to the COVID-19 pandemic is less than 10% of required information.

As part of the internal assessment for the COVID-19 pandemic, Medtronic reviewed the FDA guidance document the “FDA Guidance on Conduct of Clinical Trials of Medical Products during COVID-19 Public

16 Ware JE et al. How to Score Version 2 of the SF-12 Health Survey (With a Supplement Documenting Version 1). QualityMetric Incorporated, ISBN: 1-891810- 10- 3,

Health Emergency"[17] issued in March 2020, centers have been informed to identify study deviations and attritions due to COVID-19 impact. There are no planned changes to the CIP in response to the pandemic, and implanted subjects are to be followed per the CIP. Medtronic remains committed to providing follow-up visit support, whether in person or remotely via teleconference or videoconference. CareLink remote monitoring is not currently available for subjects with an EV ICD implant; therefore, device interrogations required at follow-up visits must be done in-person. In the event that in-person follow-up is not possible, sites are instructed to ensure that, at a minimum, the subject is contacted (e.g., via phone) and adverse events are reported accordingly. Additionally, in cases where protocol deviations (e.g., missed or out-of-window visit), or subject exit (e.g., prior to implant) are related to limitations due to the COVID-19 pandemic, sites are instructed to indicate "COVID-19 impact" on the applicable Case Report Form.

Following communication of the pause in enrollments to the investigational sites, in collaboration with the EV ICD Pivotal Steering Committee, a readiness assessment checklist was created to facilitate discussions between Medtronic and the Principal Investigator at each site that expressed the ability of the site to begin enrollments again. This assessment is conducted on a site-by-site basis. After agreement between Medtronic and the site, an Enrollment Restart Letter is issued to inform the site they are approved to enroll in the study. Other Regulatory Authorities were notified as applicable, timing was based on site status per country.

Details of protocol deviations and study exits indicated as "COVID-19 impact" have been provided in the Annual Report to the FDA in August 2020 and presented at the DMC meeting in November 2020. The study team will continue monitoring the impact of COVID-19 pandemic on the study and providing updates when deemed necessary.

7.12 Changes to Planned Analysis

Changes to the planned analyses stated in the CIP include adding the DMC interim analyses, characterization of post shock pacing effectiveness, and COVID-19 impact monitoring into the SAP.

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 non-objective related information such as baseline demographics, study deviations, follow-up compliance, and study exits.

17 FDA Guidance on Conduct of Clinical Trials of Medical Products during COVID-19 Pandemic. Guidance for Industry, Investigators, and Institutional Review Boards. March 2020.

9. Appendix

9.1 Analysis for Market Approval Outside the US

Human clinical data may be needed to support marketing applications in CE Mark countries and other geographies outside the US. Therefore, Medtronic plans to analyze the accumulated data once 60 subjects undergoing implant of the EV ICD System have completed their 3-month follow-up visit. This analysis will include characterizing both defibrillation efficacy at implant and incidence of major EV ICD System/procedure-related complications through at least 3 months. All subjects will continue to be followed and the timeline for other marketing applications will not be impacted by this analysis. This analysis will not utilize an alpha-spending function. Medtronic also plans to submit updated data from the ASD2 feasibility study and the ongoing EV ICD Pilot study for further information regarding defibrillation testing and safety.

In the EV ICD Pivotal interim report for CE Mark submission, the definitions of EV ICD system/procedure-related major complications and defibrillation testing success at implant are the same as those for the primary safety and efficacy objectives of the study. The safety endpoint (major EV ICD System/procedure-related complications) will be characterized descriptively through 3 months. The defibrillation efficacy endpoint will be characterized using descriptive statistics such as frequency and percentage. No performance goal or hypothesis testing is planned for either endpoint. When the 60-patient sample size was determined, it was expected that by the time 60 patients have completed 3 months of follow-up approximately 171 subjects would have undergone the defibrillation testing and 131 subjects would have completed at least one month of follow-up.