Medtronic

**Clinical Investigation Plan**

| | |
|---|---|
| **Clinical Investigation Plan/Study Title** | **L**ead **E**valu**A**tion for **D**efibrillation and **R**eliability (LEADR) |
| **Clinical Investigation Plan Identifier** | MDT19004 |
| **Study Product Name** | Model 093000 lead, further referenced as the 'Next Generation ICD Lead' |
| **Sponsor/Local Sponsor** | **Sponsor:**<br>**Medtronic, Inc.**<br>8200 Coral Sea Street NE<br>Mounds View, MN 55112<br>United States of America<br>+1 800 328 2518<br><br>**Local Sponsors:**<br>**Australia**<br>Medtronic Australasia Pty Ltd<br>2 Alma Road, Macquarie Park<br>NSW, 2113<br>Australia<br>+61 2 9857 9000<br><br>**Canada**<br>Medtronic Canada ULC<br>99 Hereford Street Brampton<br>Ontario, L6Y 0R3 Canada<br>+1 905 460 3800<br><br>**Mainland China**<br>Medtronic (Shanghai) Management Co., Ltd.<br>2106A, 21th Floor, No. 28. Maji Road,<br>China (Shanghai) Pilot Free Trade Zone,<br>200131, Shanghai, P.R. China<br>+86 215 866 9877<br><br>**Europe, Middle East, Africa**<br>Medtronic, Bakken Research Center B.V.<br>Endepolsdomein 5<br>6229 GW Maastricht<br>The Netherlands<br>+31 43 35 66 566<br><br>**Hong Kong** |

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# 1. Contact Information and Glossary

## 1.1. Sponsor Contact Information

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

**Table 1: Study sponsor contact information**

| **Study sponsor and contacts** | |
|---|---|
| *Worldwide Clinical Study Leader*<br>[redacted] Principal Clinical Research Specialist<br>Direct Phone: [redacted]<br>Email: [redacted] | *Australia and New Zealand*<br>[redacted], Principal Clinical Research Specialist<br>Direct Phone: [redacted]<br>Email : [redacted] |
| *Canada*<br>[redacted] Sr. Clinical Research Specialist<br>Direct Phone: + [redacted]<br>Email: [redacted] | *Europe, Middle East, and Africa (EMEA)*<br>[redacted] Sr. Clinical Research Specialist<br>Direct Phone: +31 6 5235 6924<br>Email: kevin.hermans2@medtronic.com |
| *Japan*<br>Yo [redacted] Clinical Research Manager<br>Direct Phone: [redacted]<br>Email: [redacted] | *Mainland China*<br>[redacted] Clinical Research Specialist<br>Direct Phone: [redacted]<br>Email: [redacted] |
| *United States of America (US)*<br>[redacted], Sr. Clinical Research Specialist<br>Direct Phone: [redacted]<br>Email: [redacted] | *Hong Kong*<br>[redacted], Sr. Clinical Research Specialist<br>Direct Phone: [redacted]<br>Email: [redacted] |
| *Malaysia and Singapore*<br>[redacted] Clinical Research Specialist<br>Direct Phone: [redacted]<br>Email: [redacted] | *Puerto Rico/Latin America*<br>[redacted] Sr. Clinical Research Specialist<br>Direct Phone: [redacted]<br>Email: [redacted] |
| **Monitoring contacts** | |
| *US/Canada*<br>[redacted], Sr. Clinical Monitoring Manager<br>Direct Phone: [redacted] | *EMEA/Asia Pacific/Hong Kong/Japan*<br>[redacted] Monitoring Portfolio Specialist CRHF<br>Direct Phone: [redacted] |

| | |
|---|---|
| Email: [redacted] | Email: [redacted] |

## 1.2. CROs and Core Labs

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

| Contact Information | Role |
|---|---|
| Cognizant Technology Solutions<br>500 Frank W. Burr Blvd.<br>Teaneck, NJ 07666<br>United States of America<br>Direct Phone: [redacted]<br>Direct Fax: [redacted] | • Development of study electronic case report forms, edit checks, and study management reports<br>• Review of electronic case report forms and management of discrepancies on the case report forms. |

## 1.3. Glossary

| Term | Definition |
|---|---|
| ACI tool | AccuRead analyzer cable interface tool |
| ADE | Adverse Device Effect |
| AE | Adverse Event |
| AP/PA | Anterior-Posterior/ Posterior-Anterior |
| CIP | Clinical Investigation Protocol |
| CEC | Clinical Events Committee |
| CFDA | China Food and Drug Administration |
| CRF | Case Report Form |
| CRT-D | Cardiac Resynchronization Therapy – Defibrillator |
| CTA | Clinical Trial Agreement |
| CV | Curriculum Vitae |
| DD | Device Deficiency |
| DMC | Data Monitoring Committee |
| EMEA | Europe, the Middle East, and Africa |
| eCRF | Electronic Case Report Form |
| EMI | Electromagnetic interference |
| MEC/IRB/Ethics Board | Ethics Committee |
| FAL | Foreseeable Adverse Event List |
| FDA | Food and Drug Administration |
| GCP | Good Clinical Practice |
| HCU | Health Care Utilization |

| Term | Definition |
|---|---|
| HF | Heart Failure |
| ICD | Implantable Cardioverter Defibrillator |
| ICF | Informed Consent Form |
| ICMJE | International Committee of Medical Journal Editors |
| IDE | Investigation Device Exemption |
| IFU | Instructions For Use |
| IPG | Implantable Pulse Generator |
| ISF | Investigator Site File |
| LAO | Left Anterior Oblique |
| LIA | Lead Integrity Alert |
| LNA | Lead Noise Alert |
| LSE | Lead System Event |
| LV | Left Ventricular |
| MCRD | Monolithic Controlled Release Device |
| MedDRA | Medical Dictionary for Regulatory Activities |
| MR | Magnetic Resonance |
| MRI | Magnetic Resonance Imaging |
| PCT | Pacing Capture Threshold |
| PG | Performance Goal |
| PMA | Premarket Approval |
| PMDA | Pharmaceuticals and Medical Devices Agency |
| Pt/Ir | Platinum - Iridium |
| PVC | Premature Ventricular Complex |
| RA | Right Atrium |
| RV | Right Ventricular/Right Ventricle |
| SADE | Serious Adverse Device Effect |
| SAE | Serious Adverse Event |
| SAP | Statistical Analysis Plan |
| SC | Steering Committee |
| SSI | Significant Safety Issue |
| SSVA | Sustained Shockable Ventricular Arrhythmia |
| UADE | Unanticipated Adverse Device Effect |
| US | United States |
| USADE | Unanticipated Serious Adverse Device Effect |
| VF | Ventricular Fibrillation |
| VT | Ventricular Tachycardia |

## 2. Synopsis

| | |
|---|---|
| **Title** | **L**ead **E**valu**A**tion for **D**efibrillation and **R**eliability (LEADR) |
| **Clinical Study Type** | Prospective, multi-center, single-arm, non-randomized, Bayesian, adaptive study design, pre-market, interventional pivotal clinical study |
| **Product Name** | Model 093000 lead, further referenced as the 'Next Generation ICD Lead' |
| **Sponsor** | **Medtronic, Inc.**<br>8200 Coral Sea Street NE<br>Mounds View, MN 55112<br>United States of America<br>+1 800 328 2518 |
| **Local Sponsor** | **Australia**<br>Medtronic Australasia Pty Ltd<br>2 Alma Road, Macquarie Park<br>NSW, 2113<br>Australia<br>+61 2 9857 9000<br><br>**Canada**<br>Medtronic Canada ULC<br>99 Hereford Street Brampton<br>Ontario, L6Y 0R3 Canada<br>+1 905 460 3800<br><br>**Mainland China**<br>Medtronic (Shanghai) Management Co., Ltd.<br>2106A, 21th Floor, No. 28. Maji Road,<br>China (Shanghai) Pilot Free Trade Zone,<br>200131, Shanghai, P.R. China<br>+86 215 866 9877<br><br>**Europe, Middle East, Africa**<br>Medtronic, Bakken Research Center B.V.<br>Endepolsdomein 5<br>6229 GW Maastricht<br>The Netherlands<br>+31 43 35 66 566<br><br>**Hong Kong**<br>Medtronic Hong Kong Medical Ltd.<br>1104-11, 11/F, Tower 1,<br>The Gateway, Harbour City, Kowloon<br>Hong Kong SAR, China |

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| **European Union Legal Representative of the Sponsor** | Medtronic, Bakken Research Center B.V.<br>Endepolsdomein 5<br>6229 GW Maastricht<br>The Netherlands<br>+31 43 35 66 566 |

<table>
<tr><td>Indication under investigation</td><td>The Next Generation ICD Lead is indicated for the treatment of subjects who have experienced, or are at significant risk of developing, life-threatening ventricular tachyarrhythmias.</td></tr>
<tr><td>Investigation Purpose</td><td>The purpose of this study is to assess the safety and efficacy of the Next Generation ICD Lead.</td></tr>
<tr><td>Product Status</td><td>
<table>
<tr><th>Model Number</th><th>Component (Manufacturer)</th><th>Investigational or Market-released*</th></tr>
<tr><td>093000</td><td>Next Generation ICD lead (Medtronic)</td><td>Investigational in all participating countries</td></tr>
<tr><td>C315</td><td>Delivery Catheter (Medtronic)**</td><td>Market-released in all participating countries</td></tr>
<tr><td>C304</td><td>SelectSite™ Deflectable Catheter System (Medtronic)**</td><td>Market-released in all participating countries except Malaysia where it is considered investigational</td></tr>
<tr><td>6250V / 6250VI</td><td>Attain Command™ + SureValve™ Guide Catheter for Left-Heart Delivery (Medtronic)**</td><td>Market-released in all participating countries</td></tr>
<tr><td>6248V / 6248VI</td><td>Attain Select™ II + SureValve™ Delivery Catheter System (Medtronic)**</td><td>Market-released in all participating countries</td></tr>
</table>
*Market-released catheters will become investigational when used with the Next Generation ICD Lead<br>
**Including accessories as listed in the respective instructions for use (IFU)<br><br>
The catheters will be considered investigational when used with the Next Generation ICD lead at implant. Furthermore, the study will include current and future market approved Medtronic ICD and cardiac resynchronization therapy defibrillator (CRT-D) devices that are Magnetic Resonance (MR) conditional and equipped with SmartShock™ Technology. When applicable, any commercially released right atrial (RA) and left ventricular (LV) lead may also be used.</td></tr>
<tr><td>Primary Objective(s)</td><td>Primary Safety Objective: Demonstrate that the freedom from major complications related to the Next Generation ICD lead at 6 months post-implant exceeds a pre-specified threshold of 90%.<br>The endpoint is defined as a subject’s first occurrence of a major complication related to the Next Generation ICD lead, as determined by an independent Clinical Events Committee (CEC), the event must have occurred within 182 days (inclusive) of the Next Generation ICD lead implant attempt.</td></tr>
</table>

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| | Primary Efficacy Objective: Demonstrate the percentage of patients successfully defibrillated at implant with the Next Generation ICD lead exceeds a pre-specified threshold of 88%.<br><br>The endpoint, defibrillation success, is defined as:<br>• One induced sustained shockable ventricular arrhythmia (SSVA) episode successfully terminated with 18J shock, or<br>• 2 consecutive induced SSVA episodes successfully terminated with 25J shocks |
| **Secondary Objective(s)** | The secondary objective (safety) is to estimate the fracture-free rate of the Next Generation ICD Lead throughout the study duration |
| **Study Design** | The LEADR Clinical Study is a prospective, multi-center, single-arm, non-randomized, Bayesian, adaptive study design, pre-market, interventional pivotal clinical study.<br><br>The expected total 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 18 months to approximately 3 years. Subjects will undergo assessments at baseline, implant, pre-hospital discharge, 3 months, 6 months, and every 6 months thereafter until official study closure. |
| **Sample Size** | The number of enrolled subjects in the study may vary from 500 to 900 subjects depending on the number of fractures observed during the study and on the number of implants as specified in the adaptive design decision rules. Maximum number of subjects enrolled at each site will be capped at 50 (10% of minimum number of enrollments (500)).<br>Additionally, if the sample size is increased by a certain number of patients based on the adaptive study design, the enrollment cap will increase by 10% of the sample size increase for all sites, e.g., if the sample size increases by 100 implant attempts, the enrollment cap for a given site will increase from 50 to 60 patients. If the sample size increases up to 900 enrollments, the enrollment cap will be 90 enrolled subjects per site. For the cohort of the first 150 implanted subjects, a single site cannot contribute more than 20% of the subjects, i.e., the maximum number of subjects implanted at each site will be capped at 30 subjects, to minimize site bias for the stage 1 pre-market report.<br>Simulation studies show that the sample size provides at least 90% power to reject the null hypotheses associated with the primary safety and efficacy |

| | |
|---|---|
| | objectives based on the assumed performance of the Next Generation ICD lead while maintaining a type I error rate of 2.5%. |
| **Inclusion/Exclusion Criteria** | Inclusion Criteria<br>1. Subject meets current clinical practice guidelines for ICD or CRT-D implantation and will undergo one of the following:<br>• de novo Medtronic CRT-D system implant<br>• de novo Medtronic ICD system implant (single or dual chamber)<br>2. Subject has, per local law and requirements, the minimum age for autonomously signing an ICF<br>3. Subject is willing to undergo implant defibrillation testing if requested.<br>4. Subject is geographically stable and willing and able to complete the study procedures and visits for the duration of the follow-up.<br><br>Exclusion Criteria<br>1. Subject is unwilling or unable to personally provide Informed Consent.<br>2. Subject has contraindications for standard RV transvenous lead placement (e.g., mechanical right heart valve).<br>3. Subject is contraindicated for ≤1 mg dexamethasone acetate.<br>4. Subject has a life expectancy of less than 12 months<br>5. Subject is unable to undergo defibrillation testing due to physician judgement or medical conditions such as<br>• Pre-existing or suspected pneumothorax during implant<br>• Current intracardiac left atrial or left ventricular (LV) thrombus<br>• Severe aortic stenosis<br>• Severe proximal three-vessel or left main coronary artery disease without revascularization<br>• Unstable angina<br>• Ejection Fraction less than 25%<br>• Recent stroke or transient ischemic attack (within the last 6 months)<br>• Known inadequate external defibrillation<br>• Any other known medical condition not listed that precludes their participation in the opinion of the investigator<br>6. Subject is enrolled or planning to enroll in a concurrent clinical study that may confound the results of this study, without documented pre-approval from a Medtronic study manager.<br>7. Subject with any exclusion criteria as required by local law (e.g., age or other). |

| | |
|---|---|
| | 8. Pregnant women or breastfeeding women, or women of childbearing potential and who are not on a reliable form of birth regulation method or abstinence<br>9. Subject with an existing pacemaker (including transcatheter pacing system), ICD, or CRT device or leads<br>10. Subject with any evidence of active infection or undergoing treatment for an infection<br>11. Recent (or planned) cardiac surgery or stenting less than 1 month before implant<br>12. End stage renal disease<br>13. Subjects with NYHA IV classification<br>14. Subjects with a transplanted heart<br>15. Subjects with a history of extracted leads<br>16. Subjects with Left Ventricular Assist Device |
| **Study Procedures and Assessments** | Subjects indicated for implantation of a single or dual chamber ICD, or CRT-D according to current ACC/AHA/HRS or ESC guidelines will be recruited and implanted with the Next Generation ICD Lead. Once enrolled, a subject will be assessed at the following visits.<br>• Baseline<br>• Implant<br>• Pre-Hospital Discharge (PHD)<br>• 3 Months<br>• 6 Months<br>• 12 Months<br>• 18 Months<br>• Long-term: Every 6 months thereafter until study closure (24, … Months)<br>• Unscheduled (as they occur)<br>• System Modification (as they occur)<br>• Exit<br><br>Study procedures are outlined in the table below. |

| Study Procedure | Enrollment / Baseline | Implant | PHD | 3/6/12/18 M (in office) | Long-term (post 18 M, remote or in office) | Un-scheduled | System Modification | Study Exit |
|---|---|---|---|---|---|---|---|---|
| Informed Consent | X | | | | | | | |
| Inclusion/Exclusion Assessment | X | | | | | | | |
| Physical Exam, Demographics, Cardiovascular Medical History, Surgical History | X | | | | | | | |
| Physician Lead and Catheter Handling Assessment | | X | | | | | X[3] | |
| System and procedure information | | X | | | | | X | |
| Sensing, Impedance & Pacing Tests | | X | X | X | X | X[1] | X | |
| Defibrillation Testing | | X[2] | | | | | | |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| Fluoroscopy of final lead position (LAO) | | X | | | | | X[3] | |
| Chest Radiographs (AP/PA & Lateral) | | | X | | | | X[3] | |
| Save-to-media/Save Session files | | X | X | X | X | X | X | X |
| Medications | | X | | | | | | |
| AEs (including AEs with fatal outcome), Device Deficiencies, Study Deviations, Lead and Systems Alerts, Lead Systems Events | As they occur | | | | | | | |

1 Optional
2 Required for a minimum of 95 implanted subjects.
3 Only required in case of replacement of the Next Generation ICD lead.
**Note**: In-person visits could be replaced by other options as per required per local regulations in the case of e.g., a pandemic

| | |
|---|---|
| **Safety Assessments** | All adverse events will be collected throughout the study duration, starting at the time the informed consent form is signed. For purposes of reporting, events shall be captured on an adverse event (AE) eCRF.<br><br>All instances of shocks delivered via the Next Generation ICD lead will be considered associated with a reportable AE. Shocks delivered appropriately to treat a ventricular arrhythmia should be noted as treatment delivered within the AE for the ventricular arrythmia(s) experienced. If shocks are delivered inappropriately due to a Next Generation ICD lead issue, the issue should be reported as the underlying system related AE. |
| **Statistics** | Descriptive statistics will be used to summarize baseline demographics, study deviations, system modifications, study exits, and adverse events. Bayesian statistical methods, including 95% credible intervals, will be utilized to evaluate all study objectives. A binomial distribution with Beta prior will be utilized for the primary efficacy objective, while a piecewise exponential distribution with Gamma priors will be utilized for the safety primary objective. If the lower two-sided 95% credible interval bound exceeds the pre-defined performance goal, the objective will be considered met. |

# 3. Introduction

## 3.1. Background

Cardiovascular diseases are responsible for approximately 18 million deaths every year in the world representing ≈30% of all global deaths (1). Sudden cardiac death (SCD) from cardiac arrest accounts for roughly 25% of all cardiovascular deaths (2; 3). The risk of SCD is higher in men than in women and increases with age due to the higher prevalence of coronary artery disease in older age (4). Accordingly, the SCD rate is estimated to range from 1.40 per 100,000 person-years [95% confidence interval (CI) 0.95, 1.98] in women to 6.68 per 100 000 person-years (95% CI 6.24, 7.14) in men (4). SCD in younger individuals has an estimated incidence of 0.46–3.7 events per 100,000 person-years (5; 6) corresponding to a rough estimate of 1,100–9,000 deaths in Europe and 800–6,200 deaths in the US every year (7).

Implantable cardioverter defibrillator (ICD) systems are indicated for patients who are at risk for SCD, have exhibited life threatening tachyarrhythmia, or have compromised heart function associated with heart failure. Despite enhancements in design and technologies, the ICD lead is typically the most vulnerable component of the ICD system. Lower profile leads with the same or greater reliability can provide alternatives for physicians to serve patients with challenging or small anatomies.

Current market approved ICD leads have a diameter that varies from ~6.8 to ~8.6 Fr. (2.27-2.87 mm). Previous efforts to decrease ICD lead diameter to allow for ease of implantation in certain anatomies and to reduce likelihood of venous obstruction and tricuspid valve distortion have resulted in two FDA-mediated recalls (8; 9). The Medtronic Sprint Fidelis (6.6 Fr) was recalled in 2007 due to its high incidence of premature conductor fracture and the St. Jude Medical Riata leads (6.3-7.6 Fr) were recalled in 2011 due to premature insulation failure resulting in externalization of conductor cables (10). These recalls raised the assumption that reducing lead diameter correlates to lead failure (11). However, rather than lead diameter, lead design is believed to be a critical factor for lead performance (9; 12).

Current Medtronic market released transvenous defibrillator leads (Sprint Quattro™ lead portfolio) have a lead body diameter of 8.6 Fr. To address needs for long term reliability, reduced defibrillation lead diameter, and ease of extraction for a defibrillation lead, Medtronic has developed a next generation defibrillation lead: The Model 093000 lead (further referenced as the 'Next Generation ICD lead'). The Next Generation ICD lead is built off the reliable and experienced platform of the Medtronic SelectSecure Model 3830 bradycardia lead (see Figure 1). The SelectSecure Model 3830 lead received CE mark on January 31st, 2003 and FDA approval on August 3rd, 2005. The SelectSecure Model 3830 lead failure rate is 3.1% at 8 years post implant when placed in the right ventricle (13).

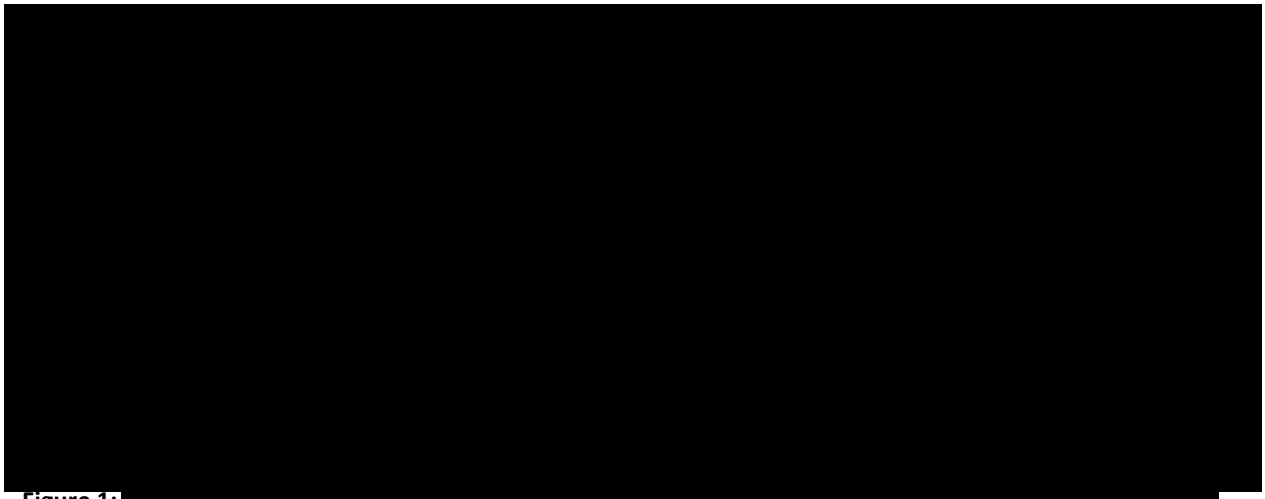


**Figure 1:**

The SelectSecure Model 3830 lead is catheter delivered, as opposed to other pacing and defibrillation leads that are delivered using a stylet. The absence of a stylet lumen allows the center lumen space to be available for a cable from the connector to the tip, enabling a smaller overall diameter and potential for improved flex performance (see Figure 1).

. The right ventricular (RV) coil delivers cardioversion and defibrillation therapies. Pacing and sensing occur between the helix and RV coil electrode. No new materials are being used in the Next Generation ICD lead (see Figure 2). It has the same insulation materials, inner conductor and insulation, helix fixation, and implant procedure as the commercially available SelectSecure Model 3830 bradycardia lead as well as the SI polyimide coating utilized in Medtronic's left heart leads. All components and/or materials have been used for more than 10 years with acceptable field performance.

When this lead is used in a CRT-D system in combination with Medtronic's smallest diameter leads, the cross-sectional lead area is significantly reduced (see Figure 3).



**Figure 2:** [redacted]



**Figure 3:** [redacted]

The components and/or materials in the Next Generation ICD lead have been used for 10+ years in other lead designs with acceptable field performance. This experience gives Medtronic knowledge of possible fracture mechanisms of the Next Generation ICD lead. With a fatigue survival engineering model that utilizes simulations to provide virtual patient modeling of predicted fracture survival, Medtronic has gained confidence in the expected high fatigue reliability of the Next Generation ICD lead. The virtual patient model incorporates current and planned use condition assessments with bench fatigue testing and numerical modeling, that replicate clinical use conditions over ten years of use. The virtual patient model has been validated against clinical data. The model will provide increased precision as to the accuracy of our clinical analysis and will supplement our clinical data to provide a robust prediction of future performance.

## 3.2. Purpose

Medtronic, Inc. is sponsoring the LEADR Clinical Study, a prospective, multi-center, single-arm, non-randomized, Bayesian, adaptive study design, pre-market interventional pivotal clinical study. The purpose of this study is to assess the safety and efficacy of the Next Generation ICD lead.

# 4. Objectives and/or Endpoints

While the primary endpoints are consistent across all geographies, the timing for the evaluation of the safety endpoint does vary between US and non-US countries.

A pre-market application will be submitted in the US following evaluation of the study's primary safety and efficacy objectives.

See section 13.3 for details regarding the analysis of relevant clinical objectives for each data reporting time point.

## 4.1. Primary Objectives

### 4.1.1. Primary Safety Objective

Demonstrate that the freedom from major complications related to the Next Generation ICD lead at 6 months post-implant exceeds a pre-specified threshold of 90%.

**Endpoint Definition**

For an adverse event to meet the endpoint, defined as a subject's first occurrence of a major complication related to the Next Generation ICD lead, as determined by an independent Clinical Events Committee (CEC), the event must have occurred within 182 days (inclusive) of the Next Generation ICD lead implant attempt and be adjudicated by the CEC as being a major complication related (causal relationship) to the Next Generation ICD lead. Major complications are those complications resulting in:

- Death
- Hospitalization (in-patient)
- Lead Fracture
- Prolongation of an existing hospitalization by at least 48 hours
- System Revision (reposition, replacement, explant)

**Rationale**

This composite endpoint was chosen to encompass adverse events related to the Next Generation ICD lead which require invasive intervention (leading to the adverse event being classified as a complication, see section 11.4) as well as severe outcome (in-patient hospitalization, prolongation of an existing hospitalization by at least 48 hours, system revision, death). While events such as lead dislodgments may occur within 3 months, the objective will be analyzed out to 6 months.

### 4.1.2. Primary Efficacy Objective

Demonstrate the percentage of patients successfully defibrillated at implant with the Next Generation ICD lead exceeds a pre-specified threshold of 88%.

**Endpoint Definition**

- Successful implant defibrillation is defined as:
  - One induced sustained shockable ventricular arrhythmia (SSVA) episode successfully terminated with 18J shock, or
  - 2 consecutive induced SSVA episodes successfully terminated with 25J shocks

**Rationale**

While defibrillation testing may not be common practice in all geographies, termination of induced ventricular arrhythmias provides a measure of anticipated device performance in an ambulatory setting, and so in this trial a subset of subjects will undergo defibrillation testing to demonstrate the performance of the lead in terminating ventricular arrhythmias exceeds a pre-specified threshold. The endpoint definition allows for termination of one episode at a lower energy level be tested first to reduce the number of ventricular arrhythmias and device shocks which the subject may experience during testing.

## 4.2. Secondary Objective

The secondary objective (safety) is to estimate the fracture-free rate of the Next Generation ICD lead throughout the study duration.

**Endpoint Definition**

The fracture survival rates will incorporate prospective follow-up and fracture data from the study as well as virtual modeling data (see section 13.7.4).

**Rationale**

While lead fractures occurring acutely will contribute to the primary safety objective, this study allows for estimation of longer term lead fracture rates by way of combining simulated fracture performance for this Next Generation ICD lead from a model developed by Medtronic with prospective clinical data obtained in this trial (see section 13.7 for more details).

## 4.3. [redacted]

[redacted]

## 4.4. Stage 1 Safety Objective

Estimate the 3-month RV lead-related major complication-free rate.

**Endpoint Definition**

The endpoint for the stage 1 safety objective is the same as for the primary safety objective with the exception that the event must occur within 90 days (inclusive) of the Next Generation ICD lead implant attempt.

**Rationale**

The majority of RV lead related complications occur within 3-months of implant attempt. Additionally, electrical performance of cardiac implantable electrical devices is stable within 3-months post-implant. The analysis of this objective will occur when 150 subjects have completed their 3-month visit and include all subjects with a Next Generation ICD lead implant at the time of the analysis. Sample size

calculations (see section 13.4.3) indicate that the 3-month RV lead related major complication free rate can be estimated with a high level of certainty at this analysis timepoint.

# 5. Study Design

The LEADR Clinical Study is a prospective, multi-center, single-arm, non-randomized, Bayesian, adaptive study design, pre-market, interventional pivotal clinical study. The study is expected to be conducted at up to approximately 60 study sites. Participating geographies are expected to include but are not limited to: Australia, China, Hong Kong, Malaysia, Singapore, Japan, EMEA (Europe, Middle East, and Africa), Canada, Puerto Rico, and the United States.

The study has an adaptive design, with decision rules for enrollment and follow-up based upon observed number of fractures at certain points in the study (see section 13.2 for details). The number of enrolled subjects in the study may vary from 500 to 900 subjects depending on the number of fractures observed during the study and on the number of implants. 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 50 (10% of the minimum number of enrollments (500)). Additionally, if the sample size is increased by a certain number of subjects based on the adaptive study design, the enrollment cap will increase by 10% of the sample size increase, e.g., if the sample size increases by 100 implant attempts, the enrollment cap for a given site will increase from 50 to 60 subjects. If the sample size increases up to 900 enrollments, the enrollment cap will be 90 enrolled subjects per site. For the cohort of the first 150 implanted subjects, a single site cannot contribute more than 20% of the subjects, i.e., the maximum number of subjects implanted at each site will be capped at 30 subjects, to minimize site bias for the stage 1 pre-market report.

## 5.1. Duration

The expected total study duration is approximately 3 years from the study's first enrollment, depending on the number of subjects that will be enrolled (see Section 13.2). The first enrollment is projected to occur in April 2021. The enrollment period is expected to take approximately 15 months. Individual subjects may be participating in the study for a period of minimum 18 months to approximately 3 years. The duration of individual subject participation will vary based on timing of study site activation and their enrollment, and the number of subjects to be enrolled which is dependent on the number of fractures observed during the study (see Section 13.2). Subjects will undergo assessments at baseline, implant, pre-hospital discharge, 3 months, 6 months, and every 6 months thereafter until official study closure. Official study closure is defined as when Medtronic and/or applicable regulatory authority agency or governing body requirements have been satisfied per the CIP and/or by a decision by Medtronic or regulatory authority to stop or close the study. Official study closure is anticipated in 2024.

Following closure of the clinical study subjects will be provided with standard medical care by their (personal) physician.

## 5.2. Rationale

The main purpose of the LEADR Clinical Study is to demonstrate safety and efficacy of the Next Generation ICD lead. The performance goals for the primary safety objective and primary efficacy objective (defibrillation testing) are chosen based on the known performance of market-approved Medtronic leads or historical study data and the objectives are designed to show that the Next Generation ICD lead will perform comparably with regard to safety and efficacy to existing leads on the market.

Implantable defibrillators have been available for 40 years with numerous reports on the performance of many defibrillation leads from which to construct performance benchmarks. Therefore, a randomized study is not warranted.

Prior to this study, bench test studies of Next Generation ICD lead prototypes have been performed to evaluate mechanical performance and reliability (further pre-clinical data are described in detail within the Investigator's Brochure). Fatigue test results have shown higher fatigue strength than predecessor leads including the Sprint Quattro ICD and SelectSecure 3830 pacing leads. Expected fatigue use conditions have been assessed in an imaging study of highly active subjects with implanted SelectSecure 3830 leads. Perforation and dislodgement performance is expected to be comparable to SelectSecure 3830 leads based on measurements of tip stiffness and fixation. In addition, components and/or materials used in the Next Generation ICD Lead have been utilized in predicate lead models with proven reliability. Therefore, human use is warranted.

## 5.3. Minimization of Bias

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

- Subject demographics and comorbidities will be collected at baseline to later assess possible characteristics that may influence endpoints
- Data collection requirements and study procedures will be standardized across all geographies
- To ensure a reasonable distribution of data among sites, the maximum number of enrollments per site will be 10% of the final sample size. Additionally, sites will be encouraged to enroll at least 5 subjects.
- For the cohort of the first 150 implanted subjects, a single site cannot contribute more than 20% of the subjects, i.e., the maximum number of subjects implanted at each site will be

capped at 30 subjects, to ensure a reasonable distribution of data among sites for the stage 1 pre-market report.

- A statistical analysis plan will be developed prior to analyzing data which will document all pre-specified analyses and analysis methods
- All study clinicians will be trained on and required to follow the CIP
- All study clinicians and Medtronic personnel will be trained on their respective aspects of the study using standardized training materials
- An independent CEC will be utilized to regularly review and adjudicate reported adverse events
- An Episode Review Committee (ERC) containing independent reviewers will be utilized to review and adjudicate device-treated episodes to determine appropriateness of therapy (shocks and ATP) delivered to subjects
- An independent Data Monitoring Committee (DMC) will be utilized to review accumulating data, help safeguard the interests of study subjects, and monitor the overall conduct of the study
- All sites will use the same version of the CIP and standardized case report forms when possible
- All study investigators will be required to meet 21 CFR Part 54, Financial Disclosure by Clinical Investigators
- Monitoring visits will be conducted to verify adherence to the CIP and source data.

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

### 5.4. Study Oversight

The study will utilize a Steering Committee. The Steering Committee is advising on the scientific content of the study and provides input during study execution. Members may be study site investigators. The purpose of the Steering Committee is to provide unbiased opinions and expertise to the clinical study design and process. The Steering Committee will support the execution of the LEADR Clinical Study and provide guidance, feedback and direction to the study. The members and contact details of the Steering Committee will be provided under separate cover.

## 6. Product Description

### 6.1. General

The study will include current and future market approved Medtronic ICD and cardiac resynchronization therapy defibrillator (CRT-D) devices that are Magnetic Resonance (MR) conditional and equipped with SmartShock™ Technology. A list of compatible ICD and CRT-D devices is included in Appendix J: List of

Compatible ICD and CRT-D Devices. When applicable, any commercially released right atrial (RA) and left ventricular (LV) lead may also be used.

Materials used for the Next Generation ICD lead have been used in previous market released devices. All catheters used in the LEADR Clinical Study are commercially available in all geographies except for Model C304 in Malaysia. Table 2 lists the lead and catheters that will be utilized in the study. An additional list of other accessories will be provided under separate cover when requested. Instructions for use of the devices in this study are provided in their respective manuals.

**Table 2: Product information**

| Model Number | Component (Manufacturer) | Investigational or Market-released* |
|---|---|---|
| 093000 | Next Generation ICD lead (Medtronic) | Investigational in all participating countries |
| C315 | Delivery Catheter (Medtronic)** | Market-released in all participating countries |
| C304 | SelectSite™ Deflectable Catheter System (Medtronic)** | Market-released in all participating countries except Malaysia where it is considered investigational |
| 6250V / 6250VI | Attain Command™ + SureValve™ Guide Catheter for Left-Heart Delivery (Medtronic)** | Market-released in all participating countries |
| 6248V / 6248VI | Attain Select™ II + SureValve™ Delivery Catheter System (Medtronic)** | Market-released in all participating countries |

*Market-released catheters will become investigational when used with the Next Generation ICD Lead

**Including accessories as listed in the respective instructions for use (IFU)

All materials from the investigational Next Generation ICD Lead as well as the market-released catheters, which become investigational upon use, that may directly contact tissues and/or body fluids are presented in Table 3. This table includes the accessories that are packaged with the lead and catheters that are in direct contact with tissues and/or body fluids.

**Table 3: Materials in contact with tissues and/or body fluids**

| Component | Materials |
|---|---|
| Next Generation ICD Lead | [redacted] |

| Component | Materials |
|---|---|
| | [redacted] |
| C315 Delivery Catheter (Medtronic) | [redacted] |
| C304 SelectSite™ Deflectable Catheter System (Medtronic) | [redacted] |
| 6250V / 6250VI Attain Command™ + SureValve™ Guide Catheter for Left Heart Delivery (Medtronic) | [redacted] |

| Component | Materials |
|---|---|
| | [redacted] |
| 6248V / 6248VI Attain Select™ II + SureValve™ Delivery Catheter System (Medtronic) | [redacted] |

The CIP permits a minimum of 500 and up to 900 enrollments based on the adaptive study design which will result in a minimum of 500 and a maximum of 900 subjects undergoing lead implant. Under the assumption that one lead is used per subject, as well as a 15% increase to account for system revisions, dropped product, etc., it is expected that a minimum of 575 to a maximum of 1035 investigational Next Generation ICD Leads may be used during the trial.

### 6.1.1. Next Generation ICD Lead

The investigational Model 093000 Lead (Next Generation ICD lead) (Figure 4) is intended for single use in the right ventricle for pacing, sensing, cardioversion, and defibrillation when a cardiac implantable electronic device is indicated to treat patients who have experienced, or are at significant risk of developing, life-threatening ventricular tachyarrhythmias.

[redacted]

[redacted]

[redacted] The 3830 is one of the most reliable lead designs produced by Medtronic. Lower profile leads with the same or greater reliability can provide alternatives for physicians to serve subjects with challenging or small anatomies.



**Figure 4: The Next Generation ICD Lead**

Table 4 gives a comparison of the SelectSecure Model 3830 and Next Generation ICD leads and includes a rationale for the change in components.

**Table 4: Comparison of the Next Generation ICD and SelectSecure 3830 Leads**

| Component or Attribute | SelectSecure 3830 lead | Next Generation ICD lead | Rationale for difference |
|---|---|---|---|
| **Implant Method** | [redacted] | [redacted] | [redacted] |
| **Lead Connector** | [redacted] | [redacted] | [redacted] |
| **Inner insulation** | [redacted] | [redacted] | [redacted] |
| **Tip Conductor** | [redacted] | [redacted] | [redacted] |

| Component or Attribute | SelectSecure 3830 lead | Next Generation ICD lead | Rationale for difference |
|---|---|---|---|
| **Outer Conductor coil** | [redacted] | [redacted] | [redacted] |
| **Conductor Coil Insulation** | [redacted] | [redacted] | [redacted] |
| **Outer Insulation** | [redacted] | [redacted] | [redacted] |
| **Defibrillation coil** | [redacted] | [redacted] | [redacted] |
| **Distal sleeve** | [redacted] | [redacted] | [redacted] |
| **Steroid** | [redacted] | [redacted] | [redacted] |
| **Helix fixation** | [redacted] | [redacted] | [redacted] |

### 6.1.2. Medtronic Catheters

Any of the market released Medtronic catheters within the families shown in Table 2 may be utilized in the LEADR Clinical Study: C304, C315, 6250V / 6250VI and 6248V / 6248VI. These catheters are market released and commercially available with the exception of Medtronic C304 which is not available in Malaysia. Indications (6250V / 6250VI & 6248V / 6248VI) or compatible lead diameter (C304 & C315) in current versions of the catheter Manuals/Instructions for use (IFU) do not allow using the Next Generation ICD Lead with these catheters (see Table 5). Hence, these catheters will be considered investigational when used with the Next Generation ICD lead in the clinical investigation at the time of implant. The Medtronic slitters, Model 6232ADJ and Model 6230UNI will be utilized with these catheters to assist in removal of catheters during the implant.

**Table 5: Catheter Families**

| | Catheter Family | | | |
|---|---|---|---|---|
| | **C315** | **C304** | **6250V / 6250VI** | **6248V / 6248VI** |
| **Compatible lead diameter** | 4.2 Fr | 4.6 Fr | 6.2 Fr | 5.3 Fr |
| **Indications** | RV indications | RV + LV indications | LV indications | LV indications |

## 6.2. Manufacturer

The investigational Next Generation ICD lead is manufactured by Medtronic. The manufacturing and validation of the lead complies with applicable national regulations.

| Manufacturer Name | Manufacturer Address |
|---|---|
| Medtronic, Inc. | Medtronic, Inc.<br>710 Medtronic Parkway<br>Minneapolis, MN 55432<br>USA<br>www.medtronic.com<br>+1 763 514 4000 |

## 6.3. Packaging

Packaging and labeling for all market approved system components can be found with each package insert. Manuals can be found on http://manuals.medtronic.com. For CE Marked devices and marketed devices in other regions where the study is executed, the labeling is in the appropriate local language. A list of compatible ICD and CRT-D devices is included in Appendix J: List of Compatible ICD and CRT-D Devices.

For investigational products, the language of labeling and clinical manuals will be in English and/or local language where it is required. Investigational products will be clearly labeled indicating they are exclusively for clinical investigation and with the study identifier “Protocol #MDT19004” per local requirements (e.g., in accordance with US law, FDA federal investigational statement is required on US clinical product). Updated catheter manuals may be appended or attached to the CIP, or provided under separate cover if required by local requirements.

In some geographies, the IFUs may be delivered via an alternate format (e.g., CD-ROM format, USB, or electronic format) if allowed within local requirements.

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

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

For Singapore the investigator shall make sure that the required information will be specified on the containers according to local requirements.

## 6.4. Intended Population

The Next Generation ICD Lead is indicated for the treatment of subjects who have experienced, or are at significant risk of developing, life-threatening ventricular tachyarrhythmias. The intended population to receive the Next Generation ICD Lead includes subjects who are indicated for implantation of a single or dual chamber ICD, or CRT-D according to current ACC/AHA/HRS or ESC guidelines.

## 6.5. Equipment

All commercially available equipment will be used according to their approved intended use.

### 6.5.1. Medtronic CareLink (2090) Programmer, Medtronic CareLink Encore 29901 Programmer and Medtronic CareLink Smart Sync™ 24970A device manager

The programmers will be used to provide user interface with which the user can interrogate and program Medtronic approved ICD or CRT-D devices. There are no updates required to programmer software with the investigational Next Generation ICD lead as manual entry for the model can occur. If remote monitoring is needed the Medtronic CareLink system should be utilized. Medtronic may incorporate additional programmers as they receive regulatory approval.

### 6.5.2. Pacing System Analyzer

Medtronic's commercially available Model 2290 or SmartSync 24970A analyzers must be available at each center during the implant procedure to determine acceptable electrical parameters. Medtronic may incorporate additional analyzers as they receive regulatory approval.

### 6.5.3. Site Equipment

Sites are responsible for maintaining and calibrating site equipment used in the course of this study (e.g., radiograph machine and fluoroscope, etc.) as applicable in accordance with established site

practice and local regulation. Records shall be maintained per site and local requirements and provided during monitoring visits and upon request by the Sponsor or regulatory agency.

## 6.6. Product Use

Instructions for use of the Next Generation ICD Lead and catheters are located in the accompanying IFU for each component. Additionally, trained and experienced Medtronic personnel may provide support at implant on-site or remote.

## 6.7. Product Training Requirements

Prior to investigation site activation or subsequent involvement in study activities, Medtronic will provide study training relevant and pertinent to the involvement of personnel conducting study activity, investigator responsibilities, as well as device training (usage and handling of device under investigation). Study-specific training will be conducted and documented prior to site activation or study related activities.

The Next Generation ICD lead implant procedure is to be performed by an investigator who has received training on the implant procedure which might include training on lead handling, implant location and catheter use as determined by previous lead handling experience. All implant training will be documented in the Investigator Site File (ISF).

## 6.8. Product Receipt, Tracking and Accountability

The Next Generation ICD Lead is investigational in all geographies. Catheters referenced in Table 2 are market-released in all geographies except for C304 in Malaysia. All catheters will be considered investigational at the time of lead implant in all geographies. As such the catheters may be labeled for exclusive use in clinical investigations per local requirements. Investigational system components will be distributed to a site only when Medtronic has received all required documentation (not limited to, Ethics Committee or Competent Authority approval, a signed Clinical Trial Agreement (CTA), and documentation of training) and has notified the site of site readiness. Investigational products will be tracked upon receipt or return of components, as well as upon implant or explant of the components.

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 investigational labeled Next Generation ICD Leads and catheters will track disposition upon receipt or return of the components, as well as upon usage, implant or explant of the components.

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

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

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

For Singapore the investigator who has introduced the lead into a subject, shall maintain proper records of the subject and the lead according local requirements.

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

## 6.9. Product Storage

All investigational products must be stored in accordance with their labeling in a secure location at the study site with access limited only to authorized personnel. It is the responsibility of the investigator to correctly handle, store, and track the investigational products maintained at the study site. Investigational products will be used only in the clinical study according to the CIP.

As required per local law, the investigator shall make sure that all investigational devices will be stored in such a manner as to be easily identifiable. If the investigational device cannot be identified, the device shall not be used.

## 6.10. Product Return

All explanted, open but unused, and potentially defective products must 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 device accountability eCRF(s) (note that this is not considered a study deviation). The Device Accountability eCRF must be updated in the event of an explant. Local Medtronic field personnel or representative can be contacted to receive a

Return Mailer Kit. All unused investigational products should be returned to Medtronic or confirmed to be destroyed at site upon study closure at the site.

# 7. Study Site Requirements

## 7.1. Investigator / Investigation Study Site Selection

All investigators must be qualified practitioners and experienced in the diagnosis and treatment of subjects indicated to receive an ICD or CRT-D per local guidelines. All implanting physicians must be trained in the handling and implantation of the Next Generation ICD Lead.

The role of the principal investigator is to implement and manage the day-to-day conduct of the clinical investigation as well as ensure data integrity and the rights, safety and well-being of the subjects involved in the clinical investigation.

The principal investigator shall:

- Be qualified by education, training, and experience to assume responsibility for the proper conduct of the clinical investigation
- Be experienced in the field of application and training in the use of the product and associated procedures
- Disclose potential conflicts of interest, including financial, that interfere with the conduct of the clinical investigation or interpretation of results
- Be able to demonstrate that the proposed investigational study site:
    - Has access to an adequate number of eligible subjects needed within the recruitment period
    - Has one or more qualified investigators, a qualified investigational study site team and adequate facilities for the foreseen duration of the clinical investigation

Study site personnel training will be completed and documented prior to participation in this study.

The following additional criteria were considered when selecting sites for the LEADR Clinical Study:

- Investigator/site expects to have adequate time and resources to conduct the study throughout the duration of the study
- Ability to comply with applicable Ethics Committee and regulatory requirements
- Investigator is not debarred, disqualified, or working under sanctions in applicable regions
- Site has demonstrated experience working (well) with Medtronic clinical research in the last 3 years
- Site can support timely data entry (e.g., coordinator)

- Site has the ability to treat adverse events (AEs) that require surgical intervention in the location where they plan to perform the procedure

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

## 7.2. Study Site Activation

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

- Regulatory authority approval or notification (as required per local law)
- Ethics Committee approval (and voting list, as required by local law) of the current version of the CIP and Informed Consent Form (ICF)
- Fully executed CTA
- Curriculum Vitae (CV) of investigators and key members of the investigation study site team (as required). The signature on the CV must be dated within 3 years prior to the date of activation of the study site.
- Financial disclosure for investigators
- Documentation of delegated tasks
- Documentation of study training
- Additional requirements imposed by local regulations, the EC and RA shall be followed, if appropriate.

Medtronic will provide each study site with written documentation of study site/investigator readiness. This letter must be received prior to performing study-related procedures.

For China, the medical institution shall be filed at the China Food and Drug Administration (CFDA) Filing System.

## 7.3. Role of the Sponsor Representatives

In addition to performing monitoring and auditing activities, sponsor representatives may provide support at the study site, 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
- May provide technical support at study visits (on site or remote) under the supervision of a study investigator, including device programming, but no data entry on eCRFs shall be performed by Medtronic personnel or their representatives at sites

In addition, for this study, sponsor representatives may be authorized by the Principal Investigator to perform the following significant trial related duties:

- Support a study investigator at the Implant Visit (on site or remote) by proactively providing support and feedback during the implant procedure, and may include support in data collection during the implant procedure and device testing.
- Support data collection (on site or remote) during the follow-up visits.

Any data collection completed by Medtronic personnel will be clearly identifiable, it being completed by Medtronic personnel.

# 8. Selection of Subjects

## 8.1. Study Population

Subject of both genders that are of legal age to give Informed Consent per local and national law who have an indication for implantation of a single or dual chamber ICD or a CRT-D according to current ACC/AHA/HRS or ESC guidelines (2; 3; 14; 15) and who meet all inclusion criteria and no exclusion criteria are eligible for enrollment in the study.

## 8.2. Subject Enrollment

Subjects who meet all of the inclusion and none of the exclusion criteria are eligible to be enrolled in this study. When a subject and the principal investigator or authorized designee, as required, have personally signed and dated the ICF, the subject is considered a subject enrolled in the study.

## 8.3. Inclusion Criteria

**Table 6: Subject Inclusion Criteria**

| | Inclusion Criteria | Rationale |
|---|---|---|
| 1. | Subject meets current clinical practice guidelines for implantation of ICD or CRT-D and will undergo one of the following:<br>• *de novo* Medtronic CRT-D system implant<br>• *de novo* Medtronic ICD system implant (single or dual chamber) | Study will be evaluated in the standard subject population that is indicated for the device under evaluation. |
| 2. | Subject has, per local law and requirements, the minimum age for autonomously signing an ICF | Ensure age is appropriate to provide Informed Consent autonomously. |
| 3. | Subject is willing to undergo implant defibrillation testing if requested. | Ensure ascertainment of data required for study objectives. |
| 4. | Subject is geographically stable and willing and able to complete the study procedures and visits for the duration of the follow-up. | Ensure ascertainment of data required for clinical evaluation. |

## 8.4. Exclusion Criteria

**Table 7: Subject Exclusion Criteria**

| | Exclusion Criteria | Rationale |
|---|---|---|
| 1. | Subject is unwilling or unable to personally provide Informed Consent. | Subjects must agree to study participation. Informed Consent by legally authorized representatives are not allowed. |
| 2. | Subject has contraindications for standard RV transvenous lead placement (e.g., mechanical right heart valve). | Standard exclusion criterion to minimize lead displacement and untoward complications associated with mechanical right heart valve |
| 3. | Subject is contraindicated for ≤1 mg dexamethasone acetate. | Ensure subjects contraindicated for ≤1 mg dexamethasone acetate (e.g. due to allergy) are not included in the study. |
| 4. | Subject has a life expectancy of less than 12 months | Standard exclusion criterion to ensure study cohort is expected to survive to the time of primary endpoint evaluation. |
| 5. | For subject undergoing defibrillation testing the following medical conditions exclude them: | Exclude subjects who may be more vulnerable to potential increased risk during the |

| | Exclusion Criteria | Rationale |
|---|---|---|
| | • Pre-existing or suspected pneumothorax during implant<br>• Current intracardiac left atrial or left ventricular (LV) thrombus<br>• Severe aortic stenosis<br>• Severe proximal three-vessel or left main coronary artery disease without revascularization<br>• Unstable angina<br>• Ejection Fraction less than 25%<br>• Recent stroke or transient ischemic attack (within the last 6 months)<br>• Known inadequate external defibrillation<br>• Any other known medical condition not listed that precludes their participation in the opinion of the investigator | evaluation of the clinical study defibrillation protocol. |
| 6. | Subject is enrolled or planning to enroll in a concurrent clinical study that may confound the results of this study, without documented pre-approval from a Medtronic study manager. | Standard exclusion criterion to avoid confounding procedural requirements due to multiple experimental studies. |
| 7. | Subject with any exclusion criteria as required by local law (e.g., age or other). | Standard exclusion criterion to comply with any additional local requirements which may apply. |
| 8. | Pregnant women or breastfeeding women, or women of childbearing potential and who are not on a reliable form of birth regulation method or abstinence[1] | Pregnant women are excluded to avoid harm to the fetus caused by fluoroscopy/x-ray requirements. |
| 9. | Subject with an existing pacemaker (including transcatheter pacing system), ICD, or CRT device or leads | Avoid possible confounding factors (e.g., complications due to changeout procedure). |
| 10. | Subject with any evidence of active infection or undergoing treatment for an infection | Standard exclusion criterion for device implant, to reduce the risk of possible explant, system modification and ongoing |

[1] If required by local law, women of child-bearing potential must undergo a pregnancy test within seven days prior to study procedures

| | Exclusion Criteria | Rationale |
|---|---|---|
| | | complications related to infection which could impact attrition and confound study results. |
| 11. | Recent (or planned) cardiac surgery or stenting less than 1 month before implant | Avoid increased risk of lead damage and infection |
| 12. | End stage renal disease | Avoid impact on subject life expectancy |
| 13. | Subjects with NYHA IV classification | Contraindication for a primary prevention ICD unless a CRT device is implanted. Avoid impact on subject life expectancy. |
| 14. | Subjects with a transplanted heart | Avoid increased complication risk |
| 15. | Subjects with previously extracted leads | Avoid associated events which could confound complication rates |
| 16 | Subjects with Left Ventricular Assist Device | Avoid impact on subject life expectancy, increased complication risk and unexpected interactions with the implanted device |

## 9. Study Procedures

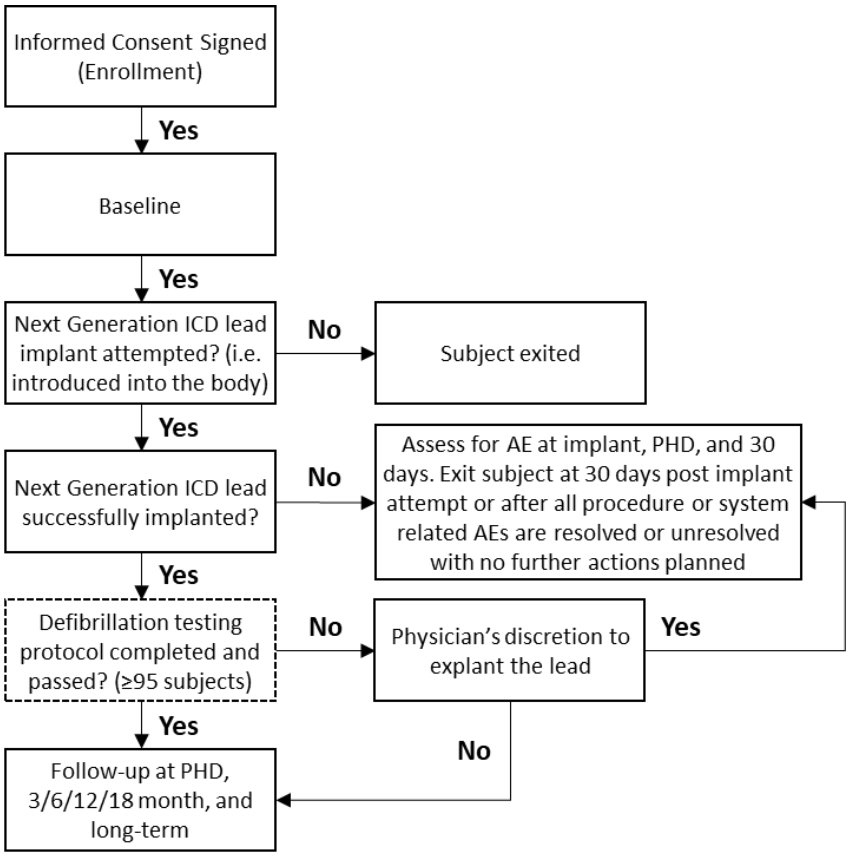



**Figure 5: Overview of the LEADR Clinical Study**

## 9.1. Schedule of Events

Clinical data will be collected at the study visits detailed in Table 8. Data will be collected via eCRFs, Chest X-ray, fluoroscopic cine images, analyzer/programmer printouts, and interrogation files. Post-implant follow-ups apply only to those subjects in whom a Next Generation ICD Lead was successfully implanted. Subjects with an unsuccessful implant will be followed for 30 days or after all procedure or system related AEs are resolved or are unresolved with no further actions planned, whichever occurs later, after which they will exit the study. Subject visits will occur at enrollment, baseline, implant, pre-hospital discharge (PHD), 3-, 6-, 12-, 18-months post-implant and every 6 months thereafter until study closure. Trained Medtronic personnel may assist study personnel during implant and study visits on site or remotely.

**Table 8: Data Collection and Study Procedure Requirements at Subject Visits**

| Study Procedure | Enrollment / Baseline | Implant | PHD | 3/6/12/18 Months (in office) | Long-term (post 18 months, remote or in office) | Un-scheduled | System Modification | Study Exit |
|---|---|---|---|---|---|---|---|---|
| Informed Consent | X | | | | | | | |
| Inclusion/Exclusion Assessment | X | | | | | | | |
| Physical Exam, Demographics, Cardiovascular Medical History, Surgical History | X | | | | | | | |
| Physician Lead and Catheter Handling Assessment | | X | | | | | X[3] | |
| System and procedure information | | X | | | | | X | |
| Sensing, Impedance & Pacing Tests | | X | X | X | X | X[1] | X | |
| Defibrillation Testing | | X[2] | | | | | | |
| Fluoroscopy of final lead position (LAO) | | X | | | | | X[3] | |
| Chest Radiographs (AP/PA & Lateral) | | | X | | | | X[3] | |
| Save-to-media/Save Session files | | X | X | X | X | X | X | X |
| Medications | | X | | | | | | |
| AEs (including AEs with fatal outcome), Device Deficiencies, Study Deviations, Lead and Systems Alerts, Lead Systems Events | As they occur | | | | | | | |

1 Optional

2 Required for a minimum of 95 subjects.

3 Only required in case of replacement of the Next Generation ICD lead.

**Note**: In-person visits could be replaced by other options as per required per local regulations in the case of e.g., a pandemic.

## 9.2. Scheduled Follow-up Visit Windows

After receiving notice of successful implantation/device application, Medtronic will provide the target dates and windows for each visit to the study site. Should a subject miss a visit or the visit fall outside the pre-specified window, a study deviation must be reported, and the original follow-up schedule maintained for subsequent visits.

Data analyses include follow-up visits, regardless of whether the visit occurs within the window. Therefore, a late visit is preferred over a missed visit but must be accompanied by a deviation report. Follow-up visit windows are listed in Table 9 and are based on days post-implant.

**Table 9: Scheduled Follow-up Visit Windows**

| Study Follow-up Visit | Window (Calculated days post-implant) | | |
|---|---|---|---|
| | Window Start (days post-implant) | Target (days post- implant) | Window End (days post- implant) |
| 3 Month | 90 | 90 | 120 |
| 6 Month | 182 | 182 | 210 |
| 12 Month (1 Year) | 335 | 365 | 395 |
| 18 Month | 518 | 548 | 578 |
| 24 Month (2 Year) | 701 | 730 | 760 |
| 30 Month | 883 | 913 | 943 |
| 36 Month (3 Year) | 1066 | 1096 | 1126 |

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

## 9.3. Subject Screening

A screening log is not required for the study. A screening log will be utilized in those geographies where required and implemented per local requirements.

## 9.4. Prior and Concomitant Medications

There are no medication/therapy restrictions in the study unless they are investigational and may confound the study results, in which case, prior approval would be needed from Medtronic.

## 9.5. Subject Consent

Informed Consent is defined as a legally effective documented confirmation of a subject's voluntary agreement to participate in a particular clinical study. This confirmation occurs after information has been given to the subject on all aspects of the clinical study that are relevant to the subject's decision to participate. This process includes obtaining an ICF and an Authorization to Use and Disclose Personal Health Information/Research Authorization/HIPAA/other privacy language as required by law. The ICF and Authorization to Use and Disclose Personal Health Information/Research Authorization/HIPAA/other privacy language as required by law shall be approved by Medtronic and

each study site's Ethics Committee (EC) prior to enrolling subjects. These shall be signed and personally dated by the subject and the Principal Investigator or authorized designee as required.

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

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

Prior to enrollment and initiation of any study-specific procedures, Informed Consent must be obtained from the subject. Likewise, privacy or health information protection regulation may require subjects to sign additional forms to authorize study sites to submit subject information to the study sponsor.

The process of obtaining Informed Consent shall:

- Ensure that the Principal Investigator or an authorized designee conducts the Informed Consent process.
- Include all aspects of the LEADR Clinical Study that are relevant to the subject's decision to participate throughout the clinical study.
- Be conducted without using coercion or undue improper influence on, or inducement of the subject to participate by the investigator or other study site personnel.
- Not waive or appear to waive the subject's legal rights.
- Ensure the ICF and Authorization to Use and Disclose Personal Health Information/Research Authorization/HIPAA/other privacy language, as required by law, are given to the subject in a language the subject is able to read and understand.
- The language used shall be as non-technical as possible and must be understandable to the subject and the impartial witness, where applicable.
- Provide ample time and opportunity for the subject to read and understand the ICF to inquire about details of the study, and to decide whether or not to participate in the study. All questions about the study should be answered to the satisfaction of the subject.
- Be personally signed and personally dated by the subject, acknowledging that their participation in the study is voluntary.
- Be personally signed and personally dated by the Principal Investigator or authorized designee responsible for conducting the Informed Consent process, as required by local law.
- Include any other locally required signatories, such as witnesses, as indicated by country-specific legislations.

- Provide the subject with a copy of the ICF and Authorization to Use and Disclose Personal Health Information/Research Authorization/HIPAA/other privacy language as required by law, and any other written information, signed and dated if required by local law.

If the Informed Consent 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 Informed Consent process shall be documented in the subject's medical chart, regardless of circumstance.

In the event the subject cannot read and/or write, the Informed Consent process shall be obtained through a supervised oral process. An independent and impartial witness must be present during this process. The ICF and any other information must be read aloud to the prospective subject. Whenever possible, the subject shall sign and personally date the ICF. The witness signs and personally dates the ICF attesting that the information was accurately explained and that informed consent was freely given. The original signed ICF must be filed in the hospital/clinical chart and/or with the subject's study documents.

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

In Japan, only the monitor assigned to this study may be able to review the signed ICF as direct access or source data verification.

## 9.6. Enrollment

A subject is considered enrolled when the consent process has been finalized. The date the subject signed the ICF and Data Protection Authorization, as required by law, must be documented in the subject's medical records. A log of all subjects enrolled in the study should be maintained (for those study sites following the ISO 14155:2020). Enrollment can be a stand-alone visit or can occur on the same day as the baseline visit. Medtronic shall be notified (via Enrollment eCRF) as soon as possible to aid in enrollment tracking. Once Informed Consent is obtained, report adverse events, device deficiencies, study deviations, system modifications, and subject exits or deaths as they occur.

## 9.7. Baseline Visit

The baseline visit can be a stand-alone visit or can be performed on the same day, but prior to the implant procedure. The following procedures will be completed/data will be collected at the baseline visit:

- Inclusion/Exclusion Assessment
- Physical Exam: a basic physical exam will be performed, including height and weight
- Patient activity information
- Demographics
- Relevant cardiovascular medical history
- Relevant Surgical History
- Primary indication for ICD or CRT-D implant

If implant does not occur within 30 days of enrollment, verification of all inclusion and all exclusion criteria must be repeated before an implant attempt.

## 9.8. Implant Visit

It is recommended that the implant visit occurs within 30 days of study enrollment. The implant and electrical measurements eCRFs will be used to collect data at implant. The implanted system device must include a Medtronic commercially released MR conditional ICD or CRT-D device equipped with SmartShock™ Technology (see section 6.1). Any commercially released RA and LV lead may also be implanted. The implant of the market released ICD or CRT-D device and market released leads must be performed according to the IFU provided with the applicable device. Off-label use of market released leads is not allowed.

The system is successfully implanted when the ICD or CRT-D device is successfully connected to the leads and the pocket closed. The configuration of the successfully implanted system components will be collected. This will include the serial number of each implanted component and the location of RV lead placement.

### 9.8.1. Medications

The start date and dosage of the following medications will be collected at implant:

- Sotalol
- Amiodarone
- Propafenone
- Flecainide
- Mexiletine
- Dofetilide

- Dronedarone

### 9.8.2. Next Generation ICD Lead Implant Procedure Steps

The Next Generation ICD Lead must be implanted in the Right Ventricle according to the implant instruction in the IFU. For complete information regarding the Next Generation ICD Lead, reference the IFU which is provided under separate cover. Prior to performing the implant procedure, it is important that implanting investigators underwent documented training by Medtronic. The implant eCRF will be used to collect data at implant.

In an event that the Next Generation ICD lead is determined to be not suitable for a patient after the initial lead insertion; the implanting physician must assess the onset of any potential AEs. A second Next Generation ICD lead may only be introduced upon confirmation that no system-related AEs resulted from the first Next Generation ICD lead implant attempt. If a second attempt is unsuccessful no additional Next Generation ICD lead implant attempts are allowed. Any RV lead related AE observed during the initial RV lead attempt prohibits an attempt of a second Next Generation ICD lead.

If the subject does not have a successful Next Generation ICD Lead implant at the conclusion of the initial implant procedure, the subject should be followed until procedure or system related AEs are resolved or are unresolved with no further actions planned, whichever occurs later. If an attempt to implant the Next Generation ICD Lead does not occur, or if the Next Generation ICD Lead cannot be implanted, the reasons why the lead implant was not attempted or attempted but not implanted must be documented on the Study Exit or on the lead implant eCRF respectively. See additional definitions below.

**No Next Generation ICD Lead Attempted (lead not inserted into the body)**

A Next Generation ICD Lead attempt is defined as any time a Next Generation ICD Lead is introduced into the body. Subjects that do not have a Next Generation ICD Lead implant attempted will be exited from the study following their implant procedure unless another Next Generation ICD Lead attempt is scheduled. Adverse events, device deficiencies and deviations must be documented before the subject is exited.

**Next Generation ICD Lead Attempted but Not Implanted**

A Next Generation ICD Lead that is inserted into the body that is not successfully placed will be considered an unsuccessful Next Generation ICD Lead attempt. Note: An unsuccessful implant itself is not considered an AE. AEs occurring during an unsuccessful implant (e.g. dissection, perforation) will be recorded and classified. Subjects with an unsuccessful Next Generation ICD Lead attempt will be followed until procedure or system related AEs have been resolved or are deemed unresolvable with no further action planned.

### 9.8.3. Next Generation ICD Lead Implant Electrical Testing

#### 9.8.3.1. Pacing System Analyzer Testing

Perform the following tests of the implanted Next Generation ICD Lead by connecting the lead to the preferred Pacing System Analyzer via cables (see section 6.5.2).

**Sensing Testing**

Assess the measured R-Wave amplitude as described in the Next Generation ICD Lead IFU. Adjust sensing parameters to avoid T-wave oversensing, P-wave oversensing, or other oversensing. It is recommended that the R-wave amplitude for sensing be greater than or equal to 5mV. If the R-wave amplitude is less than 5mV inspect lead position on fluoroscopy and adjust or reposition as needed.

Record the measured R-Wave amplitude on the CRF, save and print the Sensing Test Report on the Analyzer to PDF or paper and store at site and send a copy to Medtronic.

**Impedance Testing**

Assess the measured pacing lead impedance as described in the Next Generation ICD Lead IFU and record the measured impedance on the CRF. The pacing lead impedance is to measure between 200 – 1500 ohms. If the impedance is outside this range inspect on fluoroscopy for lead position and drape and adjust or reposition as needed.

Save and print the impedance Test Report on the Analyzer to PDF or paper and store at site and send a copy to Medtronic.

**Pacing Testing**

Pacing capture threshold testing will be performed using the Lead Analysis Threshold Test. Adjust the lower rate to an appropriate rate to assess pacing capture. Using a pulse width of 0.4 ms, decrement pacing voltage amplitude starting at 5.0 volts until capture is lost and record the pacing capture threshold on the CRF. Sensitivity settings during pacing capture threshold testing are at the discretion of the physician.

Save and print the Lead Analysis Threshold Test Report on the Analyzer to PDF or paper and store at site. Print final capture threshold report to PDF or paper and send a copy to Medtronic.

#### 9.8.3.2. Device Testing

Perform the following tests of the implanted ICD/CRT-D System after the Next Generation ICD Lead is connected to the ICD/CRT-D device and the device is placed into the pocket. Use a device programmer as mentioned in section 6.5.1. A final (interrogate all) save-to-media/save session file must be collected at the end of the implant visit.

**Sensing Testing**

Perform a R-Wave sensing test. Adjust sensing parameters to avoid T-wave oversensing or P-wave oversensing, or other oversensing. Once configured, perform the Sensing Test. Print the Sensing Test Report on the programmer to PDF or paper and store at site. It is recommended that the R-wave amplitude for sensing be greater than or equal to 5mV. If the R-wave amplitude is less than 5mV, run the EGM on paper and assess R-wave amplitude for greater than or equal to 5mV. Report on the programmer to PDF or paper and store at site. If still less than 5mV, inspect on fluoroscopy and adjust or reposition as needed.

**Impedance Testing**

Ensure the device is programmed “SVC OFF” and the “Pace Polarity” and “Sense Polarity” are set to “Tip to Coil”. Measure subthreshold lead impedance by performing a lead impedance test and the RV impedances will be measured for the following electrode pairs:

- Pacing impedance (RVtip to RVcoil)
- RV Defib impedance

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

**Pacing Testing**

Pacing capture threshold testing will be performed using the Pacing Threshold Test. Adjust the lower rate to an appropriate rate to assess pacing capture. Using a pulse width of 0.4 ms, decrement pacing voltage amplitude until capture is lost and record pacing capture threshold on eCRF. Sensitivity settings during pacing capture threshold testing are at the discretion of the physician.

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

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

### 9.8.4. Induction and Defibrillation Testing

Routine defibrillation testing is not common practice in many geographies. To estimate the Next Generation ICD Lead defibrillation testing success rate, sustained shockable ventricular arrhythmia (SSVA) induction and defibrillation testing is required at implant for at least the first 95 consecutive implanted subjects (see Section 13.6.5). Adjust device programming to minimum sensitivity to assess VF sensing and set defibrillation energies as specified by the defibrillation protocol during SSVA induction and defibrillation testing (see Section 9.8.4.2).

The testing protocol may require up to 6 successful SSVA episodes induced and up to 9 device shocks and up to 3 rescue shocks delivered (Figure 6).

#### 9.8.4.1. General Requirements

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

- 50 Hz Burst Induction
- T-shock (up to 20J)

If a subject cannot be induced using these methods, other methods may be employed at the discretion of the investigator (e.g., EP catheter). The investigator may choose to attempt induction on another day prior to discharge. If the investigator determines the subject cannot be induced, a local Medtronic representative should be contacted.

Ensure a Wavelet template is collected and the detection is enabled prior to induction. Ensure an external transthoracic defibrillation system is present and ready to deliver rescue shocks during defibrillation testing, and at least one set of rescue patches are in place in locations that will not compromise the implanted system defibrillation vector or sterile operating field. If the subject's health is at risk, defibrillation testing should be terminated.

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

Defibrillation testing may continue on a future day, but prior to hospital discharge, if episodes remain within the testing protocol.

Reminder: After each induced SSVA episode, save-to-media/save session files shall be collected (see section 9.12 ). Print the live strip for the duration of each SSVA episode. Retain a copy of the live strip for each episode not recorded by the ICD. If requested, send a copy of the live strip to Medtronic (e.g., a scan). Print the SSVA episode report to PDF or paper and store at the site.

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

#### 9.8.4.2. Testing and Programming Defibrillation Therapy

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

- Single SSVA conversion at 18J, or
- Conversion of two consecutive episodes of SSVA at 25J in final system configuration.

Follow the defibrillation testing as outlined in Figure 6, beginning at Episode 1 (18J). The following requirements shall be observed while conducting defibrillation testing:

- Defibrillation at a given energy will be deemed successful if SSVA is terminated, regardless of whether the shock is delivered manually or automatically by device.
- In one of the two consecutive SSVA episodes, up to two 25J shocks are permitted.
- To achieve final system configuration, changing the position of the device generator and/or the lead, or changing shock polarity is permitted. All previous device electrical measurements must be reassessed if the lead or device generator is modified (see section 9.8.3.2).
- If the device or lead position are altered prior to completing the defibrillation protocol (e.g., position changed as part of troubleshooting), defibrillation success must be demonstrated with the new system configuration. Defibrillation testing will resume at the point in the protocol where the system modification occurred. Additional episodes will not be allowed within the protocol.
- If defibrillation protocol episodes are not exhausted, remaining episodes may be used on a subsequent day (e.g., next day or during the admission) to complete the defibrillation testing protocol
- For the first episode following the 18J therapy or the first 25J episode following a "Troubleshoot System" step in Figure 6, program Rx1 polarity to either A>B or B>A, and program Rx2 polarity the opposite of Rx1 polarity.
- If the episode follows a defibrillation success at 25J, and the previous episode had a defibrillation success with Rx1, program Rx1 to the same polarity of Rx1 in the previous episode and program Rx2 off.
- If the episode follows a defibrillation success at 25J, and the previous episode had a defibrillation success with Rx2, program Rx1 to the same polarity as Rx2 in the previous episode and program Rx2 off.

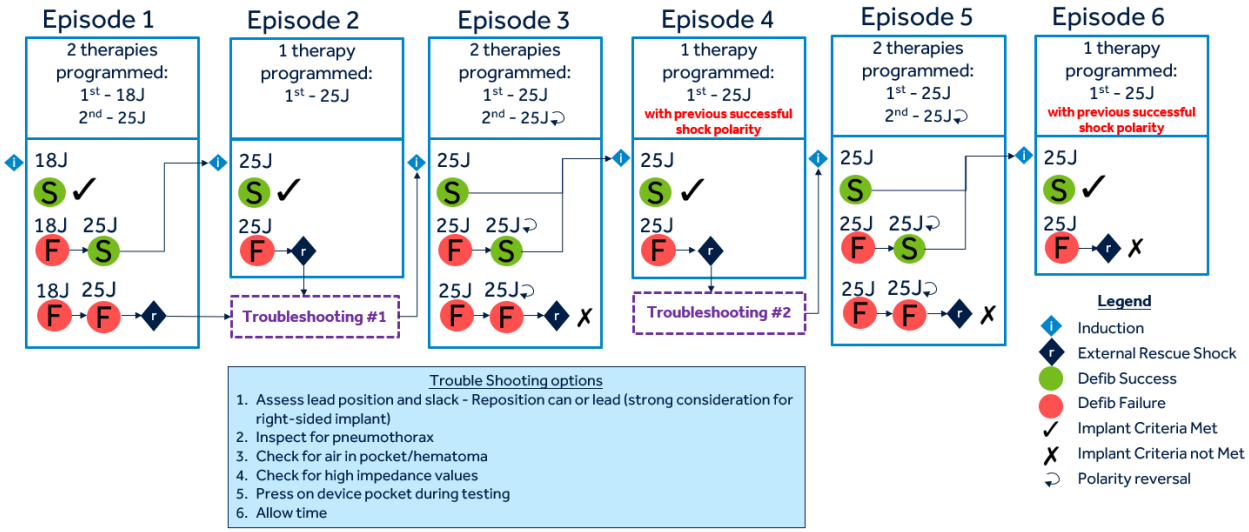



**Figure 6: Diagram outlining the process of SSVA induction and defibrillation testing**

#### 9.8.4.3. Testing and Programming VF Detection

VF detection success at implant is defined as successful VF detection in a single SSVA episode in the RVtip - RVcoil configuration at the minimum sensitivity value of 1.2 mV. VF detection and defibrillation success do not need to be demonstrated on the same episode(s), but each must be demonstrated in the final system configuration.

Follow the VF detection testing as outlined below, beginning at Episode 1. The following requirements shall be observed while conducting VF detection testing:

- The VF detection shall be demonstrated in the RVtip - RVcoil vector with Number of Intervals to Detect (NID) setting of 30/40.
- Begin Testing with VF sensitivity programed to RV tip-RV Coil, 1.2 mV. If VF detection is demonstrated in the RVtip - RVcoil vector on a SSVA with current lead position, the remaining induction attempts may be programmed with a NID setting of 18/24.
- Redetect NID should be programmed to 9/12 when Rx2 is enabled.
- If undersensing of VF occurs at the 1.2 mV, the sensitivity can be adjusted at the investigator's discretion for additional episodes. All setting must be recorded on subsequent attempts.
- Additional inductions beyond those specified in Figure 6 are allowed if needed per medical judgment (e.g., to program sensitivity or to obtain supplementary information on an alternate energy setting).
- If undersensing occurs leading to a manual shock, VF detection must be demonstrated using 30/40 NID using a sensitivity setting at the physician's discretion.
- If the lead position is altered (e.g., as part of troubleshooting), previously demonstrated VF detection success is invalidated and success must be demonstrated with the new system configuration with an NID setting of 30/40.

#### 9.8.4.4. Implant Defibrillation Troubleshooting Recommendations

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

- Check for/resolve pneumothorax (e.g., fluoroscopy)
- Check for lead position, lead slack and dislodgement (e.g., fluoroscopy)
- Change shock polarity
- Check for/resolve high impedance values
- Check for/resolve air in pocket (e.g., flush with saline or antibiotic wash, massage air out of pocket)
- Press on device pocket during testing

- If all of the above measures are exhausted, evaluate the position of the Next Generation ICD Lead and ICD/CRT-D device. If required, consider repositioning of ICD/CRT-D generator or Next Generation ICD Lead.
- Allow time (e.g., next day or during the admission) to minimize transient factors affecting defibrillation success

Note: Troubleshooting attempts after episode 4 (Figure 6) may not leave enough remaining episodes to confirm both defibrillation and VF detection success.

When the device is unable to detect an SSVA following troubleshooting the lead shall be explanted. When the device does detect the SSVA but defibrillation protocol cannot be successfully completed it is at the physician's discretion to explant the lead.

#### 9.8.4.5. Programming Requirements at End of Implant Procedure

At the end of the procedure, VF Detection, VF Therapies and Pacing therapies shall be programmed at the discretion of the investigator however, 'SVC' shall be programmed OFF. It is recommended to program pace and sense polarities to 'Tip to Coil'. Refer to section 9.15 for the required alert programming.

Final device interrogation data via a save-to-media/save session file must be collected (see section 9.12) and must be sent to Medtronic, with a copy being maintained at the site in the subject's file. Device data shall be sent to Medtronic using secure and compliant electronic file transfer services (e.g., Box).

### 9.8.5. Final Lead Placement Data Collection

Following fixation and once the final position of the lead is determined, it is required to collect a LAO fluoroscopic image of the final placement of the lead. Copies of the images will be submitted to Medtronic (see section 9.14) and kept on file at the center.

### 9.8.6. Physician Lead and Catheter Handling Assessment

Following each Next Generation ICD Lead implant attempt, the implanting physician will assess the Next Generation ICD Lead and catheter handling.

### 9.8.7. Subject Exit for Incomplete Implant Visit

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

- The Next Generation ICD Lead is not implanted.
- The subject fails or begins but does not complete the defibrillation protocol and the lead is explanted per physician's discretion.
- Adequate ventricular sensing or SSVA sensing cannot be achieved and the lead is explanted

- Adequate pacing thresholds cannot be achieved and the lead is explanted.

If the subject does not complete the implant visit due to any of the reasons specified above, the Next Generation ICD Lead shall be explanted, and the subject shall be followed and assessed for AEs through 30 days or until procedure or system related AEs have been resolved or are unresolved with no further actions planned, whichever occurs later, at which point the subject can be exited (see Section 9.23). If the subject receives an alternative lead, any AEs related to the alternate lead will be recorded during the course of subject participation but will not be considered related to the Next Generation ICD Lead.

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

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

## 9.9. Pre-Hospital Discharge

The following procedures will be completed and data will be collected during the pre-hospital discharge visit. This should be completed at any time after implant, but prior to discharge.

- Electrical testing of the Next Generation ICD lead (Sensing, Impedance, Pacing test (see section 9.10.3))
- Initial (interrogation) and final (interrogate all) save-to-media/save session files (see section 9.12)
- Lead and System Alert assessment (including Lead Noise Alert, Lead Integrity Alert, Battery Depletion Alert etc. (see section 9.16))
- Lead System Event assessment (see section 9.17)
- Adverse Event assessment
- Device Deficiencies assessment
- Study Deviations
- Chest X-ray Anterior-Posterior/ Posterior-Anterior (AP/PA) and Lateral

## 9.10. Scheduled Follow-up Visits

### 9.10.1. 3-,6-,12- and 18-Month Follow-up Visits

The following procedures will be completed and data will be collected during in office follow-up visit.

- Electrical testing of the Next Generation ICD lead (Sensing, Impedance, Pacing test (see section 9.10.3))
- Initial (interrogation) and final (interrogate all) save-to-media/save session files (see section 9.12)
- Lead and System Alert assessment (including Lead Noise Alert, Lead Integrity Alert, Battery Depletion Alert etc. (see section 9.16))
- Lead System Event assessment (see section 9.17)
- Adverse Event assessment
- Device Deficiencies assessment
- Study Deviations

**Note**: In-person visits could be replaced by other options as per required per local regulations in the case of e.g., a pandemic.

### 9.10.2. Long-term follow-up Visits

Subjects will be followed up at 24 months post-implant and every 6 months thereafter until the study is closed. These scheduled follow-ups are considered “Long-term follow-up visits”. These scheduled follow-ups may be done remotely or in office. For remote visits, CareLink transmissions are required. The following procedures will be completed during these visits:

The following data will be collected at these visits

- Electrical testing of the Next Generation ICD lead (Sensing, Impedance, Pacing test (see section 9.10.3)) (in office visit only)
- Initial (interrogation) and final (interrogate all) save-to-media/save session files (see section 9.12) (in office visit only)
- Lead and System Alert assessment (including Lead Noise Alert, Lead Integrity Alert, Battery Depletion Alert etc. (see section 9.16))
- Lead System Event assessment (see section 9.17)
- Adverse Event assessment
- Device Deficiencies assessment
- Study Deviations

### 9.10.3. Next Generation ICD Lead Electrical Testing

Subjects' medical records shall be made available prior to performing electrical testing. An initial interrogation save-to-media/save session file shall be collected at the beginning of the visit, and a final (interrogate all) save-to-media/save session file shall be collected at the end of the visit (see section 9.12).

#### 9.10.3.1. Sensing Testing

At the PHD, 3-Month, 6-Month, 12-Month, 18-Month and Long-Term follow up visits, perform the Sensing Test. Print the Sensing Test Report to PDF or paper and send a copy of the report to Medtronic. A Sensing Test is not required at Long-Term follow-up visits if the long-term visit is conducted remotely. However, in this case a CareLink transmission is required.

#### 9.10.3.2. Impedance Testing

At the PHD, 3-Month, 6-Month, 12-Month, 18-Month and Long-Term follow up visits, perform the Impedance Test. Print the Impedance Test Report to PDF or paper and send a copy of the report to Medtronic. An Impedance Test is not required at Long-Term follow-up visits if the long-term visit is conducted remotely. However, in this case a CareLink transmission is required.

#### 9.10.3.3. Pacing Capture Threshold Test

At the PHD, 3-Month, 6-Month, 12-Month, 18-Month and Long-Term follow up visits, perform pacing capture threshold testing. The RVtip - RVcoil configuration will be evaluated. Pacing capture will be defined as loss of capture at 0.4 ms pulse width. If post pace oversensing is observed, sensing parameters should be adjusted to eliminate or minimize oversensing. Print the final capture threshold report to PDF or paper and send a copy to Medtronic. A Pacing Capture Threshold Test is not required at Long-Term follow-up visits if the long-term visit is conducted remotely. However, in this case a CareLink transmission is required.

## 9.11. Unscheduled Follow-up Visits

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

If an Unscheduled Visit occurs:

- Document any adverse events and/or device deficiencies on the associated eCRFs, as applicable.

- Where possible, initial (beginning of the visit) and final (end of the visit) device interrogation data should be collected via a save-to-media/save session file (see section 9.12).
- If electrical testing is conducted (see section 9.10.3), print the Testing Reports to PDF or paper and send a copy of the reports to Medtronic.

## 9.12. Device Interrogation and Save-to-Media/Save Session Files

For use with the 2090 Programmer: When a save-to-media file should be collected, a device interrogation (full summary interrogation/interrogate all is best practice) must be performed and saved in a digital format (.pdd) on a USB or other removable electronic media. Save-to-media files shall be sent to Medtronic, with a copy being maintained at the site in the subject's file. It is recommended that data are not cleared during any interrogation.

For use with the SmartSync Programmer: When the interrogated device data from a patient session should be collected, a device interrogation must be performed and the saved to the SmartSync tablet via SAVE SESSION. The save operation generates a PKG file that includes the implantable device data (PDD file) and any reports generated during the session. The saved session data are then exported from the SAVED REPORTS on the SmartSync tablet via SEND TO… of the PKG file. As with the Save-to-media files from the 2090, files shall be sent to Medtronic, with a copy being maintained at the site in the subject's file. It is recommended that data are not cleared during any interrogation.

## 9.13. CareLink Transmissions

For 3-, 6-, 12- and 18-months follow up visits an in-office visit is required. However, for those visits and in those scenarios (e.g. a pandemic) where the hospital/clinic does not allow in-clinic visits it is acceptable to collect and utilize data via CareLink transmissions. A CareLink file collected within a visit window will be considered equivalent to an in-office save-to-media/save session file, but a save-to-media/save session file for in-office visits is preferred. If review of a CareLink transmission results in a subject visit to the study center between scheduled visit windows, an Unscheduled Visit eCRF shall be completed. Long-term follow-up visits may be done remotely or in office. For those remote visits, CareLink transmissions may substitute device interrogations.

## 9.14. Images and recordings

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

## 9.15. Required Alert Programming

Table 10 displays the required programming. All required programming parameters that are different from their nominally set values are in bold. Note that impedance alerts and Number of Shocks Delivered in an Episode are required to be enabled, but the thresholds triggering those alerts are left to the discretion of the clinician.

**Table 10: Programming Requirements**

| Parameter Type | Parameter | Device Model | Required Value | Nominal Value |
|---|---|---|---|---|
| Alerts | RV Lead Integrity Enable | Evera, Cobalt/Crome | ON for Device Tone<br>ON for Patient Home Monitor/Wireless Alert | ON for Device Tone<br>ON for Patient Home Monitor/Wireless Alert |
| | RV Lead Noise Enable | Evera, Cobalt/Crome | ON for Device Tone<br>ON for Patient Home Monitor/Wireless Alert | ON for Device Tone<br>ON for Patient Home Monitor/Wireless Alert |
| | RV Pacing Impedance Enable | Evera, Cobalt/Crome | ON for Device Tone<br>ON for Patient Home Monitor/Wireless Alert | ON for Device Tone<br>ON for Patient Home Monitor/Wireless Alert |
| | RV Defibrillation Impedance Enable | Evera, Cobalt/Crome | ON for Device Tone<br>ON for Patient Home Monitor/Wireless Alert | ON for Device Tone<br>ON for Patient Home Monitor/Wireless Alert |
| | SVC Defibrillation Impedance Enable | Evera, Cobalt/Crome | **OFF for Device Tone**<br>**OFF for Patient Home Monitor**/Wireless Alert | ON for Device Tone<br>ON for Patient Home Monitor/Wireless Alert |
| | All Therapies in a Zone Exhausted for an Episode | Evera | **ON for Device Tone**<br>**ON for Patient Home Monitor** | OFF for Device Tone<br>OFF for Patient Home Monitor |
| | Number of Shocks Delivered in an Episode | Evera, Cobalt/Crome | **Off for Device Tone**<br>**On for Wireless Alert** | Off for Device Tone<br>Off for Wireless Alert |
| Diagnostic | EGM Vectors for CRT-D | Evera, Cobalt/Crome | EGM1: Atip-Aring<br>EGM2: Can-RVcoil<br>**EGM3: RVtip-RVcoil**<br>**LECG: Can-RVcoil (if available)** | EGM1: Atip-Aring<br>EGM2: Can-RVcoil<br>EGM3: RVtip-RVring<br>LECG: dependent on CRT-D model used |
| | EGM vectors for DR | Evera, Cobalt/Crome | EGM1: Atip-Aring<br>EGM2: Can-RVcoil<br>**EGM3: RVtip-RVcoil** | EGM1: Atip-Aring<br>EGM2: Can-RVcoil<br>EGM3: RVtip-RVring |

| | | | | |
|---|---|---|---|---|
| | | | **LECG: Can-RVcoil (if available)** | LECG: dependent on ICD model used |
| | EGM vectors for VR | Evera, Cobalt/Crome | EGM1: RVtip-RVring<br>EGM2: Can-RVcoil<br>EGM3: RVtip-RVcoil<br>**LECG: Can-RVcoil (if available**) | EGM1: RVtip-RVring<br>EGM2: Can-RVcoil<br>EGM3: RVtip-RVcoil<br>LECG: dependent on ICD model used |
| Therapy Delivery | Active Can/SVC Coil | Evera, Cobalt/Crome | **OFF** | ON |

Note: Evera devices include: Evera MRI, Visia AF MRI, Primo MRI, Claria MRI, Amplia MRI, Compia MRI.

## 9.16. Lead and System Alerts

All Lead and System alerts listed in Table 11 must be recorded on the Lead and System alerts eCRF.

**Table 11: Lead and System Alerts**

| Device Model | Programmable Alerts | System Alerts |
|---|---|---|
| Evera, Cobalt/Crome | RV Lead Integrity | Active Can Off without SVC |
| Evera, Cobalt/Crome | RV Lead Noise | |
| Evera, Cobalt/Crome | Number of shocks delivered in an episode (Threshold) | |
| Evera | All Therapies in a Zone Exhausted | |
| Evera, Cobalt/Crome | Lead Impedance Out of Range | |
| Cobalt/Crome | Monitored VT Episode Detected | |
| Cobalt/Crome | Daily VT/VF Episodes | |
| Cobalt/Crome | Capture Management High Threshold | |
| Evera, Cobalt/Crome | Low Battery Voltage RRT | |

Note: Evera devices include: Evera MRI, Visia AF MRI, Primo MRI, Claria MRI, Amplia MRI, Compia MRI.

If the lead and/or system alert is associated with a potential lead event refer to Section 9.17 for data collection requirements. If the lead and/or system alert have a non-RV lead cause (e.g. electromagnetic interference (EMI), myopotential oversensing, R-wave or premature ventricular complex (PVC) double sensing, or T-wave oversensing) the following data is required:

- Perform an initial device interrogation refer to section 9.12 on device interrogation/Save-to-Media/Save Session. Device interrogation data must be sent to Medtronic, with a copy being maintained at the site in the subject's file. Device data shall be sent to Medtronic using secure and compliant electronic file transfer services (e.g., Box).
- Record any actions taken (including programming changes) on the Lead and System alerts eCRF
- Assess for adverse events (e.g. inappropriate shock)
- Perform a final device interrogation refer to section 9.12 on device interrogation/Save-to-Media/Save Reports. Device interrogation data must be sent to Medtronic, with a copy being

maintained at the site in the subject's file. Device data shall be sent to Medtronic using secure and compliant electronic file transfer services (e.g., Box).

## 9.17. Potential Lead System Event

Lead System Events (LSEs) are defined as events affecting the sensing, pacing or defibrillation circuit of the RV defibrillation lead. Examples of LSEs include lead failure, connector issue, dislodgement, perforations, and lead-lead interactions as described in Table 12. If a potential LSE is suspected, detailed data must be obtained to properly adjudicate the event.

**Table 12: Lead Events Definitions**

| Classification | Lead Event Type | Definition |
|---|---|---|
| RV Lead System Event | RV Lead Failure | • An event affecting the sensing, pacing, or defibrillation circuit of the RV defibrillation lead.<br>• Lead Failure: involving either a fracture of one or more conductor filars or an insulation breach surrounding one or more of the conductor(s) has occurred.<br>• RV Lead Fracture: An RV lead fracture is an RV lead failure that results from a fracture of one or more of the RV conductors.<br>• Specific Cause Unknown |
| | RV Lead Dislodgement/Perforation | • Dislodgement: lead detaches from the implant location<br>• Perforation: lead protrudes through the heart |
| | RV Lead-Device Connector Issue | • Connector Issue: a loose set screw or lead pin not completely inserted<br>• Specific cause unknown |
| | RV Lead Placement Issue | • Lead-lead interaction: Mechanical interactions between the ICD sensing electrodes and other intracardiac leads causing additional electrical signals to the sensing electrogram.<br>• P wave oversensing in the right ventricular sensing channel that requires invasive intervention to move the placement of the lead to resolve the issue |

| Classification | Lead Event Type | Definition |
|---|---|---|
| Non RV Lead System Event | Physiologic oversensing | • An event affecting the RV defibrillation lead which creates sensing issues not related to the pacing, sensing or defibrillation circuit.<br>• T-wave oversensing: one additional oversensed event during the T-wave<br>• Myopotentials: oversensing pectoral or diaphragmatic muscle signals.<br>• Non-sustained episode that is a result of oversensing<br>• Intervention for treatment of Non-RV Lead related event<br>• Intervention for treatment of device related events<br>• Specific Cause Unknown |
| | Double R wave counting | • One additional sensed event by the device for a single QRS signal<br>• Increments the SIC to a high value |
| | Electromagnetic Interference (EMI) | • External electrical noise that is not physiological (e.g. ungrounded plumbing) |
| | Electrode myocardial interface | • Gradually increasing impedance trend due to deposits at the electrode myocardial interface |
| | Normal Lead, Physiologic Impedance Variation | • Investigators may program the Lead impedance alerts to lower levels than nominals to have an early alert to impedance fluctuations that are indicators of a lead function anomaly.<br>• Patient bio-impedance may fluctuate in response to medications and health changes. |
| | Normal Lead, Single Anomalous Impedance Value | • Investigators may program the Lead impedance alerts to lower levels than nominals to have an early alert to impedance fluctuations that are indicators of a lead function anomaly.<br>• A single anomalous impedance measurement result is not an indication of lead failure nor enough evidence to initiate invasive intervention. |

| Classification | Lead Event Type | Definition |
|---|---|---|
| Other | Indeterminate Event | • Limited supporting data to classify an event.<br>• Patient follow-up disrupted. |

A common reason for suspecting an LSE is notification (trigger) of RV LIA, RV LNA, and/or impedance out of range alert. All such alerts should be recorded on the Lead and System alerts eCRF along with the investigator's assessment of the alert and any actions taken regardless of whether the event is associated with a reportable adverse event.

At the time an LSE is suspected the following procedures are requested:

- Perform an initial device interrogation and save on a USB flash drive (.pdd) or to SmartSync tablet (.pkg). Device interrogation (save-to-media files) data must be sent to Medtronic, with a copy being maintained at the site in the subject's file. Device data shall be sent to Medtronic using secure and compliant electronic file transfer services (e.g., Box).
- Record any alerts on the Lead and System alerts eCRF
- Review all device data along with any relevant CareLink® reports if the subject uses the CareLink® system. Evaluate the episode history, lead performance trends, short interval count (SIC), and sensing EGMs (for non-physiological noise).
- If a device alert occurred, assess for potential causes. LSEs may include lead failure (fractures or insulation breaches), lead dislodgements, perforations, or connector issues. Non-lead causes may include EMI, myopotential oversensing, lead-to-lead interaction, R-wave or PVC double sensing, or T-wave oversensing.
- Digitally obtain AP/PA and Lateral chest X-rays of the entire lead body.
- Note: If device diagnostics are abnormal and no EGM is available, a DR220 Holter (North East Monitoring, Inc.) may be needed. Contact a Medtronic study representative to obtain a Medtronic DR220 Holter and obtain a Holter recording.
- If a perforation, lead dislodgement, or lead-lead interaction is suspected obtain a digitally acquired X-ray
- If a lead failure or connector issue is suspected, obtain a digitally acquired X-ray image with a magnified view of the header and connection leg(s) inside the connector block (with the view perpendicular to the plane of the header).
- If a high voltage failure is suspected, consider a test shock to confirm lead status; study site standard procedures should be followed.
- Perform a final device interrogation following any intervention (e.g. programming change, test shock, surgery)
- Provide any surgical notes if the system is modified

- Provide all available diagnostic data such as results of any test shocks, digital X-ray images, provocative testing, surgical notes, and device interrogation files to Medtronic via secure and compliant electronic file transfer services (e.g., Box)
- Assess for adverse events

Complete the following eCRFs for each LSE:

- Complete the suspected Lead System Event eCRF
- Adverse event form (if applicable)
- Complete Lead and System alerts eCRF (if applicable)
- System modification form (if a system modification is performed). If the lead is extracted return the lead to its manufacturer.

## 9.18. System Modification

A system modification eCRF form shall be completed in the event the device and/or leads require invasive modification (e.g. generator or lead explant, generator or lead replacement, lead repositioning, etc.) after the subject has been transported out of the procedure room from their initial implant. In the event of a system modification, subjects should remain in the study when possible if a Next Generation RV lead remains in the body and the follow-up visit schedule for the subject will remain unchanged.

Prior to a system modification a save-to-media/save session file (initial, see section 9.12) shall be collected. For a system modification, the following information/activities are required to be collected:

- Modification or replacement/explant date
- Reason for modification
- Information on device or lead modified
- Information on any replacement device(s)
- Evaluate electrical performance
- Reprogramming
- Final device interrogation/save-to-media/save session
- Study deviations (as applicable)
- AEs (as applicable)

**Next Generation ICD Lead Explanted and Not Replaced with a Next Generation ICD Lead**

In cases where a Next Generation ICD lead is explanted the subject will be exited according to section 9.23.

**Next Generation ICD Lead Explanted and Replaced with a Next Generation ICD Lead**

Lead replacement with a new Next Generation ICD lead is allowed within 30 days post initial implant. The same data must be collected as during the initial implant (except DFT testing and medications) visit. The procedure shall be completed by a physician who has undergone Next Generation ICD lead implant procedure training as specified by Medtronic.

All explanted products should be returned to Medtronic for analysis when permissible by local laws and regulations. See Section 6.10 for final product disposition details.

**Next Generation ICD lead capped and Not Replaced with Next Generation ICD Lead**

If the Next Generation ICD lead is capped while the subject is in the study and not replaced with a new Next Generation ICD Lead, subjects will continue to be followed per their original follow-up schedule for safety monitoring until study closure. RV lead electrical testing and interrogation files will not be required at follow-ups for subjects without the full protocol required system implanted.

**Next Generation ICD lead capped and Replaced with Next Generation ICD Lead**

If the Next Generation ICD lead is capped while the subject is in the study and replaced with a new Next Generation ICD Lead within 30 days post initial implant the same data must be collected as during the initial implant (except DFT Testing and medications). The procedure shall be completed by a physician who has undergone Next Generation ICD lead implant procedure training as specified by Medtronic.

**Medtronic CRT-D or ICD device explanted without replacement and the Next Generation ICD Lead remains implanted**

If the Medtronic CRT-D or ICD device is explanted, all attempts should be made to replace it with another Medtronic CRT-D or ICD device. In the event that an explanted Medtronic CRT-D or ICD device cannot be replaced with a new Medtronic CRT-D or ICD device, subjects who still have the Next Generation ICD lead implanted will continue to be followed for safety monitoring in person per their original follow-up schedule until study closure. Events related to the Next Generation ICD lead should be reported. Right ventricular lead electrical testing and interrogation files will not be required at follow-ups for subjects without the full protocol required system implanted.

## 9.19. Assessment of Efficacy

Efficacy of the Next Generation ICD lead with regards to defibrillation testing will be assessed per the primary efficacy objective at implant (see section 13.6). In addition, efficacy with regard to pacing, sensing, and impedance will be assessed using the ancillary objectives (see section 13).

## 9.20. Assessment of Safety

Safety of the Next Generation ICD lead with regard to major complications related to the lead will be assessed by way of the primary safety objective (see section 13.5). All Adverse Events will be collected throughout the study duration, starting at the time of signing the ICF. The fracture-free rate of the Next Generation ICD lead throughout the study will be assessed by way of the secondary safety objective (see section 13.7). The prevalence of adverse events will further be summarized by MedDRA key terms. Additionally, any device deficiencies related to the Next Generation ICD lead or accessories will be collected. Further information on the collection of Adverse Events is discussed in section 11.

## 9.21. Recording Data

This study will be conducted using an electronic data capture system (e.g., Oracle Clinical Remote Data Capture system, or OC RDC). The electronic data capture system, which allows the study sites to enter study data into the sponsor's database over a secure internet connection, will be used to capture study required eCRF information. The Principal Investigator or an individual delegated by the Principal Investigator is responsible for entering data for the study on the eCRFs. The Principal Investigator or Sub-Investigator designee (if allowed by local regulation) is required to approve all data on eCRFs via electronic signature.

Data entered must be traceable to source documents. Source documentation is defined as the first time data appear, and may include original documents, data, and records (e.g., hospital records, recorded data from automated instruments, X-rays, subject files, device data).
In general, eCRFs (or paper copies) may not serve as source documents. Source documentation for data elements not routinely captured in medical records may vary from study site to study site; the study site may use source document worksheets if identified as source documents.

The investigator must ensure the availability of source documents from which the information on the eCRFs was derived. The type and location of source documents should be documented. Where printouts of electronic medical records, are provided as source documents, or where copies of source documents are retained as source documents, those should be certified per good documentation practice such as the signature of the individual making the copy, a statement attesting to the accuracy and completeness of the copy etc.

The source documents must be made available for monitoring or auditing by Medtronic's representative or representatives of the competent authorities and other applicable regulatory agencies.

The eCRF may be considered source for the following data collection elements:

- Implant CRF
    - Lead and catheter handling assessment

- Device Deficiency
  - Date site became aware of event
- Device Accountability Log
  - Next Generation ICD lead (except for date used/explanted)
  - Catheters (except for date used)
- AE eCRF
  - Date study site became aware of event
  - Relatedness
  - Seriousness
- Non-Subject AE
  - Date study site became aware of event
  - Relatedness
  - Seriousness
- Deviations
  - Reason for deviation

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

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

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

## 9.22. Deviation Handling

A study deviation is defined as an event within a study that did not occur according to the CIP. Prior approval by designated personnel at Medtronic is expected in situations where the investigator anticipates, contemplates, or makes a conscious decision to deviate. The investigator is not allowed to deviate from the CIP, except under emergency circumstances to protect the rights, safety and well-being of human subjects in an emergency or in unforeseen situations beyond the investigator's control (e.g., subject failure to attend scheduled follow-up visit, inadvertent loss of data due to computer malfunction, inability to perform required procedures due to subject illness).

For medically justifiable conditions which preempt a subject's ability to complete a study-required procedure, it may be permitted to report only one deviation which will apply to all visits going forward.

This may also apply for other unforeseen situations (e.g., the subject permanently refuses to complete a study required procedure and the data will not contribute to the primary endpoint analysis). However, prior approval from Medtronic is required for such situations.

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

Refer to section 15.8 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 CIP, conduct additional training, analyzing variables, terminate the investigation). Repetitive or serious investigator compliance issues may result in initiation of a corrective and preventative action plan with the investigator and study site, and in some cases, may necessitate suspending enrollment until the problem is resolved or ultimately terminating the investigator's participation in the study. Medtronic will provide study site-specific reports to investigators summarizing information on deviations that occurred at the investigational study 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
- Inclusion/exclusion criteria not met
- Missing required device interrogation files
- Missed Visits

## 9.23. Subject Exit, Withdrawal or Discontinuation

### 9.23.1. Study Exit

A study exit eCRF is required for all subjects. Prior to exiting a subject from the study, it is recommended to follow the subject until all ongoing system and/or procedure related AEs are resolved or unresolved with no further actions planned. Following exit, subjects will continue to receive standard medical care.

Subjects are urged to remain in the study as long as possible but may be exited from the study for any of the following situations:

- Subject has completed the study

- Subject lost to follow-up
- Subject death
- Subject did not meet inclusion or met exclusion criteria
- Subject does not meet inclusion or meets exclusion criteria due to change since initial evaluation, prior to implant
- Subject was not implanted with a Next Generation ICD lead, or the Next Generation ICD lead was explanted without replacement
- Subject did not provide consent
- Subject chooses to exit (e.g., consent withdrawal, relocation to another geographic location)
- Investigator deems withdrawal necessary (e.g., medically justified)

If possible, the following procedures should be performed / data collected at the study exit:

- Reason for exit (this shall be documented on the Study Exit eCRF and in the subject's medical record)
- Final interrogation file (or CareLink transmission) for exits occurring prior to the 18 month visit
- AEs and device deficiencies (as applicable)
- Lead and System Alert Assessment
- Lead System Event Assessment
- Study deviations

Subjects who had undergone an implant attempt and did not have a Next Generation ICD lead implanted or had their Next Generation ICD lead removed without replacement with a Next Generation ICD lead may be exited by phone at the end of 30 days following implant attempt or system removal, or once all system and procedure-related AEs are resolved or are unresolved with no further actions planned, whichever occurs later.

### 9.23.2. Lost to Follow-up

When subjects are lost to follow-up the investigator will make efforts to confirm the vital status of the subject, as described in the informed consent. If allowed per local regulations, a person identified by the subject is informed of the possibility to be contacted by the principal investigator regarding how to reach the subject and the subject's health status and a civil register may be contacted by the principal investigator to inquire about the subject's whereabouts. 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 documented in the subject's medical record with possible reasons of the lost to follow-up. In addition, regulation set forth by the governing EC must be followed. Upon withdrawal from the study, no further study data will be collected, and no additional study visits will occur for the subject. Subjects that are lost to follow-up will not be replaced.

### 9.23.3. Subject Chooses to Exit (i.e. Revokes Consent)

A subject can withdraw from the study at any time. If the subject wishes to exit from the study (i.e. the subject revokes consent), the study site is required to document the reason for exit on the Exit eCRF. In addition, study sites shall follow the regulations set forth by the governing EC. If possible, the following data should be collected prior to subject withdrawal:

- Reason for exit
- Save-to-media/save session
- AEs and device deficiencies (as applicable)
- Study deviations

A withdrawn subject will be treated according to standard of medical care. Subjects will be included in the analyses up to the time that consent was withdrawn, or up to the time that the subject is exited.

### 9.23.4. Investigator Withdraws Subject

No subjects should be withdrawn by investigators unless compelling medical justification is present. It is recommended investigators discuss any withdrawals with Medtronic study team prior to withdrawing subjects. If an Investigator Withdrawal is necessary, the following data should be collected prior to subject withdrawal if possible:

- Reason for subject withdrawal
- Save-to-media/save session (if possible)
- AEs and device deficiencies (as applicable)
- Study deviations

# 10.Risks and Benefits

## 10.1. Potential Risks

Medtronic follows rigorous Quality Assurance and Control procedures throughout the life of a product, from the business analysis phase through development, market release, and post-market surveillance. The risk analysis process for the Next Generation ICD lead is being performed in accordance with EN ISO 14971:2019 and will ensure that the level of risk is as low as possible and acceptation prior to starting the study.

The Next Generation ICD lead is assessed via structured risk analysis process to ensure all potential risks are evaluated and minimized via risk controls. The risk assessment evaluates potential risks associated with lead implant/explant procedure, biological compatibility, therapy delivery, and potential failure modes associated with the finished devices. Risk control strategies for the LEADR study risks were

developed by a cross functional team and in accordance with the Risk Management process. Risk controls are implemented via safety by design, preventive measures, information for safe use. The effectiveness of the risk control measure has been demonstrated via verification and validation activities.

During the course of the study, risks will be continuously monitored, assessed and documented by the investigators. It is the Principal Investigator's decision to assess whether to continue the study at the respective site, should safety-related concerns arise. The risks are reduced as much as possible, with residual risk being documented within the Risk Management Report and disclosed in the ICFs provided to subjects. A summary of the risk analysis and risk assessment will also be listed in the Next Generation ICD Investigator's Brochure.

Standard risks associated with the market released ICD/CRT-D and pacing leads used in this study, an analysis of Adverse Device Effects and a history of modification or recall of device under investigation or equivalent devices are listed in the Instruction for Use Manual or Clinical Manual of those devices.

Possible additional risks for participating in this study include the following (although others are possible):

- The Next Generation ICD lead is investigational and may be no more effective or less effective than a commercially available ICD lead.
- Defibrillation testing at implant could cause tissue, muscle or vascular damage and could potentially lead to death when there is a failure or delay in defibrillation therapy
- Study sponsor may decide to stop the study before getting approval of the investigational product but will continue to monitor subjects for safety.
- There may be other discomforts and risks related to the Next Generation ICD lead and/or this study that are not foreseen at this time.

Possible additional adverse events related to the use of the Next Generation ICD lead include but are not limited to the conditions listed in Table 13.

Note: Implant and usage of the Next Generation ICD lead may result in Adverse Events, which may lead to injury, death, or other serious adverse reactions.

**Table 13: Potential Adverse Events Related to the Use of the Next Generation ICD lead**

| Potential Adverse Events | |
|---|---|
| Allergic reaction | Lead fracture |
| AV fistula | Lethargy |
| Bradyarrhythmia | Loss of capture |
| Cardiac arrest | Loss of pacing |

| Potential Adverse Events | |
|---|---|
| Cardiac inflammation | Mental anguish |
| Cardiac perforation | Nerve damage |
| Cardiac tamponade | Oversensing |
| Cardiac valve damage | Palpitations |
| Discomfort | Pericardial effusion |
| Dislodgement | Pneumothorax |
| Dizziness | Return of cardiac symptoms |
| Dyspnea | Seroma |
| Embolism | Skeletal muscle sensation or twitching |
| Erosion | Skin disorders |
| Extracardiac stimulation | Stroke |
| Excessive fibrotic tissue growth | Superior Vena Cava tear |
| Fever | Syncope |
| Hiccups | Tachyarrhythmia |
| Heart block | Threshold elevation |
| Heart failure decompensation (hospitalization) | Thrombosis |
| Hematoma | Tissue trauma |
| Hemorrhage | Toxic reaction |
| Hemothorax | Tricuspid valve regurgitation |
| Hospitalization | Undersensing |
| Inappropriate shock | Vascular tear |
| Infection | Venous occlusion |
| Insulation failure | Vessel perforation |

Subjects who are pregnant may be at increased risk (e.g., radiation exposure, and other unforeseen risk to the fetus), and are excluded from participation in the study. If a subject becomes pregnant during the study, she must notify the physician immediately. The subject will remain in the study for analysis, but the investigator will avoid any procedures that may be determined harmful.

There may be other discomforts and risks related to the ICD or CRT-D system and the Next Generation ICD lead, and/or this study that are not foreseen at this time. No additional interactions (adverse events) with concomitant medical treatments are expected other than the ones identified in the risk analysis process (see Table 13).

The adverse event collection requirements in this study will ensure that risks associated with the Next Generation ICD lead are adequately monitored.

## 10.2. Risk Minimization

The potential risks associated with the Next Generation ICD lead were identified and have been successfully mitigated (Table 14). Potential risks associated with this study are also minimized by selecting qualified investigators and training study personnel on the CIP and hands-on training. Medtronic has also attempted to minimize risk to subjects implementing a DMC to review safety issues as part of the study.

In addition, investigators will be actively involved in the implantation and follow-up of the subjects implanted with the Next Generation ICD lead.

Risks will be minimized by careful assessment of each subject prior to, during, and after implant of the Next Generation ICD lead. Prior to implant, it is recommended subjects undergo a complete physical evaluation.

Medtronic has further minimized the possibility of risks by performing required laboratory and pre-clinical testing prior to the LEADR Clinical Study, implementing quality control measures into production processes, providing guidelines for subject selection and evaluation, and providing adequate instructions and labeling.

After implantation, subjects in the LEADR Clinical Study will be followed at regular intervals to monitor the condition of the implanted system. At each in person follow-up, the investigator must interrogate the device to verify appropriate function of the Next Generation ICD lead and to evaluate pacing and sensing characteristics and to assess any adverse events.

**Table 14: Potential risks and risk minimization**

| Potential risk | Risk Minimization |
|---|---|
| Procedural risk such as infection, Acute/chronic tissue trauma | • Model 093000 design verification ensuring sterility/cleanliness of the device is maintained including adequate instructions in instruction for use.<br>• Model 093000 design verification and reliability analysis ensuring freedom from failures as specified.<br>• Model 093000 design utilizes materials that have proven biological compatibility and performance as demonstrated by a biocompatibility assessment. |
| Toxicity | • Model 093000 design utilizes materials that have proven biological compatibility and performance as demonstrated by a biocompatibility assessment. |

| Potential risk | Risk Minimization |
|---|---|
| Bio-incompatibility | • Model 093000 design utilizes materials that have proven biological compatibility and performance as demonstrated by a biocompatibility assessment. |
| Bio-instability | • Model 093000 design utilizes materials that have proven biological compatibility and performance as demonstrated by a biocompatibility assessment. |
| Insufficient pacing support | • Model 093000 design verification and reliability analysis ensuring freedom from failure as specified. |
| Arrhythmia induction (pacing during vulnerable period, proarrhythmic pauses, electrical/mechanical stimulus) | • The IFU indicates the lead as magnetic resonance (MR) conditional. In addition, the IFU indicates warning / precautions related to use of lead under magnetic resonance imaging (MRI).<br>• Model 093000 design verification and reliability analysis ensuring freedom from failure under MRI condition as prescribed per IFU.<br>• Model 093000 design verification and reliability analysis ensuring freedom from failure as specified.<br>• Limitation on SSVA induction attempts during defibrillation testing at implant<br>• Induction protocols being used in this protocol are considered methods standard in cardiac medicine<br>• Physician discretion to halt procedure at any time, should a patient's safety be of concern |
| Inadequate tachyarrhythmia therapy | • Model 093000 design verification and reliability analysis ensuring freedom from failure as specified.<br>• Instruction provided in IFU for implant procedure.<br>• The CIP requires that the Model 093000 implant procedure is to be performed by an investigator who has received timely hands-on training on all aspects of the implant procedure.<br>• 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. |

| Potential risk | Risk Minimization |
|---|---|
| | • Exclusion of subjects who may be more vulnerable to potential increased risk during the evaluation of the clinical study defibrillation protocol at implant. |
| Inappropriate high-voltage therapy | • Model 093000 design verification and reliability analysis ensuring freedom from failure as specified<br>• Instruction provided in IFU for implant procedure; specifically, with the specific use in Right ventricle and avoiding exposure to Right atrium, appropriate lead fixation using fluoroscopy.<br>• The CIP requires that the Model 093000 implant procedure is to be performed by an investigator who has received timely hands-on training on all aspects of the implant procedure |
| Extracardiac stimulation | • The IFU indicates the lead as MR conditional. In addition, the IFU indicates warning / precautions related to use of lead under MRI.<br>• Model 093000 design verification and reliability analysis ensuring freedom from failure under MRI condition as prescribed per IFU. |
| Thermal hazard for implanted product heating | • The IFU indicates the lead as MR conditional. In addition, the IFU indicates warning / precautions related to use of lead under MRI.<br>• Model 093000 design verification and reliability analysis ensuring freedom from failure under MRI condition as prescribed per IFU. |
| System revision | • Model 093000 design verification and reliability analysis ensuring freedom from failure as specified<br>• Instruction provided in IFU for implant procedure; specifically, with the usage of anchoring sleeve and lead fixation using helix.<br>• The CIP requires that the Model 093000 implant procedure is to be performed by an investigator who has received timely hands-on training on all aspects of the implant procedure |

| Potential risk | Risk Minimization |
|---|---|
| Product integrity/functionality failure from environment influence | • The IFU indicates the lead as MR conditional. In addition, the IFU indicates warning / precautions related to use of lead under MRI.<br>• Model 093000 design verification and reliability analysis ensuring freedom from failure under MRI condition as prescribed per IFU. |

## 10.3. Potential Benefits

The potential benefits of having the Next Generation ICD lead implanted are consistent with the benefits of ICD/CRT-D therapy and similar market-approved transvenous RV ICD leads, which include:

- Decreased mortality risk for both primary and secondary prevention of SCD
- Appropriate therapy application (cardioversion and defibrillation) via anti-tachycardia pacing (ATP) or shock
- Preservation or improvement of quality of life
- Ease of transvenous implantation
- Lower rate of complications compared to epicardial leads

Additional Next Generation ICD lead specific potential benefits may include:

- Long term reliability
- Ease of extraction
- Potential to target specifically selected sites with the use of a catheter delivery system

The information gained from this study could result in the improved management of other ICD/CRT-D subjects. Additionally, information collected from this study may assist in the design of new product(s)/therapy(ies) and/or instructions for use.

## 10.4. Risk-Benefit Rationale

In addition to the extensive pre-clinical testing, bench testing, computational modeling, a formal risk analysis and risk assessment for the Next Generation ICD lead was performed according to EN ISO 14971:2019 and were used to ensure that the level of risk is acceptable prior to starting clinical investigations. The risk management activities reduced the risks to as low as possible and concluded that the residual risks associated with these hazards are acceptable when weighed against the benefits. The risk management file for the Next Generation ICD lead will be updated periodically for impact to the product's overall residual risk for issues that are identified during the clinical investigational study and following market release, in accordance with EN ISO 14971:2019.

A risk management plan/report establishes the strategy for performing systematic and comprehensive evaluation of potential safety risks associated with the use or performance of the Next Generation ICD lead for the investigational study, in accordance with EN ISO 14971:2019.

The risk management plan describes inputs to the hazard analysis as well as the structure of the hazard analysis activities performed for the Next Generation ICD lead project. The chosen strategy was to perform hazard analysis for the therapy to capture potential risks associated with design inputs and then also perform hazard analyses for the new lead to capture potential risks associated with the design outputs (i.e., finished devices). The hazard analysis leverages the relevant risk analysis inputs such as failure analysis and use error analysis. Furthermore, the hazard analysis captures the pertinent risk controls that serve to minimize the residual risk to as low as possible. This plan may be updated in future phases of the device development lifecycle.

A systematic process is in place to continuously collect, analyze, and assess data relevant to the safety performance of the system during human use. Furthermore, the information gained during the investigational study will be leveraged during the planning and execution of the risk management activities throughout all phases for this project and for commercial release.

In summary, the anticipated risks of the Next Generation ICD lead are consistent with the risks of similar market-approved transvenous RV ICD and catheter-delivered RV pacing leads. The potential benefits of having the Next Generation ICD lead implanted are also consistent with the benefits of ICD therapy and similar market-approved transvenous RV ICD leads. Additionally, due to the smaller lead diameter of the Next Generation ICD lead and the novel catheter delivery in tachycardia application, potential benefits may be seen in long term reliability, the ease of extraction and the potential to target specifically selected sites with the use of a catheter delivery system. The Next Generation ICD lead may also be an alternative for subjects with small vasculature anatomies.

## 10.5. Risk Determination

The LEADR Clinical Study will be conducted under an FDA Investigational Device Exemption (IDE) in compliance with 21 CFR Parts 11, 50, 54, 56 and 812. The study was determined to be significant risk thus an Original IDE is planned for submission to FDA.

# 11.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.

## 11.1. Adverse Events

Adverse Event (AE) definitions are provided in Table 15. All AEs will be collected throughout the study duration, starting at the time the ICF is signed. For purposes of reporting, events shall be captured on an AE eCRF.

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

Reporting of these events to Medtronic will occur on an Adverse Event eCRF, including a description of AE, date of onset of AE, date of awareness of site, treatment, resolution, assessment of both the seriousness and the relatedness to the system and/or procedure. Each AE must be recorded on a separate AE Form. Subject deaths are also required to be reported. Refer to section 11.8 for Subject Death collection and reporting requirements.

Documented pre-existing conditions are not considered AEs unless the nature or severity of the condition has worsened. Worsening may be identified if there is a change in frequency, associated symptoms, or the need for new/additional treatment (e.g., ventricular arrhythmias would be considered worsened if there are new associated symptoms or treatment/shock is warranted). In all geographies, Unavoidable Adverse Events, listed in Table 15 do not need to be reported unless the adverse event worsens or is present outside the stated timeframe post-implant procedure. Adverse events impacting users or other persons are also reportable during the course of the study.

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

## 11.2. Device Deficiencies

The device deficiency definition is provided in Table 15. Device deficiency information will be collected throughout the study and reported to Medtronic. An eCRF should be completed for each device deficiency that did not lead to an Adverse Event.

Note that device deficiencies that result in an adverse device effect (ADE) to the subject should be captured as an AE only. Device deficiencies that did not lead to an AE but could have led to a Serious Adverse Device Effect (SADE) (i.e., if suitable action had not been taken, if intervention had not been made, or if the circumstances had been less fortunate) require immediate reporting.

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

- Damaged components observed out of packaging
- Failed defibrillation testing
- Pervasive/persistent sensing issues occurring outside of device testing

## 11.3. Processing Updates and Resolution

For any changes in status of a previously reported AE (i.e., change in actions taken, change in outcome, change in relatedness), information needs to be updated on, or added to the original AE form. All AEs must be followed until the AE has been resolved, is unresolved with no further actions planned, the subject exits the study, or until study closure, whichever occurs first.

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

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

## 11.4. Adverse Events and Device Deficiency Definitions

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 system.

**Table 15: 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 and whether anticipated or unanticipated.<br>Note 1: This definition includes events related to the investigational medical device or the comparator.<br>Note 2: This definition includes events related to the procedures involved. |

| | |
|---|---|
| | Note 3: For users or other persons, this definition is restricted to events related to investigational medical devices or comparators.<br>(ISO 14155:2020) |
| Adverse Event (AE) – China Definition | The medical events with disadvantages occurred during the clinical trials, no matter whether they are related to investigational medical devices or not.<br>(CFDA Order No.25 Article 93) |
| Adverse Device Effect (ADE)* | AE related to the use of an investigational medical device.<br>Note 1: 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.<br>Note 2: This definition includes any event resulting from use error or from intentional misuse of the investigational medical device. (ISO 14155:2020)<br>*Singapore: Under GN-05-R2.1 section 1.4, this definition is equivalent to the definition of Adverse Effect and Adverse Event. |
| Device Deficiency (DD) | Inadequacy of a medical device with respect to its identity, quality, durability, reliability, usability, safety or performance.<br>Note 1: Device deficiencies include malfunctions, use errors, and inadequacy in the information supplied by the manufacturer including labeling.<br>Note 2: This definition includes device deficiencies related to the investigational medical device.<br>(ISO 14155:2020) |
| Device Deficiency (DD) – China Definition | Any unreasonable risk caused by a medical device in normal use during clinical trial that may endanger human health or life safety, such as label error, quality issues, malfunction and etc.<br><br>(CFDA Order No.25 Article 93) |
| **Relatedness** | |
| Procedure Related | An adverse event that is directly related to the implantation or modification of the system.<br><br>Note: In general, this excludes events that are inherent to any surgical procedure (e.g., anesthesia complications, anticoagulation interruption) as well as indirect subsequent consequences of the procedure (e.g., reaction to pain medication). |
| System Related | An adverse event that results from the presence or performance of any component of the system.<br><br>Device Related: An adverse event that results from the presence or performance (intended or otherwise) of the device.<br><br>RA lead Related: An adverse event that results from the presence or performance (intended or otherwise) of the RA lead.<br><br>RV lead Related: An adverse event that results from the presence or performance (intended or otherwise) of the RV lead.<br><br>LV lead Related: An adverse event that results from the presence or performance (intended or otherwise) of the LV lead. |
| Accessory Related | Implant Tool Related: An adverse event that results from the presence or performance (intended or otherwise) of the implant tool. |

| | |
|---|---|
| | Catheter Related: An adverse event that results from the presence or performance (intended or otherwise) of the catheter.<br><br>Programmer Related: An adverse event that results from the presence or performance (intended or otherwise) of the programmer. |
| Not Related | Relationship to the device or procedures can be excluded when:<br>• The event is not a known side effect of the product category the device belongs to or of similar devices and procedures;<br>• The event has no temporal relationship with the use of the device or the procedures;<br>• 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;<br>• 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;<br>• The event involves a body-site or an organ not expected to be affected by the device or procedure;<br>• 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);<br>• The event does not depend on a false result given by the device used for diagnosis (when applicable);<br>• Harm to the subject are not clearly due to use error;<br>• In order to establish the non-relatedness, not all the criteria listed above might be met at the same time, depending on the type of device/procedures and the event. |
| Unlikely | The relationship with the use of the device seems not relevant and/or the event can be reasonably explained by another cause, but additional information may be obtained. |
| Possible | The relationship with the use of the investigational device is weak but cannot be ruled out completely. Alternative causes are also possible (e.g., an underlying or concurrent illness/ clinical condition or/and an effect of another device, drug or treatment). Cases where relatedness cannot be assessed or no information has been obtained should also be classified as possible. |
| Probable | The relationship with the use of the investigational device seems relevant and/or the event cannot reasonably be explained by another cause, but additional information may be obtained. |
| Causal Relationship | The event is associated with the device or study procedures beyond reasonable doubt when:<br>• The event is a known side effect of the product category the device belongs to or of similar devices and procedures;<br>• The event has a temporal relationship with device use/application or procedures;<br>• 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);<br>• 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);<br>• 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;<br>• Harm to the subject is due to error in use;<br>• The event depends on a false result given by the device used for diagnosis (when applicable);<br>• 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 led to any of the following<br>a) death,<br>b) serious deterioration in the health of the subject, users or other persons as defined by one or more of the following:<br>1) a life-threatening illness or injury, or<br>2) a permanent impairment of a body structure or a body function including chronic diseases, or<br>3) in-patient or prolonged hospitalization, or<br>4) medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function,<br>c) fetal distress, fetal death or a congenital abnormality or birth defect including physical or mental impairment<br><br>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 14155:2020) |
| Serious Adverse Event (SAE) – China Definition | Any untoward medical occurrence during the clinical trial: results in death or serious deterioration in health; life-threatening diseases or injuries; causing permanent damage to the body structure or function; requires hospitalization or prolongation of hospitalization; requires medical operations or intervention for preventing from persistent or significant disability/incapacity; results in fetal distress, fetal death, or congenital anomaly/birth defect.<br>(CFDA Order No.25 Article 93) |
| Serious Adverse Event (SAE) – Singapore Definition* (SAE under HBRA for investigator reporting requirements) | Serious Adverse Event means any untoward medical occurrence as a result of any human biomedical research which<br>- results in or contributes to death;<br>- is life-threatening;<br>- requires in-patient hospitalization or prolongation of existing hospitalization;<br>- results in or contributes to persistent or significant disability or incapacity;<br>- results in or contributes to a congenital anomaly or birth defect; or<br>- results in the transmission of a communicable disease; |

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| | - results in any misidentification or mix-up of any type of human biological material, gamete or embryo<br>- results in such other event as may be prescribed<br><br>For the study involving tissue banking activity, means any untoward occurrence associated with the procurement, testing, processing, storage or distribution of human tissue (including gametes or embryos) intended for human application which<br>- results in or contributes to death;<br>- is life-threatening;<br>- requires in-patient hospitalization or prolongation of existing hospitalization;<br>- results in or contributes to persistent or significant disability or incapacity;<br>- results in the transmission of a communicable disease;<br>- results in any misidentification or mix-up of any type of tissue, gametes or embryo;<br>- results in such other event as may be prescribed<br><br>(section 2 of Human Biomedical Research Act 2015 (Act 29 of 2015, effective on 1 November 2019) & section 8A of Human Biomedical Research Regulations 2017)<br>*Note: the definition is close to SADE defined by ISO14155:2020, with all adverse events result of any human biomedical research included. In addition, the events with the following results are in the scope:<br>- results in the transmission of a communicable disease and<br>- misidentification or mix-up of any type of human biological material, gametes or embryo) |
| Serious Adverse Device Effect (SADE) | ADE that has resulted in any of the consequences characteristic of a SAE.<br>(ISO 14155:2020) |
| Unanticipated Adverse Device Effect (UADE) | Any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death, was not previously identified in a nature, severity, or degree of incidence in the investigational plan or application (including a supplementary plan or application), or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects. (21 CFR 812.3(s)) |
| Unanticipated Serious Adverse Device Effect (USADE) | SADE which by its nature, incidence, severity or outcome has not been identified in the current risk assessment.<br><br>Note 1: Anticipated Serious Adverse Device Effect (ASADE) is an effect which by its nature, incidence, severity or outcome has been identified in the risk assessment.<br>(ISO 14155:2020) |
| Serious Health Threat | Signal from any adverse event or device deficiency that indicates an imminent risk of death or a serious deterioration in the health in subjects, users or other persons, and that requires prompt remedial action for other subjects, users or other persons<br><br>Note 1: This would include events that are of significant and unexpected nature such that they become alarming as a potential serious health hazard or possibility of multiple deaths occurring at short intervals.<br>(ISO 14155:2020) |
| Significant Safety Issue (SSI) - Australia | A safety issue that could adversely affect the safety of participants or materially impact on the continued ethical acceptability or conduct of the trial. |

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| | (NHMRC Safety monitoring and reporting in clinical trials involving therapeutic goods November 2016) |
| Urgent Safety Measure (USM) - Australia | A measure required to be taken in order to eliminate an immediate hazard to a participant's health or safety.<br><br>Note: This type of significant safety issue can be instigated by either the investigator or sponsor and can be implemented before seeking approval from Human Research Ethics Committee (HRECs) or institutions<br>(NHMRC Safety monitoring and reporting in clinical trials involving therapeutic goods November 2016). |
| Event or other occurrence relating to a medical device that represents a serious threat to public health - Singapore | An event or other occurrence relating to a medical device represents a serious threat to public health if one or more of the following occur:<br>• The event or other occurrence is a hazard arising from a systematic failure of the medical device that becomes known to the manufacturer, importer or wholesaler of the medical device<br>• The event or other occurrence may lead to the death of, or a serious injury to, a patient, a user of the medical device or any other person<br>• The probable rate of occurrence of or degree of severity of harm caused by the hazard was not previously known or anticipated by the product owner of the medical device<br>• It becomes necessary for the product owner of the medical device to take prompt action (including the recall of the medical device) to eliminate or reduce the risk of the hazard.<br>(GN-05-R2.1 section 2) |
| Complication | An adverse event that includes the following is considered a complication:<br>• Results in death,<br>• Involves any termination of significant device function (i.e., defibrillation therapy), or<br>• Requires an invasive intervention<br>Non-invasive (21 CFR 812.3(k)): when applied to a diagnostic device or procedure, means one that does not by design or intention:<br>• Penetrate or pierce the skin or mucous membranes of the body, the ocular cavity, or the urethra, or<br>• 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<br>Where "penetrate" means: to pass, extend, pierce, or diffuse into or through something; to enter by overcoming resistance; to gain entrance to, and "pierce" means to force a way into or through something<br><br>Note (FDA): 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.<br><br>Note: Only system or procedure related AEs will be classified as complication (major, minor) or observation. |
| Major complication | A system or procedure-related complication which results in:<br>• Death |

<table>
<tr><td></td><td>

- Lead Fracture
- Hospitalization
- Prolongation of an existing hospitalization by at least 48 hours
- System revision (reposition, replacement, explant)

Note: Only system or procedure related AEs will be classified as complication (major, minor) or observation.
</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).<br><br>Note: Only system or procedure related AEs will be classified as complication (major, minor) or observation.</td></tr>
<tr><td>Observation</td><td>Any AE that is not a complication.<br><br>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 ICF has been signed but before the skin incision during the Model 093000 implant procedure.</td></tr>
<tr><td>During Implant Procedure</td><td>Occurs during the Model 093000 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 Model 093000 implant procedure.</td></tr>
<tr><td colspan="2">Other</td></tr>
<tr><td>Unavoidable Adverse Event</td><td>An AE inherent to a surgical procedure that is expected to occur in all subjects for a projected duration according to the Investigator’s opinion, including, but not limited to:
<table>
<tr><th>Event Description</th><th>Timeframe (hours) from the Surgical Procedure</th></tr>
<tr><td>Anesthesia related nausea / vomiting</td><td>24</td></tr>
<tr><td>Low-grade fever (oral temperature >98.6°F (>37°C) but <100.4°F (<38.0°C))</td><td>48</td></tr>
<tr><td>Pocket site / Incisional pain</td><td>72</td></tr>
<tr><td>Mild to moderate bruising / ecchymosis</td><td>168</td></tr>
<tr><td>Sleep problems (insomnia)</td><td>72</td></tr>
<tr><td>Back pain related to laying on table</td><td>72</td></tr>
<tr><td>Shoulder pain/discomfort/stiffness related to shoulder immobilization during procedure</td><td>72</td></tr>
</table>
</td></tr>
<tr><td>Hospitalization</td><td>A therapeutic inpatient hospitalization (excludes observation unit, emergency room and outpatient visits) lasting greater than or equal to 24 hours.</td></tr>
</table>

## 11.5. Adverse Event and Device Deficiency Classification

All adverse events and device deficiencies will be reviewed by a Medtronic representative. AEs will be classified according to the definitions provided in section 11.4. For the purposes of the clinical report, Medtronic will classify each AE according to ISO 14155:2020.

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

Regulatory reporting of AEs and device deficiencies that could have led to a SADE will be completed according to local regulatory requirements. Refer to Table 17 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 Events, refer to Appendix E: Foreseeable Adverse Event List. The Foreseeable Adverse Event List consists of observed adverse device effects in similar Medtronic studies, adverse events reported in published literature and other special considerations. An evaluation of potentially anticipated events, adverse device effects observed in previous clinical studies, and reported events in literature may be used in combination with device labeling, current event reporting information, and other published data to assess if an adverse event is unexpected.

AEs and Deaths will be classified according to the standard definitions as outlined in Table 16.

**Table 16: 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, RA Lead, RV Lead, LV Lead, Catheter, Implant Tool, Programmer |
| | Sponsor | Procedure, Device, RA Lead, RV Lead, LV Lead, Catheter, Implant Tool, Programmer |
| Seriousness | Investigator | SAE, Device Deficiency with SADE potential |
| | Sponsor | SAE, UADE/USADE, Complication or Observation (for all system or procedure related adverse events), Device Deficiency with SADE potential |
| Diagnosis | Investigator | Based on presenting signs and symptoms and other supporting data |

| What is classified | Who classifies | Classification Parameters |
|---|---|---|
| | Sponsor | MedDRA term assigned based on the data provided by Investigator |
| Death Classification | Investigator | Sudden Cardiac, Non-sudden Cardiac, Non-Cardiac, Unknown |

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

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

## 11.6. Adverse Event and Device Deficiency Reporting Requirements

AEs and device deficiencies will be reported according to local regulatory requirements. In countries following EU MDR 2017/745, AEs will be reported according to EU MDR 2017/745 Art. 80(2) and Medical Device Coordination Group (MDCG) 2020-10/1 guidance. It is the responsibility of the investigator to abide by the AE or device deficiency reporting requirements stipulated by local law and the study site's Ethics Committee. Reporting requirements in Table 17 have been summarized at the time of CIP creation; however, changes may occur during the course of the study. Updates may be provided under separate cover and it is the investigator's responsibility to comply with current local regulatory and institutional reporting requirements.

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

**Table 17: Adverse Event and Device Deficiency Reporting Requirements**

| Serious Adverse Events (SAEs) | |
|---|---|
| **Investigator shall submit to:** | |
| Medtronic | **Australia:** Without unjustified delay. (The National Health and Medical Research Council (NHMRC) Safety monitoring and reporting in clinical trials involving therapeutic goods November 2016 section C.2.b)<br>**China:** Immediately within 24 hours (CFDA Order No.25 Article 71) |

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| | **Europe:** To the sponsor immediately, but not later than 3 calendar days after investigational site study personnel's awareness of the event, including new information in relation to an already reported event. (MDCG 2020-10/1 or MEDDEV 2.7/3 as applicable)<br>**Japan:** Immediately (no later than 72 hours) (Japan GCP Article 68)<br>**All geographies:** Submit per local reporting requirements |
| Ethics Committee | **All geographies:** Submit per local reporting requirements |
| Regulatory authorities | **All geographies:** Submit per local reporting requirements |
| Head of Medical Institution (HOMI) | **Japan**: Immediately (Japan GCP Article 68) |
| GCP Office | **China**: Submit to GCP office per local reporting requirement. |
| **Sponsor shall submit to:** | |
| Investigators | **China:** Submit to other clinical trial institutions and investigators within 5 working days of first acknowledge (CFDA Order No.25 Article 54), only applicable for the events occur in China<br>**Japan:** Annually (Japan GCP Article 28)<br>**All geographies:** Submit per local reporting requirements |
| Regulatory authorities | **China:** Within 5 working days upon being informed (CFDA Order No.25 Article 54)<br>**Europe:**<br>**a) countries following EU MDR:** Any device and/or procedure related SAE no later than 7 calendar days after awareness; Report immediately, but no later than 2 calendar days after awareness by sponsor for any device and/or procedure related SAE which indicates an imminent risk of death, serious injury, or serious illness and that requires prompt remedial action for other patients/subjects, users or other persons or a new finding to it (occurred in the study under same CIP). (EU MDR 2017/745)<br>**b) Other countries in Europe:** No later than 7 calendar days after awareness; Report immediately, but no later than 2 calendar days after awareness by sponsor for any SAE which indicates an imminent risk of death, serious injury, or serious illness and that requires prompt remedial action for other patients/subjects, users or other persons or a new finding to it (occurred in the study under same CIP).<br>**Japan:** Annually (Enforcement Regulation of the PMDL Article 274- 2)<br>**Malaysia:** Within 48 hours of the occurrence of awareness. (NOTIFICATION OF EXEMPTION FROM REGISTRATION OF MEDICAL DEVICES FOR THE PURPOSE OF CLINICAL RESEARCH OR PERFORMANCE EVALUATION (MDA/GD/0016))<br>**All geographies**: Submit per local reporting requirements |
| Ethics Committee | **All geographies:** Submit per local reporting requirements |
| HOMI | **Japan:** Annually (Japan GCP Article 28) |
| **Adverse Device Effects (ADEs)** | |
| **Investigator shall submit to:** | |
| Medtronic | **All geographies:** Immediately after the investigator learns of the event or of new information in relation to an already reported event. |
| RA | **All geographies:** Submit to RA per local reporting requirement |
| EC | **All geographies:** Submit to EC per local reporting requirement. |
| **Sponsor shall submit to:** | |
| RA | **All geographies:** Submit to RA per local reporting requirement. |
| EC | **All geographies:** Submit to EC per local reporting requirement. |
| Investigators | **All geographies:** Submit per local reporting requirement. |
| **Serious Adverse Device Effects (SADEs)** | |
| **Investigator shall submit to:** | |

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| Medtronic | **Australia:** Without unjustified delay. (NHMRC Safety monitoring and reporting in clinical trials involving therapeutic goods November 2016 section C.2.b)<br>**Canada:** SADEs on the patient, the user or any other person must be reported to the regulator and to the Sponsor within 72 hours after it comes to the attention of the qualified investigator.<br>**Japan:** Immediately (no later than 72 hours) (Japan GCP Article 68)<br>**All geographies:** Submit per local reporting requirements |
| Ethics Committee | **All geographies:** Submit per local reporting requirements |
| Regulatory authorities | **Canada:** SADEs on the patient, the user or any other person must be reported to the regulator and to the Sponsor within 72 hours after it comes to the attention of the qualified investigator.<br>**All geographies:** Submit per local reporting requirements |
| HOMI | **Japan:** Immediately (Japan GCP Article 68) |
| Institution | **Singapore**: Submit to research institution per local reporting requirement. |
| **Sponsor shall submit to:** | |
| Investigators | **Japan:** Annually (Japan GCP Article 28)<br>**All geographies:** Submit per local reporting requirements |
| Regulatory authorities | **Canada:** As soon as possible to meet regulatory reporting requirements within 10 days after the date the sponsor becomes aware. For SADE's occurring outside Canada requiring corrective action or imposed by local regulatory authorities, the incident must be reported to Health Canada as soon as possible after either Medtronic has reported to the local regulatory authority or a corrective action has been imposed by the local regulatory authority.<br>**Singapore:** All SADEs should be reported immediately and not later than 10 calendar days (GN-05-R2.1 section 4)<br>**Japan:** [Life threatening or death] Individual reporting within 15 calendar days after awareness, and [All SADEs] Annually (Enforcement Regulation of the PMDL Article 274- 2)<br>**All geographies:** Submit per local reporting requirements |
| Ethics Committee | **All geographies:** Submit per local reporting requirements |
| HOMI | **Japan:** Annually (Japan GCP Article 28) |
| **Unanticipated Adverse Device Effects (UADEs) and Unanticipated Serious Adverse Device Effects (USADEs)** | |
| **Investigator shall submit to:** | |
| Medtronic | **Canada:** USADEs on the patient, the user or any other person must be reported to the regulator and to the Sponsor within 72 hours after it comes to the attention of the qualified investigator.<br>**US and Puerto Rico:** An investigator shall submit to the sponsor and to the reviewing IRB a report of any UADE occurring during an investigation as soon as possible, but in no event later than 10 working days after the investigator first learns of the effect. (21 CFR 812.150(a))<br>**Europe:** To the sponsor immediately, but not later than 3 calendar days after investigational site study personnel's awareness of the event, including new information in relation to an already reported event. (MDCG 2020-10/1 or MEDDEV 2.7/3 as applicable)<br>**Japan:** Immediately (no later than 72 hours) (Japan GCP Article 68)<br>**All geographies:** Submit per local reporting requirements |
| Regulatory Authority | **Canada:** USADEs on the patient, the user or any other person must be reported to the regulator and to the Sponsor within 72 hours after it comes to the attention of the qualified investigator.<br>**All geographies:** Submit per local reporting requirements |
| Ethics Committee | **Australia:** Report USADE to their institution without undue delay and no later than 72 hours of the Principal Investigator becoming aware of the event. (NHMRC Safety monitoring and reporting in clinical trials involving therapeutic goods November 2016 section C.2.g)<br>**US and Puerto Rico:** An investigator shall submit to the sponsor and to the reviewing IRB a report of any UADE occurring during an investigation as soon as possible, but in no event later than 10 working days after the investigator first learns of the effect. (21 CFR 812.150(a))<br>**All geographies:** Submit per local reporting requirements |

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| Institution | **Australia:** Report USADE to their institution without undue delay and no later than 72 hours of the Principal Investigator becoming aware of the event. (NHMRC Safety monitoring and reporting in clinical trials involving therapeutic goods November 2016 section C.2.g)<br>**Singapore**: Submit to research institution per local reporting requirement. |
| HOMI | **Japan:** Immediately (Japan GCP Article 68) |
| **Sponsor shall submit to:** | |
| Investigator | **US and Puerto Rico:** Notification as soon as possible, but not later than 10 working days after the sponsor first learns of the effect. (21 CFR 812.150(b))<br>**Japan:** Immediately (Japan GCP Article 28)<br>**All geographies:** Submit per local reporting requirements |
| Regulatory authorities | **Australia:** Fatal or life-threatening Australian USADE – No later than 7 calendar days after being made aware of the case with any follow up information within a further 8 calendar days. Other Australian USADEs- No later than 15 calendar days after being made aware of the case. (NHMRC Safety monitoring and reporting in clinical trials involving therapeutic goods November 2016 section C.1.f)<br>**Canada:** As soon as possible to meet regulatory reporting requirements within 10 days after the date the sponsor becomes aware. For USADEs occurring outside Canada requiring corrective action or imposed by local regulatory authorities, the incident must be reported to Health Canada as soon as possible after either Medtronic has reported to the local regulatory authority or a corrective action has been imposed by the local regulatory authority.<br>**Japan:** [Life-threatening or death] Individual reporting within 7 calendar days after awareness, [Non-life threatening or death] Individual reporting within 15 calendar days after awareness, and [All USADE] Annually. (Enforcement Regulation of PMDL Article 274-2)<br>**Singapore:** All USADEs should be reported immediately and not later than 10 calendar days (GN-05-R2.1 section 4)<br>**US and Puerto Rico:** Notification as soon as possible to FDA, but not later than 10 working days after the sponsor first receives notice of the effect. (21 CFR 812.150(b))<br>**All geographies:** Submit per local reporting requirements |
| Ethics Committee | **US and Puerto Rico:** Notification as soon as possible, but not later than 10 working days after the sponsor first learns of the effect. (21 CFR 812.150(b))<br>**All geographies:** Submit per local reporting requirements |
| HOMI | **Japan:** Immediately (Japan GCP Article 28) |
| **Device Deficiencies with SADE potential** | |
| **Investigator shall submit to:** | |
| Medtronic | **Australia:** Without unjustified delay. (NHMRC Safety monitoring and reporting in clinical trials involving therapeutic goods November 2016 section C.2.b)<br>**Canada:** DDs that have resulted in any of the consequences characteristic of an SAE on the patient, the user or any other person or could do so were it to reoccur must be reported to the regulator and the Sponsor within 72 hours after it comes to the attention of the qualified investigator.<br>**Europe**: To the sponsor immediately, but not later than 3 calendar days after investigational site study personnel's awareness of the event, including new information in relation to an already reported event. (MDCG 2020-10/1 or MEDDEV 2.7/3 as applicable)<br>**Japan:** Immediately (no later than 72 hours) (Japan GCP Article 68)<br>**All geographies:** Submit per local reporting requirements |
| Regulatory authorities | **Canada:** DDs that have resulted in any of the consequences characteristic of an SAE on the patient, the user or any other person or could do so were it to reoccur must be reported to the regulator and the Sponsor within 72 hours after it comes to the attention of the qualified investigator.<br>**All geographies:** Submit per local reporting requirements |
| Ethics Committee | **All geographies:** Submit per local reporting requirements |

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| HOMI | **Japan:** Immediately (Japan GCP Article 68) |
| **Sponsor shall submit to:** | |
| Investigator | **Japan:** Immediately per the direction of Pharmaceuticals and Medical Devices Agency (PMDA) and/or annually (Japan GCP Article 28)<br>**China:** Submit to other clinical trial institutions and investigators within 5 working days of first acknowledge (CFDA Order No.25 Article 54), only applicable for the events occur in China<br>**All geographies:** Submit per local reporting requirements |
| Regulatory authorities | **Canada:** As soon as possible to meet regulatory reporting requirements within 30 days after the date the sponsor becomes aware. For Device Deficiencies occurring outside Canada requiring corrective action or imposed by local regulatory authorities, the incident must be reported to Health Canada as soon as possible after either Medtronic has reported to the local regulatory authority or a corrective action has been imposed by the local regulatory authority.<br>**China:** Within 5 working days upon being informed (CFDA Order No.25 Article 54)<br>**Europe:**<br>**a) Countries following EU MDR**: No later than 7 calendar days after awareness; Report immediately, but no later than 2 calendar days after awareness by sponsor for any SAE and/or DD that may have led to a SADE which indicates an imminent risk of death, serious injury, or serious illness and that requires prompt remedial action for other patients/subjects, users or other persons or a new finding to it (occurred in the study under same CIP).<br>**b) Other countries in Europe:** No later than 7 calendar days after awareness; Report immediately, but no later than 2 calendar days after awareness by sponsor for any DD that may have led to a SADE which indicates an imminent risk of death, serious injury, or serious illness and that requires prompt remedial action for other patients/subjects, users or other persons or a new finding to it (occurred in the study under same CIP).<br>**Japan:** Within 30 calendar days after awareness and annually (Enforcement Regulation of PMDL Article 274-2)<br>**Singapore:** All DDs with SADE potential should be reported immediately and not later than 30 calendar days (GN-05-R2.1 section 4)<br>**All geographies:** Submit per local reporting requirements |
| Ethics Committee | **All geographies:** Submit per local reporting requirements |
| HOMI | **Japan:** Immediately per the direction of PMDA and/or annually (Japan GCP Article 28) |
| **Significant Safety Issue (SSI): Reporting in Australia** | |
| **Investigator responsibilities:** | |
| **Events to Report** | **Reporting Requirements and Timeframe to submit to Sponsor, HREC and institution** |
| Significant Safety Issues | • Urgent Safety Measure (USMs): Within 24 hours (NHMRC Safety monitoring and reporting in clinical trials involving therapeutic goods November 2016 section C.2.c)<br>• All other significant safety issues: without undue delay and no later than 72 hours of the principal investigator becoming aware of the event<br>(NHMRC Safety monitoring and reporting in clinical trials involving therapeutic goods November 2016 section C.2.g) |
| **Sponsor responsibilities:** | |
| **Events to Report** | **Reporting Requirements and Timeframe** |
| Significant Safety Issue | Urgent Safety Measure (USMs): within 24 hours (where possible) to TGA and without undue delay to investigators & HREC and in any case, no later than 72 hours of the measure being taken.<br>• Reasons for the urgent safety measure, Measures taken, Further actions planned<br>• Reasons for the termination, Measures taken, Further actions planned<br>(NHMRC Safety monitoring and reporting in clinical trials involving therapeutic goods November |

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| | 2016 section C.1.k) |
| Significant Safety Issue (continued) | Submit to TGA<br>• Notification of an amendment: Without undue delay and no later than 15 calendar days Note: TGA should receive notification that a SSI has occurred but the amendment revising trial documentation should be submitted to the HREC only<br>• Action taken with respect to safety that has been taken by another country's regulatory agency (relevant to an ongoing clinical trial in Australia): Without undue delay and no later than 72 hours of the trial sponsor becoming aware of the action (Australian clinical trial handbook version 2.4) |
| Significant Safety Issue (continued) | Submit to TGA, any Australian investigator and HREC<br>• Other significant safety measures: Without undue delay and no later than 15 calendar days of the sponsor being aware of the issue. Details of significant safety issue, further actions planned<br>• Temporary halt of a trial for safety reasons: Without undue delay and no later than 15 calendar days of the sponsor's decision to halt the trial.<br>• Reasons for the halt, the scope of the halt, Measures taken, Further actions planned<br>• Early termination of a trial for safety reasons: Without undue delay and no later than 15 calendar days of the sponsor's decision to termination the trial. |
| **Other Reporting in Singapore** | |
| **Sponsor Responsibilities:** | |
| **Events to Report** | **Reporting Requirement and Timeframe** |
| Event or other occurrence relating to a medical device that represents a serious threat to public health | Submit to the Health Sciences Authority (HSA) All events should be reported immediately and not later than 48 hours (GN-05-R2.1: section 4) |
| ADE that occurs outside of Singapore | Submit to the Health Sciences Authority (HSA) All events that occur outside of Singapore but where the medical devices have also been supplied in Singapore do not require reporting unless the registration or license conditions of those medical devices require so, or a notice requesting for AE information has been issued by the Authority.<br>(GN-05-R2 section 2) |
| **Investigator Responsibilities:** | |
| **Events to Report** | **Reporting Requirement and Timeframe** |
| Serious Adverse Event (as defined under HBRA for investigator reporting requirements) | Submit to Research Institution<br>The investigator shall report SAE immediately. A detailed written report on the SAE is required.<br><br>Note: It's under the responsibility of Research Institution to report the unexpected serious adverse event to the Director.<br>(Human Biomedical Research Regulation 2017 section 9(1) (2) |
| | Submit to IRB (if required)<br>The investigator shall report SAE to IRB per IRB requirements.<br>(Human Biomedical Research Regulation 2017 section 9 (3) |
| **All other Adverse Events, Device Deficiencies, and new information that may adversely affect safety of the subjects or the conduct of the study** | |
| **Investigator shall submit to:** | |
| Medtronic | **Europe:** Submit in a timely manner after the investigator first learns of the event |

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| | **All geographies:** Submit per local reporting requirements |
| Regulatory Authorities | **All geographies:** Submit per local reporting requirements |
| Ethics Committee | **All geographies:** Submit per local reporting requirements |
| **Sponsor shall submit to:** | |
| Investigator | **All geographies:** Submit per local reporting requirements |
| Regulatory authorities | **All geographies:** Submit per local reporting requirements |
| Ethics Committee | **All geographies:** Submit per local reporting requirements |

## 11.7. Subject Death

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

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

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

## 11.8. 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: 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 CEC will also review all deaths and provide an adjudication of the death classification. See section 12 for handling events where the adjudication of the investigator and the CEC differ.

Regulatory reporting of Subject Deaths will be completed according to local regulatory requirements.

## 11.9. Product Complaint Reporting

A product Complaint is 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.

The reporting of product complaints is not part of the LEADR Clinical Study and should be done in addition to the AE/DD reporting requirements. It is the responsibility of the investigator to report all product complaints associated with a medical device distributed by Medtronic, regardless of whether they are related to intended use, misuse or abuse of the product. Reporting must be done immediately and via the regular channels for market-released products. The reporting of product complaints by the clinical team must be done according to the local Standard Operating Procedures. Medtronic will notify the RAs (e.g. CA) as applicable for the following incidents immediately upon learning of them and is not limited to AEs and device deficiencies only:

- Any malfunction or deterioration in the characteristics and/or performance of a device, as well as any inadequacy in the labeling or instructions for use which led or might have led to the death or serious deterioration in the state of health of a patient, user, or other person.
- Any technical or medical reason resulting in withdrawal of a device from the market by the manufacturer.
- Any serious deterioration in the state of health, including:
    - Life-threatening illness or injury
    - Permanent impairment of a body function or permanent damage to a body structure
    - A condition necessitating medical or surgical intervention to prevent permanent impairment of a body function or permanent damage to a body structure

# 12.Data Review Committees

## 12.1. Clinical Events Committee Review

The study will utilize an independent CEC. At regular intervals, an independent CEC will review and adjudicate at a minimum all system and procedure-related AEs and all Lead System Events as classified by investigator or Medtronic. Additionally, the CEC will provide an adjudication of the death classification for all reported deaths.

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

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

For AEs and deaths reviewed by the CEC, Medtronic will provide the CEC with the Investigator's description and supportive documentation (when available). The CEC is responsible for reviewing the Investigator's description, 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 classify all lead and system alerts/events as well as all potential LSEs identified by the clinician in the absence of a device alert as RV lead system events (RV LSE), Non-RV lead system events (Non-RV LSE)), or other events based on the definitions in Table 12 .

The CEC may use diagnostic information contained on device interrogation files as well as source data such as diagnostic tests (e.g. X-rays, Holter data), clinician notes, and data collected on the lead event eCRF in making their classifications.

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 rationale will be provided to the investigator. If the investigator agrees with the CEC's adjudication, the eCRF documenting the AE will be updated accordingly.

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

## 12.2. Data Monitoring Committee

Ongoing oversight for this study will be provided by an independent DMC. The DMC will be established by Medtronic and will be responsible for safeguarding the scientific integrity of the study and assessing the accumulating data on safety of the device/therapy and interventions during the study. The DMC will be responsible for safeguarding the interests of the study participants and for monitoring the overall conduct of the study. The DMC will give recommendations to Medtronic and/or the Steering Committee regarding study conduct and subject safety.

The DMC for this study will consist of a minimum of three and up to seven non-Medtronic members with study related backgrounds and not from sites participating in the study. Medtronic will appoint members of the Committee and the Chairperson. Up to two additional investigators participating in this study may participate in the meetings to offer clarification of events, but none will be given voting privileges. Medtronic personnel may facilitate the DMC meeting (e.g., study manager, statistician), but they will not be voting members.

A quorum of the committee may review interim analyses in which the results are analyzed against the primary objective. A summary of AEs will be reviewed at this time also. Review and consensus by the entire committee is required to recommend to the sponsor that the study should be stopped for safety reasons. The DMC will operate according to a charter under a separate cover and is available upon request.

## 12.3. Episode Review Committee

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

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

# 13.Statistical Design and Methods

## 13.1. General Considerations

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

The cohort will include all enrolled subjects who undergo the study procedures. For ancillary endpoints involving only measurements that may be obtained at follow-up visits, only subjects who complete those visits will be included in the analysis of those endpoints unless otherwise stated.

Bayesian methodology will be employed for the evaluation of all objectives. Further details are provided in the Analysis Methods subsection of each objective in section 13.

Any statistical tests will be conducted using two-sided 95% credible intervals unless otherwise stated.

A subgroup analysis may be conducted using subgroups based on age or body mass index. This analysis will provide insights regarding the impact of younger, more active patients on lead performance. The following subgroups may be considered:

- subjects younger than or equal to 20 years versus subjects older than 20 years, if there is a sufficient number of subjects per group
- Race or ethnicity, as applicable by geography

No subjects or data will be excluded to account for a learning curve. For the primary safety objective, the learning curve has been accounted for in the prespecified performance goal criteria.

The study will feature an adaptive design as described in section 13.2.

A Statistical Analysis Plan (SAP) will be developed and kept under separate cover, however, the statistical methods for the primary and secondary objectives are provided in detail below. The SAP may elaborate on these methods such as including computer code for implementing the statistical methods described in the CIP. 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. For China, the Clinical Study Report will be compliant with the elements from the CFDA 2016 No. 58 Announcement Annex 5 ‘Template of Clinical Trial Report of Medical Devices’.

Baseline data, e.g., medical history, and implant procedure data will be summarized in tables using descriptive statistics. Categorical data will be summarized using percentages while continuous data will be summarized using mean, median, standard deviation, as applicable. Descriptive statistics will also be used to summarize study deviations, system modifications, study exits, and adverse events.

### 13.1.1. Poolability and Multiplicity

Poolability assessments for gender and geographic region will be assessed for both primary objectives. In each case a significance level of 0.15 will be utilized to evaluate whether the endpoint(s) differ by values of the covariate. In the case of the primary safety objective, a Cox proportional hazards model will be fit with gender and geographic region included. Additionally, the estimated hazard rate through 6

months will be determined for each investigational site with at least five subjects. In the case of the efficacy objective, the effect of gender and region on defibrillation efficacy will be evaluated separately using Fisher's exact tests.

The primary efficacy objective will be performed once all required subjects have completed defibrillation testing, and provided in the stage 1 report (see section 13.3). The stage 1 safety objective will be evaluated at 3 months once 150 subjects undergoing implant of the Next Generation Lead have completed their 3-month follow-up visit. Depending on the study's enrollment rate it is projected that several hundred subjects will have a Next Generation ICD lead implant attempt at the time the stage 1 safety objective is evaluated. The study's primary safety objective will be evaluated once with a timing dictated by the study's adaptive design (see section 13.2 for details). While the same endpoint, and a similar parametric approach will be employed for both the analysis of the stage 1 safety objective and the primary safety objective, there will not be an adjustment for multiplicity as the former analysis is not compared against a pre-specified performance goal and the Bayesian paradigm allows for refinement of the posterior distribution of the hazard rate parameters as additional data is compiled.

## 13.2. Adaptive Design

The LEADR Clinical Study design is adaptive with regard to both sample size and follow-up duration. It features two decision points based on Next Generation ICD lead fractures observed in the trial, which are an important component of the primary safety endpoint and a key measure of lead reliability. At these decision points only the number of fractures will be assessed. The primary and ancillary objectives will not be evaluated. Enrollment will not be stopped at the timepoints for these decision points until a decision has been reached to halt enrollment and communicated to the study sites.

The first decision point occurs by the time of 500 subject implant attempts (see Table 18). If no fractures have been observed based on the data snapshot at that time point, enrollment will be halted and all enrolled subjects will be followed. If instead six or more fractures have been observed, the trial will be halted for safety. If 1 to 5 fractures have been observed, the sample size will be increased accordingly.

The second decision point will be when the first 500 subjects with an implant attempt have had the opportunity to have a six month visit (i.e. either the close of the 6 month visit window for the 500th subject with an implant attempt if that subject is still enrolled but did not have 6 month visit, or the date of the 6 month visit for the 500th subject undergoing an implant attempt if the subject is still enrolled, or the date when the last still enrolled subject among the first 500 subjects with implant attempt had their 6 month visit). If based on the data snapshot taken at that time point, no more than one fracture has been observed in the trial, the data will be analyzed when the first 500 subjects with an implant attempt have had the opportunity to be followed for 12 months, and an initial pre-market application report submitted to applicable regulatory agencies for review as needed. If instead more than one

fracture has been observed by this time point, the data will be analyzed once the last (e.g. 600th, 700th, 800th) subject with an implant attempt has had the opportunity to reach a 12 month follow-up, and at that point an initial pre-market application report will be submitted to applicable regulatory agencies. Regardless, approximately 6 months later a follow-up report will be submitted with most subjects followed to 18 months.

The following table provides the likelihood of these decision point outcomes based on 10,000 simulations of the study under two scenarios. The first scenario is the assumed Next Generation ICD lead true performance, which assumes a fracture-free rate of 99.9% at 12 months, is accurate. In this scenario there is an over 85.7% chance of observing no fractures by the 500th implant attempt, and a 99.2% chance of observing at most 1 fracture by the 500th implant attempt. There is also a 94.3% chance of observing at most one fracture by 6 months following the 500th implant attempt, which would determine the time frame for the initial pre-market report.

The second scenario is that the Next Generation ICD lead true performance is similar to that of the Fidelis lead, with an estimated 6-month fracture-free rate of 99.2% and 12-month fracture-free rate of 98.4%.In this scenario there is an 89.9% chance of observing one or more fractures by the 500th implant attempt, and a 98.6% chance of observing more than 1 fracture by the second decision rule of 6 months after the 500th implant attempt.

See section 13.7 for more information on projected fracture rates and analysis methods.

**Table 18: Adaptive Design Decision Rules & Operating Characteristics**

| Stage | Time Point | Decision Rule | Chance of Occurrence | |
|---|---|---|---|---|
| | | | Next Generation ICD lead | Fidelis-like Lead |
| Sample Size Assessment | 500th Implant Attempt | **0 Fractures Observed**: Halt enrollment | 85.7% | 10.1% |
| | | **1 Fracture Observed**: Increase to 600 implant attempts | 13.4% | 23.4% |
| | | **2 Fractures Observed**: Increase to 700 implant attempts | 0.8% | 26.5% |
| | | **3-5 Fractures Observed**: Increase to 800 implant attempts | 0.03% | 37.1% |
| | | **6+ Fractures Observed**: Halt Trial | 0.0% | 2.9% |
| Follow-up Assessment | 6 months after 500th implant Attempt | **≤ 1 Fracture Observed**: Analyze at 12 months post-500th implant attempt | 94.3% | 1.4% |
| | | **> 1 Fracture Observed**: Analyze at 12 months post-last implant attempt | 5.7% | 98.6% |

The data freeze for the initial pre-market approval report will occur either when all of the first 500 subjects undergoing an implant attempt have had an opportunity to reach 12 months of follow-up or when all implanted subjects have had the opportunity to reach 12 months of follow-up. This will depend on the decision rules outlined in the table above.

An updated report will be generated approximately 6 months after the initial pre-market approval report, allowing a majority of implanted subjects to reach 18 months of follow-up.

## 13.3. Data Reporting Frequency

### 13.3.1. Annual Reporting

It is anticipated that some regulatory authorities will require annual reporting of study progress. These reports will include summaries of subject enrollment, baseline and medical history, study deviations, and adverse events.

### 13.3.2. DMC Reporting

DMC reports will be developed at a frequency requested by the DMC. Reporting to the DMC will include an open report available to the steering committee and study team. The open report will include content similar to that provided for annual regulatory reporting. In addition, a closed report may be developed that will include summaries of primary safety and efficacy endpoints. The closed report will be treated as confidential and only available to members of the DMC and those preparing the closed report.

### 13.3.3. Stage 1 Pre-Market Reporting

A stage 1 pre-market report will be developed once the requirements for analyzing the study's primary efficacy (section 13.6) and stage 1 safety objective (section 13.11) have been satisfied (i.e. when 150 subjects with a Next Generation ICD Lead complete the 3-month visit). The stage 1 pre-market report will be used to support marketing applications in countries outside the US where applicable. Frozen datasets used to develop the stage 1 pre-market report will be stored by Medtronic in a secure network location.

Depending on the study's enrollment rate it is projected that several hundred subjects will have an implant attempt at the time the stage 1 safety objective is evaluated. This report will include evaluation of the study's primary efficacy objective, stage 1 safety objective, and ancillary objectives and include all data from subjects enrolled at the time of the database freeze for this report.

The inclusion of 150 patients followed for 3 months will demonstrate electrical performance due to the stabilization of a lead implant occurring at around 6 weeks, after which electrical performance is not anticipated to change. Therefore, by the 3-month time point, lead stabilization, maturation and

encapsulation has occurred, and electrical performance is considered to be stabilized.[2] This timeline and patient sample size is consistent with previous Medtronic lead studies e.g. Sprint Quattro Secure Model 6947, 5076 pacing lead, 3830 pacing lead. In addition, the Next Generation ICD lead is expected to perform very similarly as compared to existing Medtronic pacing and defibrillation leads based on the similarity of design described in the above sections.

### 13.3.4. Initial US Pre-Market Application Report

An initial pre-market application (PMA) report will be developed once the requirements for analyzing the study's primary safety objective has been satisfied as determined by the adaptive study design described in section 13.2. This report will include evaluation of the study's primary efficacy (section 13.6) and safety objective (section 13.5), secondary objective (section 13.7), and ancillary objectives and include all data from subjects enrolled at the time of the database freeze for this report. The initial US PMA report will be used to support a marketing application in the US.

### 13.3.5. Updated US Pre-Market Application Report

An updated PMA report will be developed approximately 6-months following submission of the initial US PMA report. This report will include updated information regarding the performance of the Next Generation ICD lead with respect to the secondary objective (lead fractures). At the time of the database freeze for this report it is anticipated that most subjects will have had the opportunity to complete their 18-month follow-up visit. This report will provide the US FDA updated information on the performance of the Next Generation ICD lead and provide updated information on lead performance for other geographies requiring Clinical Evidence Reports.

### 13.3.6. Final Report

A final report will be developed after all subjects have exited the study.

### 13.3.7. Other Reports

Other reports may be generated at the request of international regulatory bodies if applicable.

## 13.4. Sample Size

There are two primary objectives (safety and efficacy). The safety primary objective sample size requirement will refer to subjects who undergo an implant attempt of the Next Generation ICD lead, while the efficacy primary objective sample size will be defined as subjects who complete the implant

[2] K. B. Stokes et al: The Electrode-Tissue Interface: The Revolutionary Role of Steroid Elution;1992.

defibrillation testing protocol (see section 9.8.4 for the definition of the protocol). Furthermore, as described in section 13.2, the adaptive sample size of the study is based on the observed number of fractures in the study. Based on the decision rules outlined in section 13.2 the initial sample size is 500 subjects, but may be increased to 800 subjects undergoing an implant attempt. To further account for subjects who enroll in the study but exit prior to an implant attempt, up to 900 subjects may be enrolled.

### 13.4.1. Primary Objective #1: Safety

To evaluate the primary safety objective metric of the Next Generation Lead-related major complication-free rate at 6 months, a Performance Goal (PG) of 90% was chosen based on both past transvenous RV defibrillation lead performance and accounting for possible acute differences between catheter delivery and stylet delivery (see section 13.5.3 for rationale). The assumed Next Generation ICD Lead-related major complication-free rates through 6 months are provided in Figure 7. They are modeled using a piecewise exponential distribution assuming a rate of 95.5% at one month and 94.5% at 6 months. A solid red line denoting the performance goal of 90% is also provided. It is also assumed that attrition (exit or death) will follow a Weibull distribution, with an attrition rate of 4% at one month (allowing for unsuccessful implants) through 10% one-year post-implant.

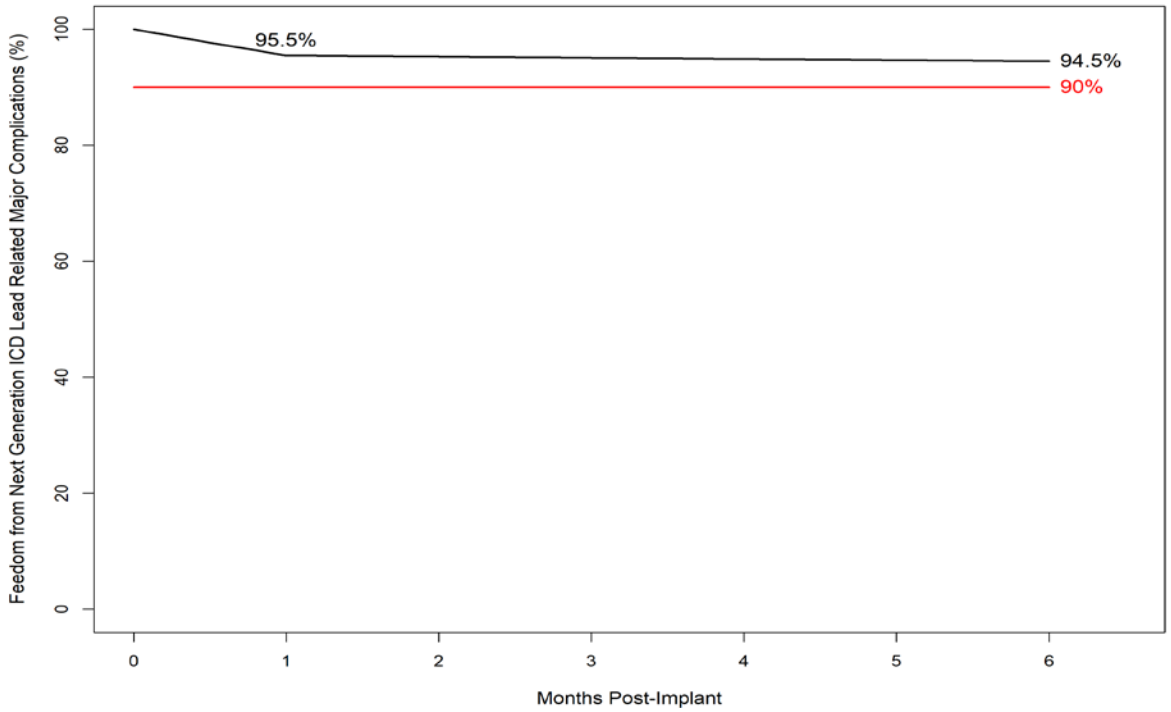



**Figure 7: Assumed Freedom from Model Next Generation Lead-related Major Complications**

The trial was simulated 10,000 times under both the null and alternative hypotheses. For each simulation, an initial sample size of 500 subjects was enrolled with the final number of subjects enrolled and final follow-up time allowed to adapt based on the adaptive design described in section 13.2. Each subject had their time to safety endpoint and time to attrition simulated using the assumptions described above.

Let $\lambda_1$ denote the endpoint hazard rate through one month, and let $\lambda_2$ denote the endpoint hazard rate beyond 1 month. Using the shape and rate parameterization of the Gamma distribution, the prior distributions for $\lambda_1$ and $\lambda_2$ were defined as:

$\lambda_1$~ Gamma(1,3.48) and $\lambda_2$~Gamma(1,12.33). This results in a skeptical prior distribution for the 6-month endpoint free rate that has a median of 56.2% which is well below the 90% performance goal. This prior was selected based on simulation studies showing that it protected the frequentist type 1 error rate across a range of null hypothesis scenarios.

In each simulated trial, these priors were combined with the simulated survival times for the subjects, and posterior distributions for $\lambda_1$ and $\lambda_2$ were determined to be as follows:

$\lambda_1$~ Gamma(1 + # of subjects with events through 1 month, 3.48 + #survival months through 1 month)

$\lambda_2$~ Gamma(1 + # of subjects with first event between 1 and 6 months, 12.33 + #survival months between 1 and 6 months).

Using these data, the posterior distribution for the 6-month Next Generation ICD Lead-major complication-free rate was determined, and the lower 95% credible bound was generated for each trial. It was determined that based on these assumptions, an initial sample size of 500 subjects undergoing an implant attempt would yield 94.4% power for assessing this objective. This sample size would have a false positive rate (i.e. chance the lower 95% bound exceeds 90% when the true Next Generation ICD Lead 6-month major complication-free rate is 90%) ranging from 1.3% to 1.7% under a range of null hypothesis scenarios.

### 13.4.2. Primary Objective #2: Efficacy

A performance goal of 88% was chosen to evaluate the primary efficacy objective metric of implant testing success defined as successfully terminating one or more induced SSVA episodes (see section 13.6.3 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 97.9%.

Let $\pi$ = P(a patient is a success). The following Beta prior distribution is used: $\pi$ ~Beta(1.0,1.2), which has an expected value of 1.0/(1.0+1.2) = 0.45. This prior was selected as it maintained a false positive rate of ≤2.5% across a range of sample sizes from 40 to 150. The resulting Beta posterior distribution for $\pi$ will be Beta(1.0 + # of successes, 1.2 + # of failures). Assuming a true success rate of 97.9%, the required sample size such that the lower two-sided 95% credible interval for the proportion of successful patients exceeds 0.88 with at least 0.9 probability (90% power) is 72 subjects completing the defibrillation

protocol, while a sample size of 95 would be required if the true defibrillation efficacy was 97.0%. The false positive rate (i.e. chance the lower 95% bound exceeds 88% when the true defibrillation rate is 88%) would be less than 2.5% with 95 subjects. Thus, a sample size of at least 95 completing the defibrillation testing protocol will be required.

### 13.4.3. Stage 1 Safety Objective

The goal of the stage 1 safety objective is to provide an estimate of the 3-month RV lead-related major complication-free rate after 150 subjects have at least 3-months (90 days) of post-implant follow-up experience. As described in section 13.11 a 95% credible interval for the 3-month RV lead related major complication free rate will be computed to quantify the level of the uncertainty of the estimate at the time of the stage 1 analysis. The analysis of the stage 1 safety objective will include all subjects with a Next Generation RV lead implant attempt at the time of the analysis. Table 19 displays the estimated 3-month RV lead related major complication free rate and a measure of its uncertainty based on 10,000 simulations of the study based on its planned enrollment rate. Table 19 shows that at the time of the stage 1 pre-market report, the lower credible interval for the RV lead related major complication freedom rate should be within 5% of its point estimate.

**Table 19: Precision of 3-Month RV Lead Related Complication Free Rate at the Stage 1 Safety Analysis Timepoint**

| Subjects with Implant Attempt (95% Monte Carlo Interval) | Scenario | Estimated 3-month Freedom Rate[1] | Estimated Lower 95% Credible Interval[1] | Probability Distance Between Point Estimate and Lower Credible Interval within 5.0%[2] |
|---|---|---|---|---|
| 362 (334 – 391) | Planned (6-month freedom rate is 94.5% as shown in Figure 7) | 94.5% | 91.6% | >99.9% |
| | 6-month freedom rate is 92% | 93.6% | 90.3% | >99.9% |
| | Null Hypothesis (6-month freedom rate is 90%) | 92.8% | 89.3% | >99.9% |

[1]Median estimate across 10000 simulations.
[2]Proportion of simulations where distance between the 3-month freedom rate and its lower two-sided 95% credible interval was ≤ 5.0%.

## 13.5. Primary Objective #1: Safety

The primary objective is to demonstrate that the freedom from major complications related to the Next Generation ICD lead at 6 months post-implant exceeds a pre-specified threshold of 90%. The endpoint is

defined as a subject's first occurrence of a major complication related to the Next Generation ICD lead, as determined by an independent Clinical Events Committee, 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 Next Generation ICD lead implant and be adjudicated by the CEC as being a major complication related (causal relationship) to the Next Generation ICD lead. Major complications are those complications resulting in:

- Death
- Lead Fracture
- Hospitalization (in-patient)
- Prolongation of an existing hospitalization by at least 48 hours
- System Revision (reposition, replacement, explant)

### 13.5.1. Hypothesis

The hypotheses for this objective are as follows, with $\pi_6$ denoting the 6 month freedom from major RV lead related complications:

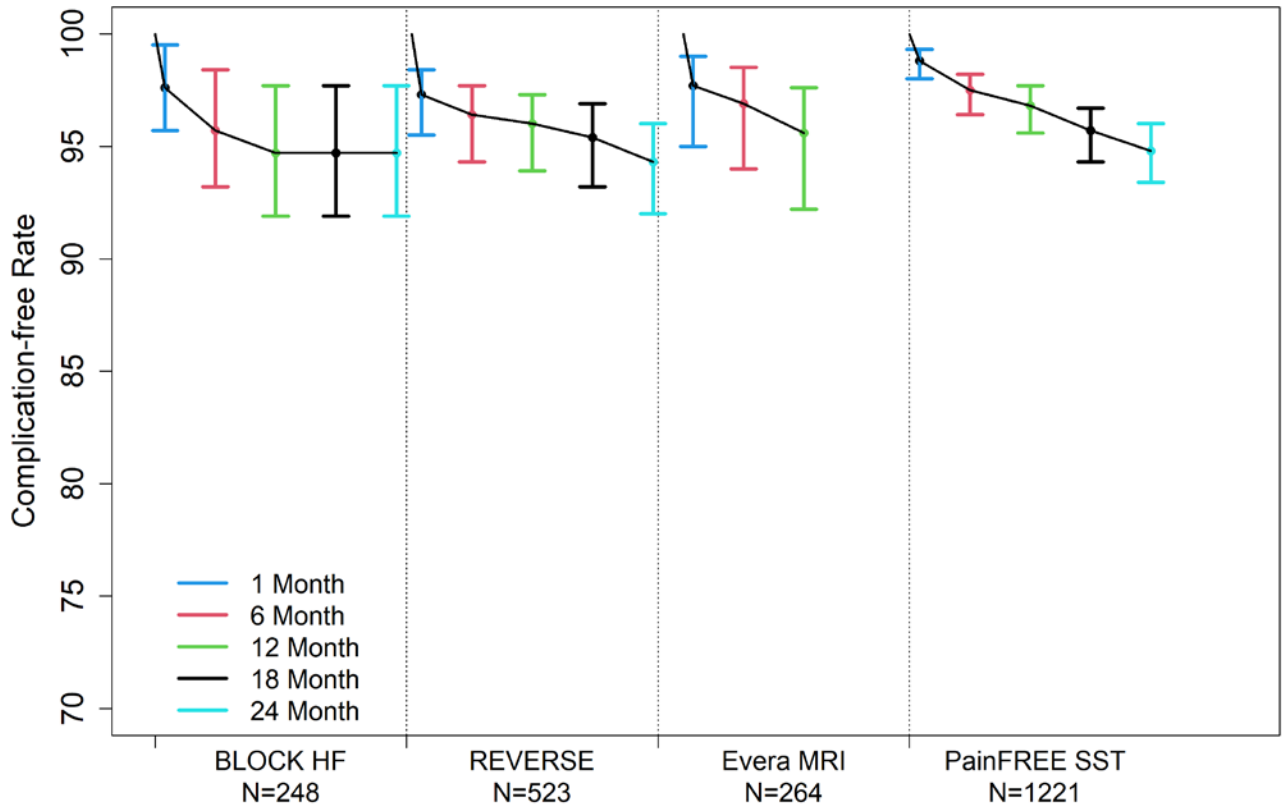
$H_O: \pi_6 \leq 0.90$
$H_A: \pi_6 > 0.90$

### 13.5.2. Performance Requirements

The 95% lower credible bound for the 6-month RV lead-related major complication-free rate must exceed a pre-specified threshold of 90%.

### 13.5.3. Rationale for Performance Criteria

The safety primary objective addresses the entire safety profile of the Next Generation ICD lead as fractures are included in major complications. The determination of the pre-specified performance goal of 90% for the lead-related major complication endpoint aligns with a review of internal Medtronic transvenous ICD and CRT-D trial data. An assessment of comparable major complication-free rates at 6 months for Medtronic transvenous devices showed observed rates as low as 95.7% (Figure 8). Furthermore, the event rate is highest in the first month and tends to decrease with a lower constant event rate after the first month (Figure 8 and Table 20).




*Analysis cohorts from these studies were restricted to include patients with ICD or CRT-D devices. Patients with successful and unsuccessful implant attempts were included.

**Figure 8: Historical Transvenous RV lead-related Major Complication-free Rates**

The following table provides further detail regarding these trials.

**Table 20: Historical Medtronic Transvenous ICD Trial Major Lead-related Complication-free Rates**

| Study | Study Description | 30-day Freedom Rate (95% CI) | 6-Month Freedom Rate (95% CI) |
|---|---|---|---|
| BLOCK HF[3] | IDE (G030156) study comparing efficacy of CRT to RV pacing in AV block patients | 97.6% (95.7%, 99.5%) | 95.7% (93.2%, 98.4%) |

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

| Study | Study Description | 30-day Freedom Rate (95% CI) | 6-Month Freedom Rate (95% CI) |
|---|---|---|---|
| REVERSE[4] | IDE (G040004) study comparing efficacy of CRT to ICD/OMT therapy in NYHA II patients | 97.3% (95.5%, 98.4%) | 96.4% (94.3%, 97.7%) |
| Evera MRI[5] | IDE (G140039) study evaluating safety and efficacy of the Medtronic Evera MRI ICD System | 97.7% (95.0%, 99.0%) | 96.9% (94.0%, 98.5%) |
| PainFREE SST[6] | Randomized study to evaluate the Medtronic Protecta ICD System | 98.8% (98.0%, 99.3%) | 97.5% (96.4%, 98.2%) |

The Next Generation ICD lead has a different delivery system (catheter delivery) compared to stylet-delivered leads, and so it is unknown whether that may result in a higher rate of acute major complications. Reasons the complication rate may acutely be higher include:

- As compared to Sprint Quattro leads, complications could include more frequent dislodgment due to catheter removal.
- Catheter delivery is unlike the typical implanter experience with stylet delivered Sprint Quattro high power leads, thus placement could feel different.
- The fixed helix with 3830 and the Next Generation ICD lead is unlike the Sprint Quattro extendable/retractable helix design, thus training and handling experience will support improved technique.
- There is expected to be a learning curve in the clinical study, and Medtronic intends to provide appropriate training.

Medtronic reviewed the IDE study report for the catheter-delivered 3830 pacing lead, which the Next Generation ICD lead is derived from. The 3830 Pacing Lead Clinical Study enrolled up to 350 subjects at 35 sites. These subjects were enrolled in one of two groups. The first 2 subjects per site were enrolled as Roll-In subjects (total of 86 Roll-In subjects), while the remaining subjects were enrolled as Non-Roll-In subjects (total of 176 Non-Roll-In subjects). This design was consistent with the 5076 Pacing Lead study

[4] 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.
[5] 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.
[6] 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.

design, which served as a historical control. There were additional subjects enrolled under a Continued Access Protocol.

Only the 176 Non-Roll-In subjects were included in the analysis of the safety primary objective, which involved an endpoint of RV lead-related complications. The objective compared the 3-month complication-free rates of 5076 and 3830, with an equivalence margin of 6%. [redacted]

**Table 21: Ventricular Lead-Related Complication Free Summary at 3 Months (3830 Pacing Lead Study)**

| Lead Model | Number of Leads | Number of Subjects with Event | Complication Free Rate at 3 Months | Std Error | Observed Difference (5076-3830) | 95% Upper Bound Difference |
|---|---|---|---|---|---|---|
| [redacted] | | | | | | |

Tables summarizing the observed 3830 ventricular lead-related complications and Kaplan-Meier rates through 30 months are excerpted below.

**Table 22: Ventricular Lead-related Complications (3830 Pacing Lead Study)**

| Adverse Event | Complications | |
|---|---|---|
| | Number of Events | Number of Subjects |
| [redacted] | | |

**Table 23: Estimated Freedom from 3830 Lead-related Complications (3830 Pacing Lead Study)**

| Time | Survival Rate | Lower 95% Confidence Bound | Upper 95% Confidence Bound | Number Failed |
|---|---|---|---|---|
| [redacted] | | | | |

| Time | Survival Rate | Lower 95% Confidence Bound | Upper 95% Confidence Bound | Number Failed |
|---|---|---|---|---|
| [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |

Given the lower 6-month complication-free rate [redacted] seen in the 3830 pacing study and given the LEADR study will not have a Roll-In arm, Medtronic feels a performance goal of 90% is appropriate for evaluating the safety primary objective.

### 13.5.4. Analysis Methods

A Kaplan-Meier curve will be generated using each subject's time to first Next Generation ICD lead - related major complication or time to last exposure to the Next Generation ICD lead if a subject does not have a major complication, in which case the subject will be censored. Last exposure to the Next Generation ICD lead will be defined as the date of their last follow-up visit, study exit date (if exited for reason other than lost-to-follow-up), or date of death, whichever is last. Additionally, if a subject has an explant of the Next Generation ICD lead that is not related to a Next Generation ICD lead major complication the subject will have their last exposure date set to their explant date. All subjects undergoing an implant attempt of the Next Generation ICD lead will be included in the analysis.

For inferential analyses, a piecewise exponential model will be assumed with two intervals of interest: 0-1-month post-implant, and 1 month and beyond post-implant, as it is possible the rate of lead-related major complications may differ in the acute (first 30 days) compared to more chronic time points. This assumption is based on the historical data from previous Medtronic studies (see section 13.5.3).

Let $\lambda_1$ denote the hazard rate for 0-1 month post-implant attempt, and let $\lambda_2$ denote the hazard rate for 1 month post-implant attempt and beyond. The survival function (S(t)), will have the equation

$$S(t) = \begin{cases} exp(-\lambda_1 t), & t \in [0, 1) \\ exp(-\lambda_1) exp\big(-\lambda_2 (t-1)\big) & t \in [1, \infty) \end{cases}$$

Using the shape and rate parameterization of the Gamma distribution, the following prior distributions are assumed for $\lambda_1$ and $\lambda_2$:

$\lambda_1$ ~ Gamma (1, 3.48), $\lambda_2$ ~ Gamma(1, 12.33)

This results in a skeptical prior distribution for the 6-month endpoint free rate that has a median of 56.2% which is well below the 90% performance goal. As described in section 13.4.1 these priors ensure the false positive rate is <2.5%.

These prior distributions will be combined with the prospective event/follow-up data to generate posterior distributions for each event rate, which will be as follows:

$\lambda_1$~ Gamma (1 + # of first endpoints within 1 month, 3.48 + Total Survival Months through 1 month),

$\lambda_2$ ~ Gamma(1 + # of first endpoints between 1 & 6 months, 12.33 + Total Survival Months between 1 and 6 months)

These posteriors will be utilized to determine the posterior distribution for the 6-month freedom from Next Generation ICD lead -related major complication rate. From this distribution a 95% two-sided credible interval will be generated. If the 6-month lower bound of the credible interval exceeds 90%, the objective will be met. The Kaplan-Meier curve will be extended through at least 12 months for longer term safety evaluation.

For subjects who do not complete follow-up through 6 months due to being lost to follow-up or unsuccessful implant, a tipping point analysis will be performed including these subjects to assess robustness of the result to incomplete follow-up. Subjects who exit the trial prior to 6 months for other reasons that may plausibly be assumed independent of lead performance (e.g. geographic relocation of subject) will not be included in the tipping point analysis. An assessment of the accuracy of the piecewise exponential assumptions will also be performed.

### 13.5.5. Determination of Subjects/Data for Analysis

All subjects undergoing an implant attempt of the Next Generation ICD lead will be included in the analysis. If a subject has multiple Next Generation ICD lead implant procedures during the study, time 0 for the subject will be set to the date of the subject's first successful Model Next Generation ICD lead implant procedure. If the subject experiences a safety endpoint prior to their first successful implant (e.g. at an unsuccessful implant attempt) or experiences a safety endpoint but does not have any successful implant the survival time will be set to time 0.

## 13.6. Primary Objective #2: Efficacy

Demonstrate the percentage of subjects successfully defibrillated at implant with the Next Generation ICD lead exceeds a pre-specified threshold of 88%.

### 13.6.1. Hypothesis

The hypotheses for this objective are as follows, with $\pi$ denoting the implant defibrillation success rate:

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

### 13.6.2. Performance Requirements

Performance Requirements for this objective define both the endpoint and the performance goal. The endpoint, defibrillation testing success, is defined as:

- One induced SSVA episode successfully terminated with a 18J shock, or
- 2 consecutive SSVA episodes successfully terminated with 25J shocks

Notes:

- In one of the two consecutive SSVA episodes, up to two 25J 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 95% lower credible bound for the percentage of subjects successfully defibrillated will be compared against a pre-specified threshold of 88%.

### 13.6.3. 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% (see Table 24)). Literature and other studies show multiple sources in which the defibrillation rates were less than 92%.

**Table 24: Historical Transvenous ICD Defibrillation Testing Success Rates**

| Reference | Sample Size | Defibrillation Implant Success |
|---|---|---|
| [redacted] | [redacted] | [redacted] |
| [redacted] | [redacted] | [redacted] |
| Leong-Sit AMJ: 2006; 152:1104-8 | N=168 | 90.5% |
| Pires JCE 2006; 17:1-6 | DFT at implant (N=129)<br>Safety Margin Testing at Implant (N=503)<br>No Testing at Implant (N=203) | 77%<br>93%<br>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)<br>No Testing at Implant (N=1227) | 91.8%<br>N/A |

The threshold of 88% has also been used in pivotal trials for alternative defibrillation devices (S-ICD and EV ICD), so there is precedent for a performance goal 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[7] 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.

### 13.6.4. Analysis Methods

Descriptive statistics will be used to summarize the results of the defibrillation testing at implant. A table or histogram will be generated to show the distribution of subjects successful at 18J, successful with two successive episodes terminated by 25J, etc. If two successive episodes are terminated by ≤ 25J , this will also be considered a successful defibrillation. The following Beta prior distribution is used for π, the proportion of subjects who would pass the defibrillation protocol for this study:

$\pi \sim Beta(1.0, 1.2)$,

which has an expected value of 1.0/(1.0+1.2) = 0.45 and the 50$^{th}$ percentile is 0.44. As described in section 13.4.2, this prior ensures a false positive rate <2.5%.

The resulting Beta posterior distribution for π will be Beta(1.0 + # of successes, 1.2 + # of failures). From this Beta posterior distribution, a posterior mean and 95% two-sided credible interval for the proportion of subjects who successfully pass the defibrillation protocol will be generated. The objective will be met if the lower 95% credible bound exceeds 88%. Subjects who cannot complete the defibrillation protocol due to an insufficient number of episodes being inducible (e.g. zero induced episodes) will be excluded from the analysis and reported separately. Results from subjects who undergo defibrillation testing only at the physician's discretion after the sample size requirement has been met for this objective will also be reported separately.

A tipping point analysis will be performed to assess the robustness of the result to missing data. Subjects, who attempted defibrillation testing (i.e. had at least one induced episode) prior to the closure of defibrillation testing as announced by Medtronic but did not complete defibrillation testing, will be included in the tipping point analysis.

[7] 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.

### 13.6.5. Determination of Subjects/Data for Analysis

Only a subset (≥95) of enrolled subjects undergoing implant of the Next Generation ICD lead are required to undergo defibrillation testing so as to reduce risk and burden to the subject. Subjects who cannot complete the defibrillation protocol for reasons such as an insufficient number of episodes being inducible will be excluded from the analysis and reported separately. However, these subjects will be included in a tipping point analysis as described above.

## 13.7. Secondary Objective #1: Safety

Estimate the fracture-free rate of Next Generation ICD lead throughout the study duration

### 13.7.1. Hypothesis

There are no hypotheses for this objective.

### 13.7.2. Performance Requirements

At each desired time point (6, 12, 18, and 24 months), two-sided 95% credible intervals for the Next Generation ICD lead fracture-free rates will be generated using a combination of prospective and virtual patient data derived from engineering models.

Long-term fracture survival of the Next Generation ICD lead will be evaluated utilizing:

- Pre-market Original IDE study with 12+ months (initial US PMA report) and 18-month follow-up (updated US PMA report).
- Virtual patient model, combining rigorous bench testing to failure with in-vivo use condition data. Virtual patients will be combined with data from study subjects using the methodology developed by industry and FDA statisticians through the Medical Device Innovation Consortium's Computing Modeling and Simulation Working Group (16) as described in section 13.7.4.

### 13.7.3. Rationale for Performance Criteria

Medtronic's fatigue reliability modeling has demonstrated a highly reliable Next Generation ICD lead, which is anticipated to perform at least as well as Sprint Quattro (Model 6935M). Medtronic will assess long term performance, specifically, Next Generation ICD lead fractures through a post market surveillance study. Medtronic believes overall safety and efficacy primary endpoints described above are adequate to confirm the safety and efficacy of the Next Generation ICD lead. While data collection occurs from consent to exit a premarket clinical setting is not ideal for studying fracture endpoints since fractures generally occur multiple years post-lead implant. However, the present adaptive study design of at least 500 prospective subjects is expected to result in over 750 device years of follow-up. The premarket clinical data will be augmented with virtual patients generated through modeling to obtain

more precise estimates of fracture rates. However, the contribution of virtual patient data derived from the fracture survival model for the estimation of the Next Generation ICD lead failure rate will not exceed the contribution of actual subjects enrolled in the LEADR study.

The projected 95% credible intervals at each time point for the initial US PMA report and updated US PMA reports with and without the inclusion of virtual data are provided in Figure 9 and Table 25, both for the assumed performance of the Next Generation ICD lead as well as for a lead with Fidelis-like fracture rates [redacted]% fracture-free at 6 months, [redacted]% fracture-free at 12 months). For the virtual data, a Gamma(0.9,6000) prior was assumed for the monthly event rate from 0 to 12 months and from 12 to 24 months. This prior was chosen based on current knowledge about the expected performance of the Next Generation ICD lead but does not reflect the final choice for the virtual prior. Section 13.7.4 provides details about the procedure and timeline for the choice of the final virtual prior to be used for analysis. With the proposed study design, even at the initial assessment the expected Next Generation ICD lead and Fidelis-like lead performances do not overlap. Additionally, while the incorporation of virtual data does result in increased precision for the Next Generation ICD lead (compare solid and dashed blue and gray lines in Figure 9), it does little to change the expected results for a Fidelis-like lead (compare solid and dashed yellow and red lines in Figure 9). This is due to virtual data being down weighted based on disagreement with clinical data, which is further explained later in section 13.7.4. The information provided in this section serves as evidence in accordance with FDA agreement.



**Figure 9: Estimated 95% Credible Intervals for Fracture-free Rates by PMA Report**

**Table 25: Fracture-free Rate Operating Characteristics**

| Analysis | Time Point | Fracture-free Rate Time Point | Data Cohort | Estimated 95% Credible Intervals | |
|---|---|---|---|---|---|
| | | | | Next Generation ICD lead | Fidelis-like Lead |
| [redacted] | | | | | |

*Virtual data refers to data generated by the engineering model
Note for example at 24-months the [redacted]% credible interval width shrinks by 10.1% when the virtual data is added relative to its width based only on clinical data for a lead with the assumed performance of the Next Generation ICD lead while it only shrinks by [redacted] when the virtual data are used for a lead with Fidelis-like failure rates.

### 13.7.4. Analysis Methods

For descriptive purposes, a Kaplan-Meier curve will be generated using each subject's time to first Next Generation ICD lead fracture or time to last exposure to the Next Generation ICD lead if the subject does not experience a lead fracture, in which case the subject will be censored. Last exposure to the Next Generation ICD lead will be defined as the date of their last follow-up visit, study exit date (if exited for reason other than lost-to-follow-up), or date of death, whichever is last. Additionally, if a subject has an explant of the Next Generation ICD lead that is not related to a lead fracture, the subject will have their last exposure date set to their explant date. All subjects undergoing an implant attempt of the Next Generation ICD lead will be included in the analysis.

**Parameter Distributions**

For inferential analyses, a piecewise exponential model will be assumed with two intervals of interest: 0-12 months post-implant, and 12 months and beyond post-implant, as it is possible the rate of fractures may vary between the first and second 12-month periods.

Let $\lambda_1$ denote the fracture hazard rate for 0-12 month post-implant attempt, and let $\lambda_2$ denote the fracture hazard rate for 12 months post-implant attempt and beyond. The survival function (S(t)), will have the equation

$$S(t) = \begin{cases} exp(-\lambda_1 t), & t \in [0, 12) \\ exp(-12\lambda_1)exp\big(-\lambda_2(t-12)\big) & t \in [12, \infty) \end{cases}$$

When *n* subjects have had an implant attempt, let $X_i$ be the time until fracture (or censoring if no event is yet observed) for subject *i*, and $d_i$ is an indicator of an event (thus d=0 implies subject *i*'s fracture time is censored). Let $X_{ij}$ be the "time spent" by subject *i* in interval *j*. Let $d_{ij}$ be the indicator of an event for subject *i* in interval *j*. The likelihood function is

$L(\lambda_1, \lambda_2 | \text{data}) = \prod_{j=1,2}(\lambda_i)^{d_{ij}} \exp(-\lambda_i x_{ij})$

Using the shape and rate parameterization of the Gamma distribution, the following prior distributions are assumed for $\lambda_1$ and $\lambda_2$: $\lambda_1$~Gamma(0.1,0.1) and $\lambda_2$~Gamma(0.1,0.1).

The posterior distribution for $\lambda_i, i$=1,2 would then be $\lambda_j|\text{data} \sim \text{Gamma}(0.1 + \sum_{i=1 \text{ to } n} d_{ij}, 0.1 + \sum_{i=1 \text{ to } n} x_{ij})$.

**Virtual Patient Data Incorporation**

The virtual data will be incorporated in the form of a discount prior Gamma($\alpha_{v1}$,$\beta_{v1}$) distribution for $\lambda_1$ and a discount prior Gamma($\alpha_{v2}$,$\beta_{v2}$) distribution for $\lambda_2$. Each prior will be down weighted by two factors:

$\rho_i$=degree of agreement between the Gamma($\alpha_{vi}$,$\beta_{vi}$) distribution and the posterior for $\lambda_i$, and

$\delta_i$= proportion of clinical follow-up data obtained relative to the minimum planned sample size of 500 subjects with an implant attempt (e.g. total patient years in that interval divided by total of 500 subjects undergoing an implant attempt). $\delta_i$ will not exceed 1 in the case more than 500 years of follow-up are accrued during an interval.

Both parameters make use of the prospective data to determine the influence of the virtual data on the overall results. In the case of $\rho_i$, for example, the difference between the posterior for $\lambda_i$ and the virtual data Gamma($\alpha_{vi}$,$\beta_{vi}$) distribution will be assessed by generating 10,000 values from each distribution and taking the difference between the 10,000 generated paired values; the 10,000 differences would then be assessed to see how often they were smaller or larger than 0.

$\rho_i$ = 2 × (1-max(proportion of differences > 0, proportion of differences < 0))

For example, if 80% of the paired differences are positive, then $\rho_i$ = 2 × (1-0.8) = 0.4. The minimum value of $\rho_i$ would be 0 if all differences were positive or all differences were negative. The maximum value of $\rho_i$ would be 1 if all 50% of the differences were positive and thus 50% of the differences also were negative.

In the case of $\delta_i$, for example, if among 500 implanted subjects the total amount of follow-up data in the interval 0-12 month post-implant period equals 475 years, then the prior for that interval would be multiplied by a factor of $\delta$=475/500 = 0.95 to down weight the influence of the prior 5%. A similar approach is employed for the 12-24 month interval.

*Obtaining Virtual Data Prior Values Based on Engineering Model*

The actual values of $\alpha_{v1}$, $\beta_{v1}$, $\alpha_{v2}$ and $\beta_{v2}$ will be determined based on the lead fracture survival engineering model which incorporates *in-vivo* stress conditions (i.e. *in-vivo* curvature), fatigue testing, and patient activity levels (i.e. cyclic use conditions). The output of this model will be fracture free survival along with its uncertainty. Medtronic will use the output of this engineering model to identify the hazard rate for lead fracture between implant and 1-year and after 1-year (i.e. $\lambda_{v1}$ and $\lambda_{v2}$). The Gamma parameters $\alpha_{v1}$, $\beta_{v1}$, $\alpha_{v2}$ and $\beta_{v2}$ will be set such that E($\lambda_{v1}$) and E($\lambda_{v1}$) equal the $\lambda_{v1}$ and $\lambda_{v2}$ values observed from the engineering model, but reflect the uncertainty (i.e. variance) observed in the engineering model associated during each yearly interval. However, $\beta_{v1}$ and $\beta_{v2}$ will be capped at 500 patient years (i.e. 6000 patient month) if the final engineering model has an uncertainty level that would be analogous to more than 500 patient years. Additionally, the value for $\beta_{v1}$ and $\beta_{v2}$ together with the parameter $\delta$ (proportion of follow-up actually observed during each interval vs the maximum possible follow-up of 500 patient years) will ensure that the virtual patients cannot contribute more than the actual clinical patients. The final fracture survival engineering model will be completed following the completion of the LEADR biplane fluoroscopy imaging sub-study which is being used to assess *in-vivo* curvature of the Model 093000 lead (Next Generation ICD Lead) during clinical use. A grid search will be used to identify the $\alpha_{vi}$ and $\beta_{vi}$ that minimize the sum of the absolute differences in the expected survival based on the virtual prior and the projected fracture free survival from the final engineering model, lower 2.5% of the survival rate based on the virtual prior and the lower 2.5% credible boundary of the engineering model, and the 97.5% of the survival rate based on the virtual prior and the upper 97.5% credible boundary of the engineering model. If there is more than one unique solution to the $\alpha_{vi}$ and $\beta_{vi}$ that minimize the sum of the absolute differences, the most parsimonious solution will be used (e.g. one where $\beta_{v1} = \beta_{v2}$ and/or $\alpha_{v1} = \alpha_{v2}$).

*Prior to Posterior Calculation Incorporating Virtual Patients*

The final posterior distributions for $\lambda_i$, $i$=1,2 would be

$\lambda_j$|data ~ Gamma($\rho_i\delta_i\alpha_{vi}$ + 0.1 + $\sum_{i=1 \text{ to } n} d_{ij}$, $\rho_i\delta_i\beta_{vi}$ +0.1 + $\sum_{i=1 \text{ to } n} x_{ij}$).

The final posterior distribution for $\lambda_1$ will be used to generate corresponding posterior distributions and 95% credible intervals for the fracture-free rate at 6 and 12 months using the formulas exp(-6$\lambda_1$) and exp(-12$\lambda_1$), respectively. The posterior distributions for $\lambda_1$ and $\lambda_2$ will be used to generate corresponding posterior distributions and 95% credible intervals for the fracture-free rates at 18 and 24 months using the formulas exp(-12$\lambda_1$)exp(-6$\lambda_2$) and exp(-12$\lambda_1$)exp(-12$\lambda_2$), respectively.

The posterior distributions using only clinical data (i.e. excluding virtual data) will be used to generate 95% two-sided credible intervals for the fracture-free rate at 6, 12, 18, and 24 months to assess the robustness of the result excluding virtual data.

### 13.7.5. Determination of Subjects/Data for Analysis

All subjects undergoing an implant attempt of the Next Generation ICD lead will be included in the analysis. If a subject has multiple Next Generation ICD lead implant procedures during the study, time 0 for the subject will be set to the date of the subject's first successful Model Next Generation ICD lead implant procedure. If the subject experiences a fracture endpoint prior to their first successful implant (e.g. at an unsuccessful implant attempt) or experiences a fracture endpoint but does not have any successful implant, the survival time will be set to set to time 0.

[redacted]

[redacted]

[redacted]

[redacted]

## 13.11.Stage 1 Safety Objective

The stage 1 safety objective is to estimate the 3-month RV lead-related major complication-free rate.

The endpoint for the stage 1 safety objective is the same as for the primary safety objective with the exception that the event must occur within 90 days (inclusive) of the Next Generation ICD lead implant attempt. This objective will be evaluated once 150 subjects complete their 3-month visit and include all subjects that have had a Next Generation ICD lead implant attempt at the time of the visit cutoff for analysis.

### 13.11.1. Hypothesis

There is no hypothesis for this objective since it is descriptive in nature. The goal is to estimate the freedom from RV lead related major complications and its 95% credible interval through 3-months post-implant.

### 13.11.2. Performance Requirements

There are no prespecified performance requirements for this objective. However, the 95% credible interval will provide the range of plausible values for the freedom from major RV lead related complications at 3-months post-implant based on the data at the time of the stage 1 pre-market report.

### 13.11.3. Rationale for Performance Criteria

Although there are no prespecified performance requirements for this objective, a timeframe of 3-months is expected to provide a robust estimate of RV lead performance. Specifically, the RV lead-tissue interface and electrical parameters have stabilized by 3-months. [8] Additionally, an estimate of the 3-month RV lead related major complication free rate can be obtained with sufficient precision once 150 subjects complete their 3-month visit (see section 13.4.3).

### 13.11.4. Analysis Methods

As described in sections 13.1.1 and 13.3.3 the stage 1 safety objective will be evaluated when 150 subjects complete their 3-month follow-up visit. The analysis of this objective will include all subjects with a Next Generation ICD lead implant attempt at the time of the database freeze for the evaluation of this objective. Depending on the study's enrollment rate it is projected that several hundred subjects will have an implant attempt by the time this objective is evaluated.

For descriptive purposes, a Kaplan-Meier curve will be generated using each subject's time to first Next Generation ICD lead related major complication or time to last exposure as defined in section 13.5.4, in which case the subject will be censored.

Additionally, a two-sided 95% credible interval will be computed from the piecewise exponential survival model described in section 13.5.4 with the exception that the posterior distribution for $\lambda_2$ will be computed as follows:

$\lambda_2$ ~ Gamma(1 + # of first endpoints between 1 & 3 months, 12.33 + Total Survival Months between 1 and 3 months)

The posteriors for $\lambda_1$ and $\lambda_2$ will be used to determine the posterior distribution for the 3-month freedom from Next Generation ICD lead-related major complication rate and its two-sided 95% credible interval.

[8] K. B. Stokes et al: The Electrode-Tissue Interface: The Revolutionary Role of Steroid Elution;1992.

### 13.11.5. Determination of Subjects/Data for Analysis

All subjects undergoing an implant attempt of the Next Generation ICD lead will be included in the analysis. If a subject has multiple Next Generation ICD lead implant procedures during the study, time 0 for the subject will be set to the date of the subject's first successful Model Next Generation ICD lead implant procedure. If the subject experiences a safety endpoint prior to their first successful implant (e.g. at an unsuccessful implant attempt) or experiences a safety endpoint but does not have any successful implant the time of their endpoint will be set to time 0.

# 14.Ethics

## 14.1. Statement(s) of Compliance

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

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

The LEADR Clinical 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 LEADR Clinical Study is designed to reflect the GCP principles outlined in ISO 14155:2020 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 14155:2020, 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. AE and Device Deficiency handling in the LEADR Clinical Study is ISO 14155:2020 compliant for all participating geographies.

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

- Principles of Declaration of Helsinki
- 21 CFR Part 11 (Electronic Records, Electronic Signatures)
- 21 CFR Part 54 (Financial Disclosure by Clinical Investigators)
- The CTA
- The procedures described within this CIP
- Local Ethics Committee Requirements
- Local regulations

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

- In Australia and New Zealand the study will be conducted in compliance with:
  - ISO 14155:2020

- In Canada the study will be conducted in compliance with:
  - SOR/98-282, Section 59-88

- In China the study will be conducted in compliance with:
  - Good Clinical Practice for Medical Devices (CFDA Order No. 25)
  - Announcement of CFDA on Filing of Medical Device Clinical Trial (2015, No.87)

- In Europe, Middle East, Africa, the study will be conducted in compliance with:
  - ISO 14155:2020
  - Local regulations

- In Hong Kong, the study will be conducted in compliance with:
  - ISO 14155:2020

- In Japan, the study will be conducted in compliance with:
  - Ministerial Ordinance Concerning Good Clinical Practice for Medical Devices (The Ministry of Health, Labour and Welfare (MHLW) Ministerial Ordinance No.36 in 2005 )

- In Malaysia, the study will be conducted in compliance with:
  - ISO 14155:2020
  - Notification of Exemption from Registration of Medical Devices for the Purpose of Clinical Research or Performance Evaluation (MDA/GD/0016)

- In Singapore, the study will be conducted in compliance with:
  - ISO 14155:2020
  - Health Products (Medical Device) Regulations 2010

- In the United States (including Puerto Rico), the study will be conducted under an FDA Investigational Device Exemption (IDE) in compliance with:
  - 21 CFR Part 50: Protection of Human Subjects
  - 21 CFR Part 56: Institutional Review Boards
  - 21 CFR Part 812: Investigational Device Exemptions

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

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

- Medtronic
- Principal Investigators (where required by local law/regulations)
- Geography-specific regulatory authorities (if regulatory approval is required)
- Ethics Committees

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

# 15.Study Administration

## 15.1. Monitoring

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

### 15.1.1. Monitoring Visits

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

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

## 15.2. Data Management

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

Only authorized persons can complete eCRFs. eCRFs shall be signed by the Principal Investigator. The Principal Investigator can delegate the eCRF sign off task to Sub-Investigators only. Delegation of authority will be specified on the delegation of authority log

All records and other information about subjects participating in this study will be treated as confidential. Pseudonymized subject data will be transferred and processed by Medtronic or a third party designated by Medtronic in a key coded form.

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

The investigator will clearly mark clinical records to indicate that the subject is enrolled in this clinical investigation.

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. See Section 9.21 for CRFs and data collection elements that may be considered source. Even when the CRF may be considered as source, an alternate method of source documentation is always strongly encouraged.

Pseudonymized device data from transmissions provided to Medtronic will be uploaded to secure servers and made accessible to the study team. Save-to-media/Save Reports files and other non-eCRF data such as Radiographs and Fluoroscopies collected via electronic media at office visits shall be pseudonymized and may be sent to Medtronic. Upon receipt via transmission or electronic media, non-eCRF data will be securely maintained, and stored, and retrieved for analysis and reporting.

## 15.3. Direct Access to Source Data/Documents

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

## 15.4. Confidentiality

All information and data sent to parties involved in study conduct concerning subjects or their participation in this study will be considered confidential. Study sites will assign a unique subject identification (SID) to each subject. Records of the subject-SID relationship will be maintained by the study site. The SID number is to be recorded on all study documents to link them to the subject's medical records at the study site. Confidentiality of data will be observed by all parties involved at all times throughout the clinical investigation. All data shall be secured against unauthorized access. The privacy of each subject and confidentiality of his/her information shall be preserved in reports and when publishing any data. In the US, "Protected Health Information" (PHI) will be maintained in compliance with the HIPAA of 1996. To maintain confidentiality, the subject's name or any other PHI should not be recorded on any study document other than the ICF. This scenario will be covered in the ICF. In the event a subject's name/PHI is included for any reason, it will be blinded as applicable. In the event of inability to blind the identification (e.g., digital media), it will be handled in accordance to local requirements by the authorized personnel. Data relating to the study might be made available to third

parties (for example in case of an audit performed by RA), provided the data are treated as confidential and that the subject's privacy is guaranteed. No identifiable subject information will be published.

## 15.5. Liability

### 15.5.1. Liability Insurance Australia

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

### 15.5.2. Liability Insurance Canada

Medtronic Canada ULC is a wholly owned subsidiary of Medtronic, which as the parent company of such entity maintains appropriate general 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 General Liability insurance statement/certificate will be provided to the EC.

### 15.5.3. Liability Insurance China

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

### 15.5.4. Liability Insurance Europe, Middle East, Africa

Medtronic Bakken Research Center B.V. (Europe, Middle East) is a wholly owned subsidiary of Medtronic, which as the parent company of such entity maintains appropriate clinical study liability insurance coverage as required under applicable laws and regulations and will comply with applicable local law and custom concerning specific insurance coverage. If required, a Clinical Trial insurance statement/certificate will be provided to the Ethics Committee.

### 15.5.5. Liability Insurance Hong Kong

Medtronic Hong Kong Medical, Ltd**.** is a wholly owned subsidiary of Medtronic, Inc., which as the parent company of such entity maintains appropriate clinical trial liability insurance coverage as required under applicable laws and regulations and will comply with applicable local law and custom concerning specific

insurance coverage. If required, a Clinical Trial insurance statement/certificate will be provided to the Ethics Committee.

### 15.5.6. Liability Insurance Japan

Medtronic Japan Co., Ltd 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. A documentation explaining compensation to the subjects in the event of study-related injuries and If required, a clinical study insurance statement/certificate will be provided to the study site for the review of Institutional Review Board.

### 15.5.7. Liability Insurance Malaysia

Medtronic Malaysia Sdn Bhd are wholly owned subsidiaries of Medtronic, which as the parent company of such entities 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 study insurance statement/certificate will be provided to the Ethics Board and/or a Competent Authority.

### 15.5.8. Liability Insurance New Zealand

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

### 15.5.9. Liability Insurance Puerto Rico

Medtronic USA INC is a wholly owned subsidiary of Medtronic, which as the parent company of such entity maintains appropriate clinical trial liability insurance coverage as required under applicable laws and regulations and will comply with applicable local law and custom concerning specific insurance coverage. If required, a Clinical Trial insurance statement/certificate will be provided to the EC.

### 15.5.10. Liability Insurance Singapore

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

## 15.6. CIP Amendments and Addenda

### 15.6.1. CIP Amendments

Any revisions or amendments to the CIP, ICF document or other study related documentation, along with a statement of justification for the changes, will be submitted to all affected RAs (FDA, CA) and governing ECs, according to applicable regulations. All amendments to the CIP shall be agreed upon between Medtronic and the principal investigator(s), or the coordinating investigator. Approval by regulatory agencies and ECs (where applicable) must be obtained prior to implementing a revision of study documentation.

### 15.6.2. CIP Addenda

Requests from ECs, IRBs and/or CAs can be stipulated in a CIP addendum applicable to a site or country upon mutual agreement between sponsor and the EC/IRB/CA.

## 15.7. Record Retention

### 15.7.1. 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 ISF (e.g., the study binder provided to the investigator) or Subject Study Binder. Electronic CRFs must be maintained and signed electronically within the electronic data capture system during the study. The following records are subject to inspection and must be retained for a period of two years (or longer as local law or hospital administration requires) after product approval or the date on which the investigation is terminated:

- All correspondence between the Ethics Committee, sponsor, monitor, regulatory authority and the investigator that pertains to the investigation, including required reports.
- Subject's case history records, including:
  - Signed and dated ICF in accordance with local requirements
  - Observations of AEs/ADEs/device deficiencies.
  - Medical history.
  - Implant and follow-up data (if applicable).
  - Documentation of the dates and rationale for any deviation from the CIP.
- Subject identification log.
- List of investigation study sites.
- Financial disclosure.
- All approved versions of the CIP, ICF and other information given to the subject and

Investigator's Brochure.

- Electronically signed and dated eCRFs and a blank set of CRFs when required by local regulations
- Signed and dated CTA.
- Current signed and dated CV of Principal Investigator and key members of the investigation site team (as required by applicable regulations).
- 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 certificate (if applicable per local law).
- Shipping records of investigational devices.
- Equipment maintenance records, if applicable.
- Any other records that local regulatory agencies require to be maintained.
- Final Study Report including the statistical analysis.

For China, clinical study institutions shall keep the clinical study data for at least ten years after the completion of clinical studies

### 15.7.2. Sponsor Records

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

- All correspondence which pertains to the investigation.
- Investigational device traceability records.
- Sample of label attached to investigational device
- Signed CTA
- Financial disclosure
- Current signed and dated CV 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 such as advertisement, 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 authority correspondence, notification and approval as required by national legislation.
- Insurance certificates (if applicable per local law).
- Names/contact addresses of monitors.
- Site visit reports and follow-up letters.
- Statistical analyses and underlying supporting data.
- Final report of the clinical study.
- The Clinical Investigation Plan, blank set of CRF, Investigator's Brochure and study related reports, and revisions.
- eCRFs, including AE and DD forms and eCRF corrections.
- Study training records for site personnel and Medtronic personnel involved in the study.
- Any other records that local regulatory agencies require to be maintained.

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 per Medtronic standards and applicable regulations.

## 15.8. Reporting Requirements

### 15.8.1. Investigator Reports

The investigator is responsible for the preparation (review and signature) and submission to the sponsor of all case report forms, including adverse events and adverse device effects (reported per the country-specific collection requirements), device deficiencies, deaths, and any deviations from the CIP. If any action is taken by an Ethics Committee with respect to this clinical study, copies of all pertinent documentation must be forwarded to Medtronic in a timely manner. Reports are subject to inspection and to the retention requirements as described above for investigator records.

Safety data investigator reporting requirements are listed in Table 17 of the Adverse Event section 11.6. The investigator shall prepare and submit in a complete, accurate and timely manner the reports listed in this section.

**Table 26: Investigator reports applicable for all geographies per Medtronic requirements**

| Report | Submit to | Description/Constraints |
|---|---|---|
| Withdrawal of Ethics Committee approval | Sponsor and Relevant Authorities, where applicable per local requirements | The investigator must report a withdrawal of approval by the reviewing Ethics Committee of the investigator's part of the investigation within 5 working days, or sooner as required per local requirements. |
| Study Deviations | Sponsor<br>Ethics Committee and Relevant Authorities, where applicable per local requirements | Any deviation from the Clinical Investigation Plan shall be reported together with the explanation of the deviation as soon as possible upon the site becoming aware of the deviation.<br>Notice of deviations from the CIP involving a failure to obtain a subject's consent, or is made to protect the life or physical well-being of a subject in an emergency shall be given within 5 working days, or sooner if required by local requirements. Except in such emergency, prior approval is required for changes in the plan or deviations. Reporting of serious breaches as per requirements in Australia must be complied with.<br><br>**Australia:** Report any suspected breaches to the sponsor and confirmed serious breaches to their institution (research governance office) within 72 hours of becoming aware or notified of the same; provide any follow-up information as required and work with the institution or sponsor, as appropriate, to implement any corrective and preventative actions<br>**Australia - Serious Breach:** A breach of Good Clinical Practice or the protocol that is likely to affect to a significant degree:<br>a) The safety or rights of a trial participant, or<br>b) The reliability and robustness of the data generated in the clinical trial.<br>Note: this guidance's definition of serious breach differs from the definition in the Australian Code for the Responsible Conduct of Research and is about deviations from the requirements of Good Clinical Practice or the clinical trials protocol. |
| Progress report | Sponsor and Ethics Committee | As required by local requirements. |
| Final Report | Ethics Committees and Relevant Authorities | This report must be submitted per local requirements. |

**Table 27: Investigator reports applicable to the United States (including Puerto Rico) per FDA regulations**

| Report | Submit to | Description/Constraints |
|---|---|---|
| Withdrawal of Ethics Committee approval (either suspension or termination) | Sponsor | The investigator must report a withdrawal of approval by the reviewing Ethics Committee of the investigator's part of the investigation within 5 working days. *(21 CFR 812.150(a)(2))*<br>For any action taken by an EC with respect to the investigation information will be forwarded to the sponsor. |
| Progress report | Sponsor and Ethics Committee | The investigator must submit this report to the sponsor and Ethics Committee at regular intervals, but in no event less than yearly intervals. *(21 CFR 812.150 (a)(3))*. |

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

**Table 28: Investigator (study site) reports applicable to Japan**

| Report | Submit to | Description/Constraints |
|---|---|---|
| Withdrawal of IRB approval | Sponsor and the Principal Investigator | The Head of Institution shall notify the principal investigator and the sponsor, including promptly issuing written instructions and decision based on the IRB, along with a copy of the dated cancellation document of the IRB. In addition, the Head of Institution shall explain in detail and in writing the decision of the IRB to the principal investigator and the sponsor. (MHLW Ordinance 36, Article 51) |
| Study Deviations | Sponsor and the Head of Institution | The Investigator may implement a deviation from, or a change in, the CIP to eliminate an immediate hazard(s) to study subjects without prior Ethics Board approval. In this case, the Investigator shall immediately submit to the sponsor, the Head of Institution, and to the Ethics Board via the Head of Institution, the description and reason for the deviation and the proposed revision to the CIP, if one is necessary, to receive agreement. It is the document submitted to the Ethics Board via the Head of Institute to discuss the appropriateness of continuing the clinical study. All deviations, regardless of the reason, shall be submitted to the sponsor. (MHLW Ordinance 36, Article 66) |
| Progress Report | The Head of Institution | The principal Investigator shall submit written summaries of the clinical study status to the Head of Institution annually, or more frequently if requested by the Ethics Board. The Head of Institution shall submit to the Ethics Board for the appropriateness of continuing the clinical study. (MHLW Ordinance 36, Article 68) |
| Suspension, Termination and Completion Report | The Head of Institution | When suspending or terminating a clinical study at his or her discretion, the principal investigator shall promptly report thereof and submit the details therefore in writing to the Head of Institution. |

| Report | Submit to | Description/Constraints |
|---|---|---|
| | | Upon completion of a clinical study, the principal investigator shall report thereof in writing and submit a summary of the results of the clinical study to the Head of Institution. (MHLW Ordinance 36, Article 69) |

**Table 29: Investigator reports applicable to China**

| Report | Submit to | Description/Constraints |
|---|---|---|
| Progress reports | GCP office, Sponsor and EC | During the clinical trials, should one of the following circumstances occurs, the investigators should notify the sponsor and report to the EC in a timely manner by promptly reporting to the medical device clinical trial administration department of the clinical trial institutions:<br>(II) Progress reports, including the safety summary and deviation report;<br>(CFDA order No.25 Article 18(II)) |
| Revision to documents approved by EC | GCP office, Sponsor and EC | (III) For any revision to documents approved by the EC, non-substantive changes that do not affect the subjects' rights and interests, safety and health, or are unrelated to the objective or end points of clinical trials do not need to be reported in advance but shall be reported in writing afterwards.<br>(CFDA order No.25 Article 18(III)) |
| Suspension, termination and application for recommencing clinical trials after suspension | GCP office, Sponsor and EC | (IV) Suspension, termination and application for recommencing clinical trials after suspension;<br>(CFDA order No.25 Article 18(IV)) |
| Protocol deviation | GCP office, Sponsor and EC | (V) Protocol deviation that may affect the subjects' rights and interests, safety, health or the scientificity of clinical trials, including deviation regarding requests and reports;<br>(CFDA order No.25 Article 18(V)) |
| Failure to obtain IC | Sponsor and EC | IC shall be obtained in writing and documented before a subject is enrolled into the clinical investigation. (ISO 14155:2020) |

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.

### 15.8.2. Sponsor Reports

Medtronic shall prepare and submit the following complete, accurate, and timely reports listed in the tables below (by geography). In addition to the reports listed below, Medtronic shall, upon request of reviewing Ethics Committee or regulatory authority, provide accurate, complete and current information about any aspect of the investigation. Safety data Medtronic reporting requirements are listed in Table 17 of the Adverse Event section 11.6.

**Table 30: Sponsor reports for Australia**

| Report | Submit to | Description/Constraints |
|---|---|---|
| Premature termination or suspension of the clinical investigation | Investigators, Ethics Committee, and relevant authorities | Provide prompt notification of termination or suspension and reason(s). (ISO 14155) |
| Recall and device disposition | Investigators, Ethics Committee, relevant authorities | Notification as per local requirements in Australia |
| Study deviation | Investigators | Ensure that all deviations from the CIP are reviewed with the appropriate clinical investigator(s), are reported on the CRFs and the final report of the clinical investigation. (ISO 14155)<br>Study site specific study deviations will be submitted to investigators periodically. |
| Serious Breach | Investigator and HREC | Serious breaches should be reported to the reviewing HREC and PI within 7 calendar days of confirming a serious breach has occurred and provide follow-up reports when required |
| Annual safety reports and single case Adverse events | TGA | Submit upon request from TGA |
| USADEs for Australia and international / Safety Report / updated IB / approved Product Information | Investigator and HREC | Per EC requirements, but at least annually:<br>• Annual safety report including; - a summary of the evolving safety profile of the trial, a brief description and analysis of new/relevant findings, implications of safety data to the risk-benefit ratio for the trial, a description of any measures taken or proposed to minimize risks<br>(NHMRC Safety monitoring and reporting in clinical trials involving therapeutic goods November 2016 section C.1.i)<br>• An updated/addenda of IB or IFU, if appropriate (e.g., when an IB is no longer maintained).<br>(NHMRC Safety monitoring and reporting in clinical trials involving therapeutic goods November 2016 section C.1.h) |
| Action with respect to safety that has been taken by another country's regulatory agency (relevant to an ongoing clinical trial in Australia) | TGA | Without undue delay and no later than 72 hours of the trial sponsor becoming aware of the action (Australian clinical trial handbook version 2.4). |

**Table 31: Sponsor reports for Canada**

| Report | Submit to | Description/Constraints |
|---|---|---|
| Premature termination or suspension of the clinical investigation/Site | Investigators, Ethics Committee, Relevant authorities, and Head of the Institution, Health Canada | Provide prompt notification within 15 calendar days of termination or suspension and reason(s). |

| Report | Submit to | Description/Constraints |
|---|---|---|
| Resumption of clinical investigation/site | Investigators, Ethics Committee, Head of the Institution, Health Canada | Resumption has to be approved by Ethics board, and acknowledged (revised Letter of Authorization) by Health Canada. |
| Recall and device disposition | Investigators, Head of Institution, Ethics Committee, relevant authorities | Notification within 30 working days and will include the reasons for any request that an investigator return, repair, or otherwise dispose of any devices. |
| Study deviation | Investigators | Ensure that all deviations from the CIP are reviewed with the appropriate clinical investigator(s), are reported on the CRFs and the final report of the clinical study.<br>Study site specific study deviations will be submitted to investigators periodically. |
| Final study Report | Investigators, Ethics Committee, Health Canada | Provide final report |

**Table 32: Sponsor reports for China**

| Report | Submit to | Description/Constraints |
|---|---|---|
| Premature termination or suspension of the clinical investigation | Investigators, Ethics Committee, Relevant authorities | For deciding to suspend or terminate clinical trials, sponsor shall notify the management department of medical device clinical trials of all clinical trial institutions within 5 days, and state the rationale in written form. Management department of medical device clinical trials in clinical trial institutions shall timely notify corresponding investigators and EC. The suspended clinical trials shall not be recommenced without the approval of EC. Upon the completion of clinical trials, sponsor shall notify in written form local FDA of the province, autonomous region and municipality directly under the central government where the sponsor is located. (CFDA order No.25 Article 46) |

**Table 33: Sponsor reports for Europe, Middle East, Africa, Hong Kong, New Zealand and Singapore**

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

| Report | Submit to | Description/Constraints |
|---|---|---|
| Withdrawal of CA approval | Investigators, Head of Institution, Ethics Committee, and relevant authorities | Investigators and Ethics Committee will be notified only if required by local laws or by the Ethics Committee. |
| Progress Reports | Ethics Committee and regulatory authorities | This will be submitted to the Ethics Committee and regulatory authorities only if required. |
| Final report | Investigators, Ethics Committee, and Regulatory authorities if required | • The investigator shall have the opportunity to review and comment on the final report.<br>• If a clinical investigator does not agree with the final report, his/her comments shall be communicated to the other investigator(s).<br>• The coordinating investigator shall sign the report. If no coordinating investigator is appointed, then the signature of the Principal Investigator in each study site should be obtained.<br>• The final report will be submitted per local requirements.<br>(ISO 14155, local requirements) |
| Study deviation | Investigators | Ensure that all deviations from the CIP are reviewed with the appropriate clinical investigator(s), are reported on the CRFs and the final report of the clinical investigation. (ISO 14155, local requirements)<br>Study site specific study deviations will be submitted to investigators periodically. |
| Study Closure | Regulatory authorities, Ethics Committees if required | **European Union:** The sponsor shall notify each Member State in which a clinical investigation was being conducted of the end of that clinical investigation in that Member State. That notification shall be made within 15 days of the end of the clinical investigation as specified in section 15.10. |

**Table 34: Sponsor reports for Japan**

| Report | Submit to | Description/Constraints |
|---|---|---|
| Premature termination or suspension of the clinical investigation | The Head of Institution and PMDA | When the sponsor suspends or discontinues the clinical trial, he or she shall promptly notify thereof and the detailed reason(s) thereof in writing to the Heads of Institutions and the PMDA (MHLW Ordinance 36, Article 32) |
| Termination of development of investigational device | The Head of Institution and PMDA, the related facilities | When the sponsor decides not to attach the documents concerning clinical trial records collected in the clinical trial to the authorization application, he or she shall promptly notify thereof and the detailed reason thereof in writing to the Heads of Institutions and related facilities. (MHLW Ordinance 36, Article 32) |

| Report | Submit to | Description/Constraints |
|---|---|---|
| Important information concerning the quality, effectiveness, and safety of the investigational device | Investigators, The Head of Institution and PMDA, IRB as applicable | Information of affecting subjects' safety, affecting clinical studies performance, or possibility changing the appropriateness of continuing clinical study judged by IRB shall be submitted to all Principal Investigators and The Head of Institutions.<br>The sponsor annually notifies Safety Periodic Report to the Principal Investigators and the Heads of Institutions since initial CTN submission to the PMDA.<br>When the sponsor recognizes safety information that is NOT been expecting from the Investigator's brochure (IB), the sponsor immediately notify thereof to the Principal Investigators and the Heads of Institutions.<br>The sponsor may directly notify above thereof to the IRBs in addition to the Principal Investigators and the Heads of Institutions based on the agreement with the IRBs and the Heads of Institutions.<br>When new, important information is obtained, the sponsor shall revise the IB. In addition, prior to revising the Investigator's brochure, the sponsor shall report the information to the principal investigator, the Heads of Institutions, and the PMDA. (MHLW Ordinance 36, Article 28) |
| Final Report | PMDA upon request | The sponsor shall prepare, according to the procedure, a clinical study report that summarizes the results, etc., of a clinical study when it is completed or discontinued. The final report should be stored to be submitted upon request from the PMDA. (MHLW Ordinance 36, Article 33) |
| Study deviation | Investigators, The Head of Institution as necessary | When the monitor confirms deviation as a result of monitoring, the monitor shall notify the principal Investigator and, as necessary, the Head of Institution thereof. The monitor shall also request for appropriate measures to be taken to prevent such deviation in the future. (MHLW Ordinance 36, Article 30) |

**Table 35: Sponsor reports for Malaysia**

| Report | Submit to | Description/Constraints |
|---|---|---|
| Premature termination or suspension of the clinical investigation | Investigators, Ethics Committee, Relevant Authorities and Head of the Institution | Provide prompt notification of termination or suspension and reason(s). (ISO 14155) |
| Study closeout | Regulatory Authority | Upon completion of the clinical research /performance evaluation, the Applicant shall make a declaration using the form in Annex E of MDA/GD/0016. This declaration shall be submitted to the Authority within 30 days after the date of completion.<br>(MDA/ GD/ 0016, NOTIFICATION OF EXEMPTION FROM REGISTRATION OF MEDICAL DEVICES FOR THE PURPOSE OF CLINICAL RESEARCH OR PERFORMANCE EVALUATION) |

| Report | Submit to | Description/Constraints |
|---|---|---|
| Early termination | Regulatory Authority | Should the clinical research /performance evaluation terminate earlier than the proposed date or temporarily suspended, Medical Device Authority shall be notified of the reasons for termination or suspension within two (2) weeks of the clinical research /performance evaluation being discontinued using the form in Annex E of MDA/GD/0016.<br>(MDA/ GD/ 0016, NOTIFICATION OF EXEMPTION FROM REGISTRATION OF MEDICAL DEVICES FOR THE PURPOSE OF CLINICAL RESEARCH OR PERFORMANCE EVALUATION) |
| Progress report | Regulatory Authority | Applicant shall submit a progress report every 6 months, following template as per form in Annex F of MDA/GD/0016.<br>(MDA/ GD/ 0016, NOTIFICATION OF EXEMPTION FROM REGISTRATION OF MEDICAL DEVICES FOR THE PURPOSE OF CLINICAL RESEARCH OR PERFORMANCE EVALUATION) |
| Final Report | Investigators, Ethics Committee, and Regulatory authorities if required | For studies with sites complying to ISO 14155:<br>• The investigator shall have the opportunity to review and comment on the final report.<br>• If a clinical investigator does not agree with the final report, his/her comments shall be communicated to the other investigator(s).<br>The coordinating investigator shall sign the report. If no coordinating investigator is appointed, then the signature of the Principal Investigator in each study site should be obtained. (ISO 14155) |
| Study deviation | Investigators | Ensure that all deviations from the CIP are reviewed with the appropriate clinical investigator(s), are reported on CRFs and the final report of the clinical investigation.<br>(ISO 14155)<br>Study site specific study deviations will be submitted to investigators periodically. |
| Clinical research changes | Regulatory Authority | Applicant shall inform Authority on the changes on clinical research under clinical research notification using form in Annex G of MDA/GD/0016. The changes involved may include:<br><br>a) Change to principal investigator;<br>b) Change in site name;<br>c) Change in site address;<br>d) Subsequent notification of additional clinical research notification site;<br>e) Change to ethic committee;<br>f) Changes of device (e.g.: quantity of device and type of device used); or<br>g) Others (e.g.: change in protocol/CIP, protocol title, subject recruitment)<br>(MDA/ GD/ 0016, NOTIFICATION OF EXEMPTION FROM REGISTRATION OF MEDICAL DEVICES FOR THE PURPOSE OF CLINICAL RESEARCH OR PERFORMANCE EVALUATION) |

**Table 36: Sponsor reports for the United States (including Puerto Rico)**

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

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

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

## 15.9. Publication and Use of Information

Refer to Appendix B: Preliminary Publication Plan for preliminary details of publication plans

## 15.10.Suspension or Early Termination

### 15.10.1. Planned Study Closure

Study Closure is a process initiated by distribution of a study closure letter. Study closure is defined as closure of a study that occurs when Medtronic and/or regulatory requirements have been satisfied per the CIP and/or by a decision by Medtronic or RA, whichever occurs first. The study closure process is complete upon distribution of the Final Report or after final payments, whichever occurs last. Ongoing EC oversight is required until the overall study closure process is complete. Following closure of the clinical study subjects will be provided with standard medical care by their (personal) physician.

### 15.10.2. Early Termination or Suspension

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 study site. Following closure of the clinical study subjects will be provided with standard medical care by their (personal) physician. 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 study site.

#### 15.10.2.1. Study-wide Termination or Suspension

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

- AEs 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 authority (where the study is operating under regulatory authority)
- If study has a DMC: Recommendation of early termination by the DMC based on interim analyses.
- Technical issues during the manufacturing process

#### 15.10.2.2. Investigator/Study Site Termination or Suspension

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

- Failure to obtain initial Ethics Committee approval or annual renewal of the study approval
- Persistent non-compliance to the CIP (e.g., failure to adhere to inclusion/exclusion criteria,

failure to follow subjects per scheduled follow-ups)
- Lack of enrollment
- Noncompliance to regulations and the terms of the CTA (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 study site
- Fraud or fraudulent misconduct is discovered (as defined by local law and regulations)
- Investigator request (e.g., no longer able to support the study)

### 15.10.3. Procedures for Termination or Suspension

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

#### 15.10.3.1. 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 Ethics Committee approval lapse, the investigator will promptly inform the Ethics Committee. 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

#### 15.10.3.2. 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 Ethics Committee, along with a detailed written explanation of the termination or suspension (where required per regulatory requirements)
- The investigator will promptly inform the regulatory authority (when applicable per local regulations)
- 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

#### 15.10.3.3. 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 Ethics Committee 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
- The investigator will promptly inform the regulatory authority (when applicable per local regulations)

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# 17.Appendices

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

Draft Case Report Forms for the LEADR Clinical 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 LEADR Clinical Study will be handled according to Standard Operating Procedures and as indicated in the CTA.

**Publication Committee**

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

The Publication Committee's role is to:

1) manage elements addressed in the publication plan as outlined in this appendix,
2) develop the final Publication Plan under separate cover,
3) finalize the Publication Plan,
4) oversee the publication of primary, secondary 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 at as needed.

**Management of Primary, Secondary and Ancillary Publications**

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

An ancillary publication is any publication that does not address the study objectives identified in the CIP. 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 study site data. Requests for publications on study objectives utilizing subset data (e.g., regional) will be evaluated for scientific validity and the ability of Medtronic to provide resources.

**Criteria for Determining Authorship**

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

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

- Substantial contributions to conception and design of the work, or the acquisition, analysis, or interpretation of data for the work; and
- Drafting the work 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 clinical 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 Regulatory Authorities of participating countries when required by local law
- Registering and posting the study results on ClinicalTrials.gov based on the posting rules stipulated
- Submitting for publication the primary study results after the study ends

- 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 study sites study data accessible to the corresponding investigator after the completion of the study, if requested.

## Appendix C: Instructions for Use

Instructions for Use (IFU) for the Next Generation ICD lead and catheters are provided with each component under separate cover.

## Appendix D: Informed Consent Templates

Medtronic 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

The information provided in this section pertains to foreseeable adverse events that may be observed in the LEADR Clinical Study and may collectively assist in identifying those events for a given device or therapy that are unexpected in nature. The foreseeable adverse events information consists of three parts: 1) rates of adverse events reported from previous Medtronic studies evaluating ICD, CRT-D and IPG systems, 2) adverse events reported in published literature for procedures similar to the ICD and CRT-D implant procedure, and 3) additional foreseeable adverse events. 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 Next Generation ICD lead and the associated ICD or CRT-D 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, etc.). 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.

Potential risks associated with the implantation of the Next Generation ICD lead as well as risk minimization are discussed within Section 10 of the CIP. Treatment required for procedure and/or system related adverse events may include medication, device reprogramming, device modification (e.g. repositioning, surgical abandonment, surgical removal), or other surgical and medical remedies.

### Adverse Events Reported in Previous Medtronic Studies

Table 37 to Table 40 below provide examples of adverse events associated with the use of ICD, CRT-D and IPG systems reported in four previous Medtronic studies. The BLOCK HF, Evera MRI and REVERSE studies were selected as a reference as they were IDE studies using ICD and CRT-D devices and used adverse event definitions consistent with those utilized in this study. The 3830 Lead IDE study was selected as a reference as the Next Generation ICD lead is built off the SelectSecure Model 3830 bradycardia lead. For the BLOCK HF, Evera MRI and REVERSE study adverse events were classified utilizing MedDRA, the Medical Dictionary for Regulatory Activities, to allow coding to a standard set of medical terms. The MedDRA Preferred Terms (PT) are provided in Table 37 and Table 38.

The four predicate Medtronic studies collected adverse event data from 1396 subjects that underwent an ICD/CRT-D or IPG implant. The average follow-up within the studies ranged from 10 to 54 months. Kaplan-Meier estimates and associated 95% confidence intervals of the adverse event rates are provided in the tables 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 system. Table 37 displays the adverse event rates classified as related to the system and/or procedure for CRT-D devices (BLOCK HF

and REVERSE study) while Table 38 shows the adverse event rate as related to the system and/or procedure for ICD devices (Evera MRI). Table 39 shows the procedure and system-related adverse events for IPG devices with a catheter delivered lead (3830 Lead IDE study). Table 40 shows RV lead related adverse events for all four studies.

**Table 37: System and Procedure-Related AEs from Previous Medtronic Studies with CRT-D Devices (n=771)**

| MedDRA Preferred Term | Within 30-days of Implant | | Within 12-months of Implant | |
|---|---|---|---|---|
| | No. Events (No. Subjects, %) | 95% CI | No. Events (No. Subjects, %) | 95% CI |
| ACUTE MYOCARDIAL INFARCTION | 1 (1, 0.13%) | 0.02% - 0.92% | 1 (1, 0.13%) | 0.02% - 0.92% |
| ACUTE PULMONARY OEDEMA | 2 (2, 0.26%) | 0.06% - 1.03% | 2 (2, 0.26%) | 0.06% - 1.03% |
| ADVERSE DRUG REACTION | 5 (5, 0.52%) | 0.20% - 1.38% | 5 (5, 0.52%) | 0.20% - 1.38% |
| ANGINA UNSTABLE | 1 (1, 0.13%) | 0.02% - 0.92% | 1 (1, 0.13%) | 0.02% - 0.92% |
| ANXIETY | 0 (0, 0%) | -- | 1 (1, 0.14%) | 0.02% - 1.00% |
| ARRHYTHMIA SUPRAVENTRICULAR | 1 (1, 0.13%) | 0.02% - 0.92% | 2 (1, 0.13%) | 0.02% - 0.92% |
| ATELECTASIS | 3 (3, 0.39%) | 0.13% - 1.20% | 3 (3, 0.39%) | 0.13% - 1.20% |
| ATRIAL FIBRILLATION | 14 (13, 1.69%) | 0.98% - 2.89% | 15 (14, 1.83%) | 1.09% - 3.07% |
| ATRIAL FLUTTER | 6 (6, 0.78%) | 0.35% - 1.73% | 6 (6, 0.78%) | 0.35% - 1.73% |
| ATRIOVENTRICULAR BLOCK COMPLETE | 3 (2, 0.26%) | 0.06% - 1.03% | 3 (2, 0.26%) | 0.06% - 1.03% |
| ATRIOVENTRICULAR BLOCK THIRD DEGREE | 6 (6, 0.78%) | 0.35% - 1.72% | 6 (6, 0.78%) | 0.35% - 1.72% |
| BODY TEMPERATURE INCREASED | 1 (1, 0.13%) | 0.02% - 0.92% | 1 (1, 0.13%) | 0.02% - 0.92% |
| BRADYCARDIA | 2 (2, 0.26%) | 0.06% - 1.03% | 2 (2, 0.26%) | 0.06% - 1.03% |
| BRONCHITIS | 1 (1, 0.13%) | 0.02% - 0.92% | 1 (1, 0.13%) | 0.02% - 0.92% |
| CARDIAC FAILURE | 15 (15, 1.95%) | 1.18% - 3.22% | 15 (15, 1.95%) | 1.18% - 3.22% |
| CARDIAC FAILURE ACUTE | 2 (2, 0.26%) | 0.07% - 1.04% | 2 (2, 0.26%) | 0.07% - 1.04% |
| CARDIAC FAILURE CHRONIC | 1 (1, 0.13%) | 0.02% - 0.92% | 2 (2, 0.27%) | 0.07% - 1.06% |
| CARDIAC PERFORATION | 1 (1, 0.13%) | 0.02% - 0.92% | 1 (1, 0.13%) | 0.02% - 0.92% |
| CARDIAC PROCEDURE COMPLICATION | 2 (2, 0.26%) | 0.06% - 1.03% | 2 (2, 0.26%) | 0.06% - 1.03% |
| CARDIAC TAMPONADE | 1 (1, 0.13%) | 0.02% - 0.92% | 2 (2, 0.27%) | 0.07% - 1.06% |
| CEREBROVASCULAR ACCIDENT | 1 (1, 0.13%) | 0.02% - 0.92% | 1 (1, 0.13%) | 0.02% - 0.92% |
| CHEST PAIN | 1 (1, 0.13%) | 0.02% - 0.92% | 1 (1, 0.13%) | 0.02% - 0.92% |
| COMPLICATION OF DEVICE INSERTION | 2 (2, 0.26%) | 0.06% - 1.03% | 2 (2, 0.26%) | 0.06% - 1.03% |
| CONTRAST MEDIA REACTION | 1 (1, 0.13%) | 0.02% - 0.92% | 1 (1, 0.13%) | 0.02% - 0.92% |
| CORONARY SINUS DISSECTION | 9 (9, 1.17%) | 0.61% - 2.23% | 9 (9, 1.17%) | 0.61% - 2.23% |
| DECREASED RV SENSING | 0 (0, 0%) | -- | 2 (2, 0.29%) | 0.07% - 1.14% |
| DEEP VEIN THROMBOSIS | 2 (2, 0.26%) | 0.07% - 1.03% | 4 (4, 0.53%) | 0.20% - 1.42% |
| DEFIBRILLATION THRESHOLD INCREASED | 1 (1, 0.13%) | 0.02% - 0.92% | 2 (2, 0.27%) | 0.07% - 1.06% |
| DEHYDRATION | 2 (2, 0.26%) | 0.07% - 1.04% | 2 (2, 0.26%) | 0.07% - 1.04% |
| DEVICE ELECTRICAL FINDING | 1 (1, 0.13%) | 0.02% - 0.92% | 1 (1, 0.13%) | 0.02% - 0.92% |
| DEVICE LEAD DAMAGE | 1 (1, 0.13%) | 0.02% - 0.92% | 2 (2, 0.27%) | 0.07% - 1.08% |
| DEVICE MIGRATION | 1 (1, 0.13%) | 0.02% - 0.92% | 2 (2, 0.26%) | 0.07% - 1.06% |
| DEVICE RELATED INFECTION | 1 (1, 0.13%) | 0.02% - 0.92% | 1 (1, 0.13%) | 0.02% - 0.92% |
| DIZZINESS | 1 (1, 0.13%) | 0.02% - 0.92% | 1 (1, 0.13%) | 0.02% - 0.92% |
| DIZZINESS POSTURAL | 0 (0, 0%) | -- | 1 (1, 0.14%) | 0.02% - 0.96% |
| DRUG HYPERSENSITIVITY | 2 (2, 0.26%) | 0.07% - 1.03% | 2 (2, 0.26%) | 0.07% - 1.03% |

| MedDRA Preferred Term | Within 30-days of Implant | | Within 12-months of Implant | |
|---|---|---|---|---|
| | No. Events (No. Subjects, %) | 95% CI | No. Events (No. Subjects, %) | 95% CI |
| DYSPNOEA | 4 (4, 0.52%) | 0.20% - 1.38% | 4 (4, 0.52%) | 0.20% - 1.38% |
| DYSPNOEA EXERTIONAL | 1 (1, 0.13%) | 0.02% - 0.92% | 1 (1, 0.13%) | 0.02% - 0.92% |
| ELECTRICAL RESET OF DEVICE | 0 (0, 0%) | -- | 2 (2, 0.28%) | 0.07% - 1.10% |
| ELECTROMECHANICAL DISSOCIATION | 1 (1, 0.13%) | 0.02% - 0.92% | 1 (1, 0.13%) | 0.02% - 0.92% |
| ELEVATED PACING THRESHOLD | 2 (2, 0.26%) | 0.07% - 1.03% | 5 (5, 0.68%) | 0.28% - 1.62% |
| ENTERITIS | 1 (1, 0.13%) | 0.02% - 0.92% | 1 (1, 0.13%) | 0.02% - 0.92% |
| EXTRASYSTOLES | 1 (1, 0.13%) | 0.02% - 0.93% | 1 (1, 0.13%) | 0.02% - 0.93% |
| FAILURE TO CAPTURE | 3 (3, 0.39%) | 0.13% - 1.21% | 5 (5, 0.67%) | 0.28% - 1.60% |
| FATIGUE | 1 (1, 0.13%) | 0.02% - 0.92% | 1 (1, 0.13%) | 0.02% - 0.92% |
| FLUID RETENTION | 1 (1, 0.13%) | 0.02% - 0.92% | 1 (1, 0.13%) | 0.02% - 0.92% |
| GASTROINTESTINAL HAEMORRHAGE | 1 (1, 0.13%) | 0.02% - 0.92% | 1 (1, 0.13%) | 0.02% - 0.92% |
| HAEMATOMA | 1 (1, 0.13%) | 0.02% - 0.92% | 1 (1, 0.13%) | 0.02% - 0.92% |
| HAEMOPNEUMOTHORAX | 1 (1, 0.13%) | 0.02% - 0.92% | 1 (1, 0.13%) | 0.02% - 0.92% |
| HAEMORRHAGE | 1 (1, 0.13%) | 0.02% - 0.92% | 1 (1, 0.13%) | 0.02% - 0.92% |
| HYPOTENSION | 8 (8, 1.04%) | 0.52% - 2.07% | 8 (8, 1.04%) | 0.52% - 2.07% |
| HYPOXIA | 1 (1, 0.13%) | 0.02% - 0.92% | 1 (1, 0.13%) | 0.02% - 0.92% |
| IMPAIRED HEALING | 1 (1, 0.13%) | 0.02% - 0.92% | 2 (2, 0.26%) | 0.07% - 1.05% |
| IMPLANT SITE CELLULITIS | 0 (0, 0%) | -- | 1 (1, 0.14%) | 0.02% - 0.96% |
| IMPLANT SITE EROSION | 0 (0, 0%) | -- | 2 (2, 0.27%) | 0.07% - 1.08% |
| IMPLANT SITE HAEMATOMA | 21 (21, 2.73%) | 1.79% - 4.15% | 23 (23, 3.00%) | 2.00% - 4.48% |
| IMPLANT SITE HAEMORRHAGE | 1 (1, 0.13%) | 0.02% - 0.92% | 1 (1, 0.13%) | 0.02% - 0.92% |
| IMPLANT SITE INFECTION | 8 (8, 1.04%) | 0.52% - 2.07% | 13 (13, 1.72%) | 1.00% - 2.94% |
| IMPLANT SITE INFLAMMATION | 0 (0, 0%) | -- | 1 (1, 0.14%) | 0.02% - 0.97% |
| IMPLANT SITE PAIN | 10 (10, 1.30%) | 0.70% - 2.40% | 18 (17, 2.26%) | 1.41% - 3.61% |
| IMPLANT SITE RASH | 1 (1, 0.13%) | 0.02% - 0.92% | 1 (1, 0.13%) | 0.02% - 0.92% |
| INAPPROPRIATE DEVICE STIMULATION OF TISSUE | 39 (36, 4.68%) | 3.40% - 6.43% | 66 (56, 7.41%) | 5.75% - 9.52% |
| INAPPROPRIATE DEVICE THERAPY | 1 (1, 0.13%) | 0.02% - 0.93% | 6 (6, 0.82%) | 0.37% - 1.82% |
| INCISION SITE HAEMORRHAGE | 1 (1, 0.13%) | 0.02% - 0.92% | 1 (1, 0.13%) | 0.02% - 0.92% |
| INFLUENZA | 1 (1, 0.13%) | 0.02% - 0.92% | 1 (1, 0.13%) | 0.02% - 0.92% |
| IODINE ALLERGY | 1 (1, 0.13%) | 0.02% - 0.92% | 1 (1, 0.13%) | 0.02% - 0.92% |
| JUGULAR VEIN THROMBOSIS | 1 (1, 0.13%) | 0.02% - 0.92% | 1 (1, 0.13%) | 0.02% - 0.92% |
| KELOID SCAR | 0 (0, 0%) | -- | 1 (1, 0.14%) | 0.02% - 0.98% |
| LV LEAD DISLODGEMENT | 28 (27, 3.51%) | 2.42% - 5.07% | 39 (36, 4.75%) | 3.45% - 6.53% |
| MEDICAL DEVICE CHANGE | 0 (0, 0%) | -- | 1 (1, 0.14%) | 0.02% - 0.99% |
| MEDICAL DEVICE COMPLICATION | 0 (0, 0%) | -- | 1 (1, 0.14%) | 0.02% - 0.97% |
| MEDICAL DEVICE DISCOMFORT | 0 (0, 0%) | -- | 1 (1, 0.14%) | 0.02% - 0.97% |
| MUSCLE SPASMS | 1 (1, 0.13%) | 0.02% - 0.92% | 2 (2, 0.27%) | 0.07% - 1.08% |
| MUSCLE STRAIN | 1 (1, 0.13%) | 0.02% - 0.92% | 1 (1, 0.13%) | 0.02% - 0.92% |
| MUSCULOSKELETAL PAIN | 1 (1, 0.13%) | 0.02% - 0.92% | 1 (1, 0.13%) | 0.02% - 0.92% |
| MYOCARDIAL INFARCTION | 1 (1, 0.13%) | 0.02% - 0.92% | 1 (1, 0.13%) | 0.02% - 0.92% |
| OEDEMA PERIPHERAL | 3 (3, 0.39%) | 0.13% - 1.20% | 4 (4, 0.53%) | 0.20% - 1.39% |
| ORTHOSTATIC HYPOTENSION | 2 (2, 0.26%) | 0.07% - 1.04% | 2 (2, 0.26%) | 0.07% - 1.04% |
| OVERSENSING | 1 (1, 0.13%) | 0.02% - 0.92% | 4 (4, 0.55%) | 0.21% - 1.45% |

| MedDRA Preferred Term | Within 30-days of Implant | | Within 12-months of Implant | |
|---|---|---|---|---|
| | No. Events (No. Subjects, %) | 95% CI | No. Events (No. Subjects, %) | 95% CI |
| OXYGEN SATURATION DECREASED | 1 (1, 0.13%) | 0.02% - 0.92% | 1 (1, 0.13%) | 0.02% - 0.92% |
| PAIN IN EXTREMITY | 2 (2, 0.26%) | 0.07% - 1.03% | 2 (2, 0.26%) | 0.07% - 1.03% |
| PERICARDIAL EFFUSION | 8 (8, 1.04%) | 0.52% - 2.07% | 9 (9, 1.17%) | 0.61% - 2.24% |
| PERICARDITIS | 0 (0, 0%) | -- | 1 (1, 0.14%) | 0.02% - 0.96% |
| PHANTOM SHOCK | 1 (1, 0.13%) | 0.02% - 0.93% | 1 (1, 0.13%) | 0.02% - 0.93% |
| PLEURAL EFFUSION | 7 (7, 0.91%) | 0.43% - 1.90% | 8 (8, 1.04%) | 0.52% - 2.08% |
| PLEURITIC PAIN | 1 (1, 0.13%) | 0.02% - 0.92% | 1 (1, 0.13%) | 0.02% - 0.92% |
| PNEUMONIA | 2 (2, 0.26%) | 0.06% - 1.03% | 2 (2, 0.26%) | 0.06% - 1.03% |
| PNEUMOTHORAX | 4 (4, 0.52%) | 0.20% - 1.38% | 4 (4, 0.52%) | 0.20% - 1.38% |
| PNEUMOTHORAX TRAUMATIC | 1 (1, 0.13%) | 0.02% - 0.92% | 1 (1, 0.13%) | 0.02% - 0.92% |
| PROCEDURAL HYPOTENSION | 2 (2, 0.26%) | 0.06% - 1.03% | 2 (2, 0.26%) | 0.06% - 1.03% |
| PULMONARY OEDEMA | 1 (1, 0.13%) | 0.02% - 0.92% | 1 (1, 0.13%) | 0.02% - 0.92% |
| PUNCTURE OF PERIOSTEUM | 1 (1, 0.13%) | 0.02% - 0.92% | 1 (1, 0.13%) | 0.02% - 0.92% |
| PYREXIA | 2 (2, 0.26%) | 0.07% - 1.03% | 2 (2, 0.26%) | 0.07% - 1.03% |
| RA LEAD DISLODGEMENT | 13 (13, 1.69%) | 0.99% - 2.89% | 16 (15, 1.96%) | 1.19% - 3.24% |
| RENAL FAILURE | 3 (3, 0.39%) | 0.13% - 1.20% | 3 (3, 0.39%) | 0.13% - 1.20% |
| RENAL FAILURE ACUTE | 3 (3, 0.39%) | 0.13% - 1.21% | 3 (3, 0.39%) | 0.13% - 1.21% |
| RV LEAD DISLODGEMENT | 13 (13, 1.69%) | 0.98% - 2.89% | 19 (19, 2.51%) | 1.61% - 3.90% |
| SHOULDER PAIN | 4 (4, 0.52%) | 0.20% - 1.38% | 4 (4, 0.52%) | 0.20% - 1.38% |
| SLEEP APNOEA SYNDROME | 1 (1, 0.13%) | 0.02% - 0.92% | 1 (1, 0.13%) | 0.02% - 0.92% |
| SUBCLAVIAN VEIN THROMBOSIS | 2 (2, 0.26%) | 0.07% - 1.03% | 2 (2, 0.26%) | 0.07% - 1.03% |
| SUPRAVENTRICULAR TACHYCARDIA | 0 (0, 0%) | -- | 2 (2, 0.28%) | 0.07% - 1.12% |
| SUTURE RELATED COMPLICATION | 0 (0, 0%) | -- | 2 (2, 0.27%) | 0.07% - 1.07% |
| SYNCOPE VASOVAGAL | 2 (2, 0.26%) | 0.06% - 1.03% | 2 (2, 0.26%) | 0.06% - 1.03% |
| THERMAL BURN | 1 (1, 0.13%) | 0.02% - 0.92% | 1 (1, 0.13%) | 0.02% - 0.92% |
| UNDERSENSING | 1 (1, 0.13%) | 0.02% - 0.92% | 2 (2, 0.27%) | 0.07% - 1.06% |
| UPPER RESPIRATORY TRACT INFECTION | 1 (1, 0.13%) | 0.02% - 0.92% | 1 (1, 0.13%) | 0.02% - 0.92% |
| URINARY RETENTION POSTOPERATIVE | 1 (1, 0.13%) | 0.02% - 0.92% | 1 (1, 0.13%) | 0.02% - 0.92% |
| VENTRICULAR ASYSTOLE | 1 (1, 0.13%) | 0.02% - 0.92% | 1 (1, 0.13%) | 0.02% - 0.92% |
| VENTRICULAR FIBRILLATION | 1 (1, 0.13%) | 0.02% - 0.92% | 1 (1, 0.13%) | 0.02% - 0.92% |
| VERTIGO CNS ORIGIN | 1 (1, 0.13%) | 0.02% - 0.92% | 1 (1, 0.13%) | 0.02% - 0.92% |
| WHEEZING | 2 (2, 0.26%) | 0.06% - 1.03% | 2 (2, 0.26%) | 0.06% - 1.03% |

**Table 38: System and Procedure-Related AEs from a Previous Medtronic Study with Single and Dual Chamber ICD Devices (n=264)**

| MedDRA Preferred Term | Within 30-days of Implant | | Within 12-months of Implant | |
|---|---|---|---|---|
| | No. Events (No. Subjects, %) | 95% CI | No. Events (No. Subjects, %) | 95% CI |
| ABDOMINAL PAIN UPPER | 1 (1, 0.38%) | 0.05% - 2.66% | 1 (1, 0.38%) | 0.05% - 2.66% |
| ATRIAL TACHYCARDIA | 0 (0, 0%) | -- | 2 (2, 0.77%) | 0.19% - 3.04% |
| ATRIAL THROMBOSIS | 0 (0, 0%) | -- | 1 (1, 0.41%) | 0.06% - 2.90% |
| BACK PAIN | 0 (0, 0%) | -- | 1 (1, 0.39%) | 0.05% - 2.73% |

| MedDRA Preferred Term | Within 30-days of Implant | | Within 12-months of Implant | |
|---|---|---|---|---|
| | No. Events (No. Subjects, %) | 95% CI | No. Events (No. Subjects, %) | 95% CI |
| BACTERAEMIA | 0 (0, 0%) | -- | 1 (1, 0.39%) | 0.05% - 2.72% |
| BURNING SENSATION | 0 (0, 0%) | -- | 1 (1, 0.38%) | 0.05% - 2.70% |
| CARDIAC FAILURE | 1 (1, 0.38%) | 0.05% - 2.66% | 1 (1, 0.38%) | 0.05% - 2.66% |
| CARDIAC PERFORATION | 1 (1, 0.38%) | 0.05% - 2.66% | 1 (1, 0.38%) | 0.05% - 2.66% |
| CARDIAC TAMPONADE | 1 (1, 0.38%) | 0.05% - 2.66% | 1 (1, 0.38%) | 0.05% - 2.66% |
| CEREBROVASCULAR ACCIDENT | 1 (1, 0.38%) | 0.05% - 2.66% | 1 (1, 0.38%) | 0.05% - 2.66% |
| CHEST DISCOMFORT | 1 (1, 0.38%) | 0.05% - 2.66% | 1 (1, 0.38%) | 0.05% - 2.66% |
| CHEST PAIN | 1 (1, 0.38%) | 0.05% - 2.66% | 1 (1, 0.38%) | 0.05% - 2.66% |
| CHRONIC OBSTRUCTIVE PULMONARY DISEASE | 3 (1, 0.38%) | 0.05% - 2.66% | 3 (1, 0.38%) | 0.05% - 2.66% |
| CONFUSIONAL STATE | 1 (1, 0.38%) | 0.05% - 2.66% | 1 (1, 0.38%) | 0.05% - 2.66% |
| DEEP VEIN THROMBOSIS | 0 (0, 0%) | -- | 1 (1, 0.39%) | 0.05% - 2.72% |
| DEVICE LEAD DAMAGE | 0 (0, 0%) | -- | 1 (1, 0.51%) | 0.07% - 3.53% |
| DEVICE MALFUNCTION | 0 (0, 0%) | -- | 1 (1, 0.41%) | 0.06% - 2.89% |
| DEVICE PACING ISSUE | 1 (1, 0.38%) | 0.05% - 2.66% | 1 (1, 0.38%) | 0.05% - 2.66% |
| ECCHYMOSIS | 1 (1, 0.38%) | 0.05% - 2.66% | 1 (1, 0.38%) | 0.05% - 2.66% |
| HYPOTENSION | 1 (1, 0.38%) | 0.05% - 2.66% | 1 (1, 0.38%) | 0.05% - 2.66% |
| IMPLANT SITE HAEMATOMA | 2 (2, 0.76%) | 0.19% - 2.99% | 2 (2, 0.76%) | 0.19% - 2.99% |
| IMPLANT SITE INFECTION | 1 (1, 0.38%) | 0.05% - 2.66% | 2 (2, 0.79%) | 0.20% - 3.12% |
| IMPLANT SITE PAIN | 2 (2, 0.76%) | 0.19% - 2.99% | 5 (4, 1.52%) | 0.57% - 4.01% |
| IMPLANT SITE WARMTH | 0 (0, 0%) | -- | 2 (2, 0.78%) | 0.19% - 3.06% |
| INCISION SITE VESICLES | 0 (0, 0%) | -- | 1 (1, 0.38%) | 0.05% - 2.70% |
| INJURY | 1 (1, 0.38%) | 0.05% - 2.66% | 1 (1, 0.38%) | 0.05% - 2.66% |
| OVERSENSING | 1 (1, 0.38%) | 0.05% - 2.66% | 3 (3, 1.15%) | 0.37% - 3.52% |
| PERICARDIAL EFFUSION | 1 (1, 0.38%) | 0.05% - 2.66% | 1 (1, 0.38%) | 0.05% - 2.66% |
| PERICARDITIS | 1 (1, 0.38%) | 0.05% - 2.66% | 1 (1, 0.38%) | 0.05% - 2.66% |
| PNEUMONIA | 1 (1, 0.38%) | 0.05% - 2.66% | 1 (1, 0.38%) | 0.05% - 2.66% |
| PNEUMONIA ASPIRATION | 1 (1, 0.38%) | 0.05% - 2.66% | 1 (1, 0.38%) | 0.05% - 2.66% |
| POSTOPERATIVE WOUND INFECTION | 0 (0, 0%) | -- | 1 (1, 0.38%) | 0.05% - 2.68% |
| PROCEDURAL NAUSEA | 1 (1, 0.38%) | 0.05% - 2.66% | 1 (1, 0.38%) | 0.05% - 2.66% |
| PULMONARY EMBOLISM | 0 (0, 0%) | -- | 1 (1, 0.40%) | 0.06% - 2.81% |
| RA LEAD DISLODGEMENT | 2 (2, 0.76%) | 0.19% - 2.99% | 2 (2, 0.76%) | 0.19% - 2.99% |
| RV LEAD DISLODGEMENT | 1 (1, 0.38%) | 0.05% - 2.66% | 1 (1, 0.38%) | 0.05% - 2.66% |
| VENOUS OCCLUSION | 1 (1, 0.38%) | 0.05% - 2.66% | 2 (2, 0.77%) | 0.19% - 3.03% |
| VENTRICULAR TACHYCARDIA | 2 (2, 0.76%) | 0.19% - 2.99% | 2 (2, 0.76%) | 0.19% - 2.99% |

**Table 39: System and Procedure-Related AEs from a Previous Medtronic Study with a Catheter-Delivered Lead and IPGs (n=361)**

| Key Term | Within 30-days of Implant | | Within 12-months of Implant | |
|---|---|---|---|---|
| | No. Events (No. Subjects, %) | 95% CI | No. Events (No. Subjects, %) | 95% CI |
| ABNORMAL LABS | 1 (1, 0.28%) | 0.04% - 1.95% | 1 (1, 0.28%) | 0.04% - 1.95% |
| AFIB/AFLUTTER | 4 (4, 1.16%) | 0.44% - 3.07% | 4 (4, 1.16%) | 0.44% - 3.07% |

| Key Term | Within 30-days of Implant | | Within 12-months of Implant | |
|---|---|---|---|---|
| | No. Events (No. Subjects, %) | 95% CI | No. Events (No. Subjects, %) | 95% CI |
| AIR EMBOLISM | 4 (4, 1.11%) | 0.42% - 2.93% | 4 (4, 1.11%) | 0.42% - 2.93% |
| ANXIETY | 1 (1, 0.29%) | 0.04% - 2.01% | 1 (1, 0.29%) | 0.04% - 2.01% |
| ATELECTASIS | 2 (2, 0.56%) | 0.14% - 2.23% | 2 (2, 0.56%) | 0.14% - 2.23% |
| ATRIAL TACHYCARDIA | 4 (4, 1.15%) | 0.43% - 3.03% | 4 (4, 1.15%) | 0.43% - 3.03% |
| BLEEDING AT INCISION SITE | 1 (1, 0.29%) | 0.04% - 2.05% | 1 (1, 0.29%) | 0.04% - 2.05% |
| CARDIAC PERFORATION | 1 (1, 0.28%) | 0.04% - 1.95% | 1 (1, 0.28%) | 0.04% - 1.95% |
| CATHETER KINKING | 4 (4, 1.11%) | 0.42% - 2.93% | 4 (4, 1.11%) | 0.42% - 2.93% |
| CELLULITIS | 1 (1, 0.28%) | 0.04% - 1.95% | 1 (1, 0.28%) | 0.04% - 1.95% |
| CHEST PAIN / ANGINA PECTORIS | 7 (6, 1.71%) | 0.77% - 3.78% | 8 (7, 2.03%) | 0.97% - 4.22% |
| CONFUSION /DISORIENTATION | 1 (1, 0.29%) | 0.04% - 2.05% | 1 (1, 0.29%) | 0.04% - 2.05% |
| CORONARY ARTERY DISEASE | 1 (1, 0.30%) | 0.04% - 2.08% | 1 (1, 0.30%) | 0.04% - 2.08% |
| DECREASED RANGE OF MOTION | 1 (1, 0.29%) | 0.04% - 2.06% | 1 (1, 0.29%) | 0.04% - 2.06% |
| DEVICE MIGRATION | 0 (0, 0%) | -- | 1 (1, 0.31%) | 0.04% - 2.18% |
| DIARRHEA | 1 (1, 0.29%) | 0.04% - 2.07% | 1 (1, 0.29%) | 0.04% - 2.07% |
| DIFFICULTY POSITIONING LEAD | 3 (3, 0.83%) | 0.27% - 2.55% | 3 (3, 0.83%) | 0.27% - 2.55% |
| DIZZINESS | 2 (2, 0.59%) | 0.15% - 2.32% | 2 (2, 0.59%) | 0.15% - 2.32% |
| DYSPNOEA | 1 (1, 0.29%) | 0.04% - 2.07% | 3 (3, 0.95%) | 0.31% - 2.92% |
| ECCHYMOSIS | 2 (2, 0.58%) | 0.15% - 2.30% | 2 (2, 0.58%) | 0.15% - 2.30% |
| EDEMA | 6 (6, 1.74%) | 0.79% - 3.84% | 6 (6, 1.74%) | 0.79% - 3.84% |
| ELEVATED PACING THRESHOLDS | 9 (9, 2.56%) | 1.34% - 4.87% | 26 (25, 8.39%) | 5.71% - 12.24% |
| EMPHYSEMA | 1 (1, 0.28%) | 0.04% - 1.95% | 1 (1, 0.28%) | 0.04% - 1.95% |
| FAILURE TO CAPTURE / LOSS OF CAPTURE | 6 (6, 1.69%) | 0.76% - 3.71% | 7 (7, 1.99%) | 0.95% - 4.12% |
| FAILURE TO SENSE / UNDERSENSING | 3 (3, 0.85%) | 0.27% - 2.61% | 3 (3, 0.85%) | 0.27% - 2.61% |
| FALL | 1 (1, 0.29%) | 0.04% - 2.01% | 1 (1, 0.29%) | 0.04% - 2.01% |
| FATIGUE / TIREDNESS | 2 (2, 0.58%) | 0.15% - 2.31% | 3 (3, 0.92%) | 0.30% - 2.85% |
| HEART FAILURE | 2 (1, 0.29%) | 0.04% - 2.05% | 3 (2, 0.63%) | 0.16% - 2.50% |
| HEART RATE VARIABILITY | 1 (1, 0.29%) | 0.04% - 2.05% | 1 (1, 0.29%) | 0.04% - 2.05% |
| HYPOTENSION | 5 (5, 1.40%) | 0.59% - 3.34% | 5 (5, 1.40%) | 0.59% - 3.34% |
| INAPPROPRIATE PROGRAMMING | 4 (4, 1.16%) | 0.44% - 3.06% | 7 (6, 1.85%) | 0.83% - 4.07% |
| INFECTION | 1 (1, 0.28%) | 0.04% - 1.95% | 1 (1, 0.28%) | 0.04% - 1.95% |
| LEAD INSERTION / ROUTE PROBLEM | 5 (5, 1.39%) | 0.58% - 3.32% | 5 (5, 1.39%) | 0.58% - 3.32% |
| LEAD INSULATION FAILURE | 1 (1, 0.28%) | 0.04% - 1.95% | 1 (1, 0.28%) | 0.04% - 1.95% |
| MEDICATION RELATED | 8 (8, 2.26%) | 1.14% - 4.48% | 8 (8, 2.26%) | 1.14% - 4.48% |
| MODE SWITCH | 0 (0, 0%) | -- | 2 (2, 0.63%) | 0.16% - 2.50% |
| MUSCLE STIMULATION | 3 (3, 0.86%) | 0.28% - 2.64% | 4 (3, 0.86%) | 0.28% - 2.64% |
| NAUSEA | 1 (1, 0.28%) | 0.04% - 1.95% | 1 (1, 0.28%) | 0.04% - 1.95% |
| NEAR SYNCOPE | 1 (1, 0.28%) | 0.04% - 1.95% | 1 (1, 0.28%) | 0.04% - 1.95% |
| NON-CARDIAC PAIN | 5 (5, 1.43%) | 0.60% - 3.40% | 5 (5, 1.43%) | 0.60% - 3.40% |
| OVERSENSING | 0 (0, 0%) | -- | 2 (2, 0.64%) | 0.16% - 2.55% |
| PACEMAKER MEDIATED TACHYCARDIA | 1 (1, 0.29%) | 0.04% - 2.01% | 1 (1, 0.29%) | 0.04% - 2.01% |
| PACEMAKER SYNDROME | 1 (1, 0.29%) | 0.04% - 2.06% | 1 (1, 0.29%) | 0.04% - 2.06% |
| PAIN AT POCKET SITE | 7 (7, 2.05%) | 0.98% - 4.24% | 12 (12, 3.83%) | 2.18% - 6.68% |
| PALPITATIONS | 2 (2, 0.59%) | 0.15% - 2.33% | 2 (2, 0.59%) | 0.15% - 2.33% |

| Key Term | Within 30-days of Implant | | Within 12-months of Implant | |
|---|---|---|---|---|
| | No. Events (No. Subjects, %) | 95% CI | No. Events (No. Subjects, %) | 95% CI |
| PAROXYSMAL ATRIAL FLUTTER / FIBRILLATION | 6 (6, 1.73%) | 0.78% - 3.81% | 6 (6, 1.73%) | 0.78% - 3.81% |
| PERICARDIAL EFFUSION | 8 (8, 2.24%) | 1.13% - 4.43% | 8 (8, 2.24%) | 1.13% - 4.43% |
| PLEURAL EFFUSION | 8 (8, 2.28%) | 1.15% - 4.51% | 8 (8, 2.28%) | 1.15% - 4.51% |
| PNEUMOTHORAX | 7 (7, 1.95%) | 0.93% - 4.04% | 7 (7, 1.95%) | 0.93% - 4.04% |
| POCKET HEMATOMA | 7 (7, 1.98%) | 0.95% - 4.10% | 9 (9, 2.58%) | 1.35% - 4.89% |
| POCKET INFECTION | 9 (9, 2.62%) | 1.37% - 4.98% | 14 (14, 4.15%) | 2.48% - 6.92% |
| RA LEAD DISLODGEMENT | 2 (2, 0.57%) | 0.14% - 2.27% | 4 (4, 1.29%) | 0.48% - 3.42% |
| RASH | 3 (3, 0.86%) | 0.28% - 2.65% | 3 (3, 0.86%) | 0.28% - 2.65% |
| RENAL INSUFFICIENCY | 1 (1, 0.29%) | 0.04% - 2.01% | 1 (1, 0.29%) | 0.04% - 2.01% |
| RV LEAD DISLODGEMENT | 4 (4, 1.13%) | 0.43% - 2.99% | 7 (7, 2.08%) | 1.00% - 4.33% |
| SURGICAL COMPLICATION | 1 (1, 0.29%) | 0.04% - 2.05% | 1 (1, 0.29%) | 0.04% - 2.05% |
| SUTURE EXPOSED | 1 (1, 0.29%) | 0.04% - 2.06% | 1 (1, 0.29%) | 0.04% - 2.06% |
| SYNCOPE | 1 (1, 0.28%) | 0.04% - 1.95% | 1 (1, 0.28%) | 0.04% - 1.95% |
| TAMPONADE | 3 (3, 0.83%) | 0.27% - 2.55% | 3 (3, 0.83%) | 0.27% - 2.55% |
| UNABLE TO SLIT CATHETER | 1 (1, 0.28%) | 0.04% - 1.95% | 1 (1, 0.28%) | 0.04% - 1.95% |
| VENOUS THROMBOSIS | 2 (2, 0.58%) | 0.15% - 2.31% | 2 (2, 0.58%) | 0.15% - 2.31% |
| VENTRICULAR ECTOPY (INCLUDING PVCS) | 1 (1, 0.29%) | 0.04% - 2.03% | 1 (1, 0.29%) | 0.04% - 2.03% |

**Table 40: RV Lead Related AEs from Previous Medtronic Studies (n=1396)**

| Key Term | Within 30-days of Implant | | Within 12-months of Implant | |
|---|---|---|---|---|
| | No. Events (No. Subjects, %) | 95% CI | No. Events (No. Subjects, %) | 95% CI |
| ATRIAL FIBRILLATION | 1 (1, 0.07%) | 0.01% - 0.51% | 1 (1, 0.07%) | 0.01% - 0.51% |
| ATRIAL THROMBOSIS | 0 (0, 0%) | -- | 1 (1, 0.08%) | 0.01% - 0.59% |
| ATRIOVENTRICULAR BLOCK COMPLETE | 2 (2, 0.14%) | 0.04% - 0.57% | 2 (2, 0.14%) | 0.04% - 0.57% |
| ATRIOVENTRICULAR BLOCK THIRD DEGREE | 3 (3, 0.22%) | 0.07% - 0.67% | 3 (3, 0.22%) | 0.07% - 0.67% |
| BACTERAEMIA | 0 (0, 0%) | -- | 1 (1, 0.08%) | 0.01% - 0.54% |
| CARDIAC FAILURE | 1 (1, 0.07%) | 0.01% - 0.51% | 1 (1, 0.07%) | 0.01% - 0.51% |
| CARDIAC PERFORATION | 3 (3, 0.22%) | 0.07% - 0.67% | 3 (3, 0.22%) | 0.07% - 0.67% |
| CARDIAC TAMPONADE | 2 (2, 0.14%) | 0.04% - 0.58% | 3 (3, 0.22%) | 0.07% - 0.68% |
| CHEST DISCOMFORT | 1 (1, 0.07%) | 0.01% - 0.51% | 1 (1, 0.07%) | 0.01% - 0.51% |
| COMPLICATION OF DEVICE INSERTION | 1 (1, 0.07%) | 0.01% - 0.51% | 1 (1, 0.07%) | 0.01% - 0.51% |
| DECREASED RV SENSING | 0 (0, 0%) | -- | 2 (2, 0.21%) | 0.05% - 0.83% |
| DEEP VEIN THROMBOSIS | 2 (2, 0.15%) | 0.04% - 0.58% | 5 (5, 0.38%) | 0.16% - 0.90% |
| DEFIBRILLATION THRESHOLD INCREASED | 1 (1, 0.07%) | 0.01% - 0.51% | 2 (2, 0.15%) | 0.04% - 0.59% |
| DEVICE ELECTRICAL FINDING | 1 (1, 0.07%) | 0.01% - 0.51% | 1 (1, 0.07%) | 0.01% - 0.51% |
| DEVICE LEAD DAMAGE | 0 (0, 0%) | -- | 2 (2, 0.18%) | 0.04% - 0.71% |
| DEVICE PACING ISSUE | 1 (1, 0.07%) | 0.01% - 0.52% | 1 (1, 0.07%) | 0.01% - 0.52% |
| DIFFICULTY POSITIONING LEAD | 1 (1, 0.07%) | 0.01% - 0.51% | 1 (1, 0.07%) | 0.01% - 0.51% |
| EDEMA | 1 (1, 0.07%) | 0.01% - 0.51% | 1 (1, 0.07%) | 0.01% - 0.51% |
| ELEVATED PACING THRESHOLD | 0 (0, 0%) | -- | 2 (2, 0.16%) | 0.04% - 0.63% |
| ELEVATED PACING THRESHOLDS | 5 (5, 0.36%) | 0.15% - 0.87% | 20 (20, 1.61%) | 1.04% - 2.49% |

| Key Term | Within 30-days of Implant | | Within 12-months of Implant | |
|---|---|---|---|---|
| | No. Events (No. Subjects, %) | 95% CI | No. Events (No. Subjects, %) | 95% CI |
| FAILURE TO CAPTURE | 0 (0, 0%) | -- | 1 (1, 0.08%) | 0.01% - 0.57% |
| FAILURE TO CAPTURE / LOSS OF CAPTURE | 5 (5, 0.36%) | 0.15% - 0.86% | 6 (6, 0.43%) | 0.20% - 0.96% |
| IMPLANT SITE INFECTION | 1 (1, 0.07%) | 0.01% - 0.52% | 2 (2, 0.15%) | 0.04% - 0.62% |
| INAPPROPRIATE DEVICE STIMULATION OF TISSUE | 3 (3, 0.22%) | 0.07% - 0.68% | 4 (4, 0.29%) | 0.11% - 0.78% |
| INAPPROPRIATE DEVICE THERAPY | 0 (0, 0%) | -- | 1 (1, 0.08%) | 0.01% - 0.54% |
| INAPPROPRIATE PROGRAMMING | 0 (0, 0%) | -- | 1 (1, 0.08%) | 0.01% - 0.56% |
| LEAD INSULATION FAILURE | 1 (1, 0.07%) | 0.01% - 0.51% | 1 (1, 0.07%) | 0.01% - 0.51% |
| MEDICAL DEVICE CHANGE | 0 (0, 0%) | -- | 1 (1, 0.08%) | 0.01% - 0.59% |
| MUSCLE STIMULATION | 2 (2, 0.14%) | 0.04% - 0.58% | 2 (2, 0.14%) | 0.04% - 0.58% |
| OEDEMA PERIPHERAL | 1 (1, 0.07%) | 0.01% - 0.51% | 1 (1, 0.07%) | 0.01% - 0.51% |
| OVERSENSING | 2 (2, 0.14%) | 0.04% - 0.57% | 8 (8, 0.61%) | 0.31% - 1.22% |
| PERICARDIAL EFFUSION | 9 (9, 0.65%) | 0.34% - 1.24% | 9 (9, 0.65%) | 0.34% - 1.24% |
| PERICARDITIS | 1 (1, 0.07%) | 0.01% - 0.51% | 1 (1, 0.07%) | 0.01% - 0.51% |
| PULMONARY EMBOLISM | 0 (0, 0%) | -- | 1 (1, 0.08%) | 0.01% - 0.56% |
| RV LEAD DISLODGEMENT | 18 (18, 1.30%) | 0.82% - 2.06% | 27 (27, 1.99%) | 1.37% - 2.89% |
| SUBCLAVIAN VEIN THROMBOSIS | 2 (2, 0.15%) | 0.04% - 0.58% | 2 (2, 0.15%) | 0.04% - 0.58% |
| TAMPONADE | 2 (2, 0.14%) | 0.04% - 0.57% | 2 (2, 0.14%) | 0.04% - 0.57% |
| VENOUS OCCLUSION | 1 (1, 0.07%) | 0.01% - 0.51% | 2 (2, 0.15%) | 0.04% - 0.59% |
| VENOUS THROMBOSIS | 1 (1, 0.07%) | 0.01% - 0.51% | 1 (1, 0.07%) | 0.01% - 0.51% |
| VENTRICULAR ECTOPY (INCLUDING PVCS) | 1 (1, 0.07%) | 0.01% - 0.51% | 1 (1, 0.07%) | 0.01% - 0.51% |
| VENTRICULAR TACHYCARDIA | 2 (2, 0.15%) | 0.04% - 0.58% | 2 (2, 0.15%) | 0.04% - 0.58% |

### Adverse Events Reported in Literature

Potential AEs associated with the implantation of ICD or CRT-D systems have been documented in various literature articles. A summary of those events and their published incidence are included below.

1. Haines DE, Wang Y, Curtis J. Implantable Cardioverter-Defibrillator Registry Risk Score Models for Acute Procedural Complications or Death After Implantable Cardioverter-Defibrillator Implantation. Circulation 2011;123:2069-2076.

The cohort of this study comprises patients undergoing ICD implantation from 1300 centers entering data in the National Cardiovascular Data Registry (NCDR) ICD Registry (USA) between January 1, 2006, and June 30, 2008. The rates of procedure related in-hospital complication and mortality were studied in patients from 268701 hospitalizations at 1300 hospitals.

**Table 41: Prevalence of Procedure-Related Complications in the Overall Population (N=268701) as Well as in Patients Undergoing Elective ICD Implantation (N=179401)**

| Description | All Patients | | Patients Undergoing Elective Implantation | |
|---|---|---|---|---|
| | N | % | N | % |
| Adverse Events | | | | |
| Cardiac arrest | 804 | 0.30 | 264 | 0.15 |
| Drug reaction | 249 | 0.09 | 152 | 0.08 |
| Cardiac perforation | 180 | 0.07 | 118 | 0.07 |
| Cardiac valve injury | 5 | <0.01 | 4 | <0.01 |
| Conduction block | 88 | 0.03 | 58 | 0.03 |
| Coronary venous dissection | 319 | 0.12 | 219 | 0.12 |
| Hematoma | 2509 | 0.93 | 1290 | 0.72 |
| Lead dislodgement | 2494 | 0.93 | 1542 | 0.86 |
| Hemothorax | 218 | 0.08 | 112 | 0.06 |
| Pneumothorax | 1126 | 0.42 | 677 | 0.38 |
| Peripheral nerve injury | 9 | <0.01 | 8 | <0.01 |
| Peripheral embolus | 75 | 0.03 | 26 | 0.01 |
| Phlebitis, superficial | 103 | 0.04 | 23 | 0.01 |
| Phlebitis, deep | 66 | 0.02 | 23 | 0.01 |
| TIA | 42 | 0.02 | 16 | 0.01 |
| CVA/Stroke | 154 | 0.06 | 52 | 0.03 |
| MI | 67 | 0.02 | 34 | 0.02 |
| Pericardial tamponade | 201 | 0.07 | 124 | 0.07 |
| AV fistula | 13 | <0.01 | 0 | <0.01 |
| Infection related to device | 76 | 0.03 | 33 | 0.02 |
| Outcomes | | | | |
| Any Complication | 8182 | 3.05 | 4441 | 2.48 |
| In-hospital death | 1021 | 0.38 | 212 | 0.12 |
| Any adverse events or in-hospital mortality | 8589 | 3.20 | 4499 | 2.51 |

TIA indicates transient ischemic attack; CVA, cerebrovascular accident; MI, myocardial infarction; and AV, arterio-venous.

2. Moore K, Ganesan A, Labrosciano C, et al. Sex Differences in Acute Complications of Cardiac Implantable Electronic Devices: Implications for Patient Safety. J Am Heart Assoc 2019;8

This study examined the influence of sex on acute complications. All patients aged >18 years from 2010 to 2015 who were a resident of Australia or New Zealand, undergoing a new pacemaker, ICD, or CRT implant were studied. A total of 81289 new implants (61658 pacemakers, 12097 ICDs, 7549 CRTs) were included.

**Table 42: Risk of Complications After Cardiac Implantable Electronic Device Implantation**

| | Pacemaker (N=61658) | | ICD (N=12097) | | CRT (N=7549) | |
|---|---|---|---|---|---|---|
| **Primary Outcome** | **N** | **%** | **N** | **%** | **N** | **%** |
| Composite device-related complications | 4702 | 7.6 | 1193 | 9.9 | 769 | 10.2 |
| In hospital complications | | | | | | |
| - Any in-hospital complication | 2036 | 3.3 | 376 | 3.1 | 298 | 3.9 |
| - Deaths | 333 | 0.5 | 15 | 0.1 | 23 | 0.3 |
| - Reoperation | 1711 | 2.8 | 356 | 2.9 | 272 | 3.6 |
| • Lead operation | 981 | 1.6 | 209 | 1.7 | 163 | 2.2 |
| ◦ Removal | 43 | 0.1 | 24 | 0.2 | 16 | 0.2 |
| ◦ Replacement | 183 | 0.3 | 37 | 0.3 | 28 | 0.4 |
| ◦ Revision | 787 | 1.3 | 153 | 1.3 | 124 | 1.6 |
| • Generator operation | 100 | 0.2 | 18 | 0.1 | 22 | 0.3 |
| • Pocket reoperation | 102 | 0.2 | 35 | 0.3 | 22 | 0.3 |
| • Pericardial/pleural drainage | 611 | 1.0 | 109 | 0.9 | 83 | 1.1 |
| ◦ Pericardial drainage | 104 | 0.2 | 14 | 0.1 | 10 | 0.1 |
| ◦ Pleural drainage | 522 | 0.8 | 95 | 0.8 | 74 | 1.0 |
| Post-discharge complications | | | | | | |
| - Any post-discharge complication | 2802 | 4.5 | 859 | 7.1 | 505 | 6.7 |
| - Deaths within 30 days | 457 | 0.7 | 50 | 0.4 | 59 | 0.8 |
| - Reoperation | 1447 | 2.3 | 497 | 4.1 | 299 | 4.0 |
| • Generator | 348 | 0.6 | 150 | 1.2 | 84 | 1.1 |
| • Lead | 970 | 1.6 | 359 | 3.0 | 219 | 2.9 |
| • Pocket reoperation | 129 | 0.2 | 56 | 0.5 | 33 | 0.4 |
| • Pleural/pericardial drainage | 320 | 0.5 | 71 | 0.6 | 45 | 0.6 |
| ◦ Pleural drainage | 73 | 0.1 | 20 | 0.2 | 12 | 0.2 |
| ◦ Pericardial drainage | 259 | 0.4 | 57 | 0.5 | 33 | 0.4 |
| - Hospitalization for complications | 1831 | 3.0 | 628 | 5.2 | 345 | 4.6 |
| • Mechanical complication | 1085 | 1.8 | 409 | 3.4 | 234 | 3.1 |
| - Infection* | 387 | 0.6 | 133 | 1.1 | 74 | 1.0 |
| - Local perforation† | 136 | 0.2 | 24 | 0.2 | 14 | 0.2 |
| - Pocket complication‡ | 146 | 0.2 | 47 | 0.4 | 30 | 0.4 |
| - VTE | 110 | 0.2 | 31 | 0.3 | 8 | 0.1 |

VTE indicates venous thromboembolism.
*Infection includes device infection, endocarditis, or systemic infection.
†Local perforation includes admissions for perforation and/or inflammation such as a pneumothorax or a pericardial effusion.
‡Pocket complication includes hematoma or wound dehiscence.

## Additional Adverse Events

The above incidences of each adverse event were reported from a collection of similar Medtronic studies or published papers. Other events that have been experienced in other studies or have the potential to be experienced by subjects, but were not recorded in these few Medtronic studies (or may have been reported with different terminology) also include:

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

## Appendix F: Participating Investigators and Institutions

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

## Appendix G: Ethics Committee and Competent Authority List

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

## Appendix H: Previous Clinical Investigations

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

## Appendix I: Investigator Agreement and Signature Page (where applicable)

| | |
|---|---|
| **Study product Name** | Model 093000 lead |
| **Sponsor** | **Sponsor:**<br>**Medtronic, Inc.**<br>8200 Coral Sea Street NE<br>Mounds View, MN 55112<br>United States of America<br>+1 800 328 2518<br><br>**Local Sponsors:**<br>**Australia**<br>Medtronic Australasia Pty Ltd<br>2 Alma Road, Macquarie Park<br>NSW, 2113<br>Australia<br>+61 2 9857 9000<br><br>**Canada**<br>Medtronic Canada ULC<br>99 Hereford Street Brampton<br>Ontario, L6Y 0R3 Canada<br>+1 905 460 3800<br><br>**Mainland China**<br>Medtronic (Shanghai) Management Co., Ltd.<br>2106A, 21th Floor, No. 28. Maji Road,<br>China (Shanghai) Pilot Free Trade Zone,<br>200131, Shanghai, P.R. China<br>+86 215 866 9877<br><br>**Europe, Middle East, Africa**<br>Medtronic, Bakken Research Center B.V.<br>Endepolsdomein 5<br>6229 GW Maastricht<br>The Netherlands<br>+31 43 35 66 566<br><br>**Hong Kong**<br>Medtronic Hong Kong Medical Ltd.<br>1104-11, 11/F, Tower 1,<br>The Gateway, Harbour City, Kowloon |

| | |
|---|---|
| | Hong Kong SAR, China<br>+852 2919 1300<br><br>**Japan**<br>Medtronic Japan Co., Ltd.<br>1-2-70 Konan, Minato-ku,<br>Tokyo Japan 108-0075<br>+81 3 6776 0105<br><br>**Malaysia**<br>Medtronic Malaysia Sdn Bhd<br>B-23-1 Level 23, The Ascent, Paradigm<br>No 1 Jalan SS7/26A Kelana Jaya 47301 Petaling<br>Jaya, Selangor, Malaysia<br>+60 378 838 000<br><br>**Puerto Rico**<br>Medtronic Inc.<br>9850 Doral Blvd – Suite 450<br>Miami FL 33178<br>United States of America<br>+1 786 709 4212<br><br>**Singapore**<br>Medtronic International Ltd (Singapore Branch)<br>50 Pasir Panjang Road<br>#04-51 Mapletree Business City<br>Singapore 117384<br>+65 6870 5510<br><br>**New Zealand**<br>Medtronic New Zealand Limited<br>Level 3, Building 5<br>666 Great South Road<br>Penrose<br>Auckland 1051<br>New Zealand<br>+64 9 634 1049 |
| **European Union Legal Representative of the Sponsor** | Medtronic, Bakken Research Center B.V.<br>Endepolsdomein 5<br>6229 GW Maastricht<br>The Netherlands |

| | |
|---|---|
| | +31 43 35 66 566 |
| **Clinical Investigation Plan Identifier** | MDT19004 |
| **Version Number/Date** | 4.0, 03-NOV-2021 |
| **Addendum for the Biplane Fluoroscopy Imaging Sub-Study Version Number/Date** | *To be completed if applicable* |
| I have read the protocol, including all appendices and applicable addenda, and I agree that it contains all necessary details for me and my staff to conduct this study as described. I will conduct this study as outlined herein and will make a reasonable effort to complete the study within the time designated. I agree to carry out all of its items in accordance with applicable regulations and in full compliance with the guidelines. I agree to ensure that the confidential information contained in this document will not be used for any purpose other than the evaluation and conduct of the clinical investigation without the prior written consent of Medtronic.<br>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:** | |

## Appendix J: List of Compatible ICD and CRT-D Devices

A complete list compatible ICD and CRT-D devices that can be utilized as part of the study will be distributed under separate cover upon request.

# Appendix K: Required Documentation for China

## A. Relevant qualification document(s)

Relevant qualification document(s) of the local sponsor will be provided under a separate cover.

## B. Investigator Statement

Investigator's statement

I agree that:

1. I will conduct this clinical trial in strict compliance with the Declaration of Helsinki, current laws and regulations of China, and the requirements of the protocol;

2. And record all required data accurately on the Case Report Form (CRF) and complete the final report of the clinical trial on time;

3. The investigational medical device will be used only for this clinical trial and the receipt and use of the investigational medical device will be recorded completely and accurately and the records will be retained during the process of the clinical trial;

4. The monitor and verifier authorized or designated by the Sponsor and the regulatory authorities are allowed to conduct monitoring, verification and inspection for the clinical trial;

5. The clinical trial should be conducted in strict compliance with contract/articles of agreement signed by all parties.

I have already read the clinical study protocol, including the above statement and I fully agree all the above requirements.

## C. Investigational Medical Device Information

Category of investigational medical device: Class III

Class III medical devices requiring clinical trial approval: Yes ☐ No ☒

Similar product in China: Yes☒ None☐

## D. CIP Signature Page

| |
|---|
| **Comments of the Sponsor**<br><br>**Signature (stamp)**<br><br>**Date: MM/DD/YYYY** |
| **Comments of the Investigator:**<br><br>**Signature:**<br><br>**Date: MM/DD/YYYY** |

| |
|---|
| **Comments of medical device clinical trial institution**<br><br>**Signature (stamp)**<br><br>**Date: MM/DD/YYYY** |

## Appendix L: Applicability to CMS Beneficiaries

There is a high prevalence of ventricular tachycardia treatable by ICD therapy in the Medicare population. Medicare claims data from 2017[9] shows 52,967 ICD insertion procedures. As described in the background section of this CIP, The Next Generation ICD Lead is indicated for the treatment of subjects who have experienced, or are at significant risk of developing, life-threatening ventricular tachyarrhythmias. The intended population to receive the Next Generation ICD Lead includes subjects who are indicated for implantation of a single or dual chamber ICD, or CRT-D according to current ACC/AHA/HRS or ESC guidelines.

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

## 18.Version History

| Version | Summary of Changes | Justification of changes | Potential impact of the change on performance, effectiveness, or safety or other endpoints | Identification of the affected study documents | Author(s)/Title |
|---|---|---|---|---|---|
| 1.0 | 1. Not Applicable, New Document | N/A | N/A | N/A | [redacted], Sr. Clinical Research Specialist<br>[redacted] Sr. Clinical Research Specialist<br>[redacted] Sr. Clinical Research Specialist |
| 2.0 | 1. Administrative changes were made.<br>2. Updated 17J to 18 J throughout the CIP.<br>3. 'Table 2: Product information' was updated.<br>4. 'Table 3: Materials in contact with tissues and/or body fluids' was updated. | 1. Correction of typo's and formatting errors.<br>2. Medtronic ICD and CRT-Ds allowed in the study cannot be programmed to 17J.<br>3. Product names were corrected and accessories removed.<br>4. Product names were corrected. | N/A | N/A | [redacted], Sr. Clinical Research Specialist<br>[redacted] Sr. |

| | | | | | |
|---|---|---|---|---|---|
| | 5. 'Table 4: Comparison of the Next Generation ICD and SelectSecure 3830 Leads' was updated. '0.003" x' was deleted in the 'defibrillation coil' row. | 5. Error: this was not correct. | | | Clinical Research Specialist [redacted], Sr. Clinical Research Specialist |
| | 6. 'Table 4: Comparison of the Next Generation ICD and SelectSecure 3830 Leads' was updated. '0.003" x' was deleted in the 'defibrillation coil' row. | 6. Catheter names were corrected. | | | |
| | 7. 'less than 1 month before implant' was added to Exclusion criterion #11: 'Recent (or planned) cardiac surgery or stenting'. | 7. Define a timeframe for this exclusion criterion. | | | |
| | 8. 'Table 8: Data Collection and Study Procedure Requirements at Subject Visits' was updated. | 8. Align data collection and procedure requirements to text in CIP. | | | |
| | 9. In Section '9.8.1. Medications', the list of medications to be collected was condensed. Timepoint of collection was changed to implant only. | 9. Revisited the need for medication data collection and determined this will be sufficient. | | | |
| | 10. In Section '9.8.4.2. Testing and Programming Defibrillation Therapy' 'STD' and 'REV' were replaced with 'A>B' and 'B>A'. | 10. Align text in CIP with programmer and CRFs. | | | |
| | 11. In Section '9.8.4.5. Programming Requirements at End of Implant Procedure' the requirement to collect final device interrogation data was added and a reference was made to section 9.15. | 11. Device interrogation data at the end of the implant procedure is needed. Section 9.15 specifies the required alert programming. | | | |
| | 12. 'Low Battery Voltage RRT' was added to 'Table 11: Lead and System Alerts. | 12. This alert has to be included in the list of programmable alerts. | | | |
| | 13. In section '9.17. Potential Lead System Event' language was added to clarify that an 'initial' and 'final' interrogation is needed. | 13. Clarification of requirements | | | |
| | 14. Section '9.18. System Modification' was updated. | 14. All system modifications have to be collected and not only system modifications of the ICD lead. Updated language to align with other text in CIP. | | | |
| | 15. Removed sentence on follow up schedule describing situations where the ICD lead is capped and replaced with a new one in section '9.18. System Modification'. | 15. Subjects will be followed per their original follow up schedule. | | | |

| | | | | | |
|---|---|---|---|---|---|
| | 16. Section '9.20.1. Conditional Disengagement' was deleted. | 16. It was determined that this is not required and not needed. | | | |
| | 17. Updated wording related to exit situations and expectations of data collection at study exit in Section '9.23.1. Study Exit'. | 17. Improved readability of exit situations and provided more details on data collection at study exit. | | | |
| | 18. Removed 'and will not be replaced' from section '9.23.3. Subject Chooses to Exit (i.e. Revokes Consent)'. | 18. Incorrect, subjects will be replaced in case they exit before implant. | | | |
| | 19. 'Smaller torso size' was removed in section '13.1. General Considerations'. | 19. No data will be collected on torso size. | | | |
| | 20. In section '13.2. Adaptive Design' language was added related to the end of enrollment. | 20. Added clarifying language. | | | |
| | 21. Changed the order of a sentence in Section '13.3.3. Stage 1 Pre-Market Reporting'. | 21. Improved readability. | | | |
| | 22. Added details on the contribution of virtual patient data in Section '13.7.3. Rationale for Performance Criteria' | 22. Provide more clarification on the contribution of virtual patient data. | | | |
| 3.0 | 1. Updated section 9.21 Recording Data | 1. Align language to eCRF | NA | NA | [redacted], Principal Clinical Research Specialist |
| | 2. Added a requirement for VF detection testing in Section 9.8.4.3. | 2. Ensure that only defibrillation therapy is delivered during testing | N/A | N/A | [redacted]g, Sr Principal Statistician, [redacted] Principal Statistician |
| | 3. Added details on Statistical Analysis Plan in Section 13.1 | 3. Clarification on content of Statistical Analysis Plan | | | |
| | 4. Updates to Table 18 and numbers from Table 18 referenced in Section 13.2 | 4. Minimal changes to numbers with newer version of study simulation program | | | |
| | 5. Indicated that the Gamma prior is in the shape and rate parameterization and changed to a prior of Gamma(1,3.48) and Gamma(1,12.33) for the first and second pieces. | 5. Need to explicitly define prior on using shape and rate parameterization and change prior to be more conservative to protect the type I error. | | | |

| | | | | | |
|---|---|---|---|---|---|
| | 6. Updates to text and numbers in Section 13.4.1 | 6. Clarification on simulations and minimal changes to numbers with newer version of study simulation program | | | |
| | 7. Added sentence about choice of Bayesian prior for primary efficacy objective in Section 13.4.2 | 7. Added justification for choice of prior | | | |
| | 8. Created a new version of Figure 8. | 8. A new version of Figure 8 was created to better illustrate the majority of major RV lead related major complications occur within 1-month of implant in prior studies. | | | |
| | 9. Added sentence in Section 13.5.3 | 9. Added sentence to help better describe Figure 8. | | | |
| | 10. Added details for computation of the last exposure date for the primary safety endpoint calculation in section 13.5.4. | 10. Added additional details regarding how the last Next Generation lead exposure date would be computed. Also added statement regarding false positive rate is <2.5%. | | | |
| | 11. Indicated that the Gamma prior is in the shape and rate parameterization and changed to a prior of Gamma(1,3.48) and Gamma(1,12.33) for the first and second pieces. | 11. Need to explicitly define prior on using shape and rate parameterization and change prior to be more conservative to protect the type I error. | | | |
| | 12. Added sentence in section 13.6.4. | 12. Sentence added to indicate the false positive rate is <2.5% based on the prior used for the primary efficacy objective. | | | |
| | 13. Added sentence in section 13.7.2, | 13. Added sentence to indicate that the virtual patients are combined with the clinical data following methodology developed by industry and FDA statisticians through MDIC. | | | |
| | 14. Added additional clarifying sentences to section 13.7.3. | 14. Added sentence to clarify that the prior used to illustrate how virtual patients are combined with the clinical data reflects the current knowledge of the expected performance of the Next Generation ICD lead, but is not yet finalized. Also added sentence in footnote of Table 25 illustrating impact of including virtual patients under the planned and poor performing lead scenarios. | | | |

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| | 15. Updated Figure 9 and Table 25 | 15. Minimal changes to numbers with newer version of study simulation program, | | | |
| | 16. Added additional details regarding calculation of time to last Next Generation ICD lead exposure for the analysis of the secondary objective to section 13.7.4 | 16. Added details regarding how time to last Next Generation ICD lead exposure will be calculated for the analysis for the secondary objective. | | | |
| | 17. Indicated that the shape and rate parameterization are used for the non-informative and priors based on virtual patients | 17. Need to explicitly define prior on using shape and rate parameterization. | | | |
| | 18. Added additional details regarding how virtual patient data will be incorporated in the analysis of the secondary objective in section 13.7.4, | 18. Indicated that the virtual data will be incorporated using a discount prior rather than a power prior. Provided additional details on downweighting the virtual patient prior. Added details on how the virtual patient prior will be derived from the engineering model. | | | |
| | 19. Indicated that pacing capture threshold will also be summarized at implant in section 13.8.4. | 19. Clarified that pacing capture threshold would also be summarized at implant. | | | |
| | 20. Indicated that R-wave sensing amplitude will also be summarized at implant in section 13.9. | 20. Clarified that R-wave sensing amplitude would also be summarized at implant. | | | |
| | 21. Indicated that pacing impedance will also be summarized at implant. | 21. Clarified that pacing impedance would also be summarized at implant. | | | |
| | 22. Updated the prior to posterior calculation in section 13.11.4 to use the updated prior using the shape scale parameterization of the Gamma function. | 22. Needed to update based on the use of the updated prior for RV lead related major complications. | | | |
| 4.0 | 1. Cover page and Section 2. Synopsis: addition of the EU Legal Representative of the Sponsor | 1. To comply with EU MDR Requirements. | N/A | Informed Consent Form for selected sites | [redacted] Principal Clinical Research Specialist |
| | 2. Table 1: Updated job roles. | 2. Updates in personal job roles. | | N/A | |
| | 3. Section 1.3: Removed BfArM and HREB from the glossary table. | 3. Term is not present in CIP. | | | |

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| | 4. Maximum Enrollment Cap:<br>• Section 2. Synopsis<br>• Section 5. Study Design<br>Updated maximum enrollment cap to 10% of minimum number of enrollments (500). Added language: For the first 150 implanted subjects, a single site cannot contribute more than 20% of subjects and that the maximum number of implanted subjects per site will be capped at 30 subjects for the stage 1 pre-market report. | 4. This change will allow for sites to enroll more patients to meet enrollment targets for the Biplane sub-study and ensure that geographic enrollment requirements are met.<br>Language regarding the first 150 implanted patients was added to ensure that subjects included in the stage 1 pre-market report are equally distributed across all contributing clinical sites to avoid bias. | | | |
| | 5. Section 3.1 Figure 3: Removed cross-sectional area calculations from figure. | 5. Image was intended for visual demonstration of lead size only, therefore specific calculations were removed. | | | |
| | 6. Section 5.3: Clarified that the maximum number of enrollments per site will be 10% of final sample size. Added language for the first 150 implanted subjects. | 6. To ensure equal distribution of enrollment across all geographies and sites to avoid bias. | | | |
| | 7. Section 7.3: Rephrased language regarding monitoring and auditing activities by sponsor representatives. | 7. Monitoring and audit activities are not performed under supervision of the Principal Investigator. | | | |
| | 8. Section 9.8.3.1 and 9.8.3.2: Clarified Device Sensing Requirements. Recommended that R-wave amplitude for sensing be greater than or equal to 5mV. | 8. Updated to allow more latitude to investigators on final lead location. | | | |
| | 9. Section 9.8.4.2: Clarified where to resume defibrillation testing when altering lead position. | 9. To clarify how to continue the defibrillation testing protocol when lead position is altered. | | | |
| | 10. Section 9.8.4.2 Figure 6: Figure was updated to clarify troubleshooting guidance and improved understanding of the protocol | 10. Updated to ensure that investigators are clear on when troubleshooting options should be utilized and to improve understanding of the protocol. | | | |
| | 11. Section 9.8.4.3: Removed redundancy in the VF detection requirements and added clarification. | 11. To further clarify the VF detection requirements. | | | |
| | 12. Table 12: Added definition of RV lead fracture. | 12. To include RV lead fracture definition in the CIP and to align with other study documents. | | | |
| | 13. Section 9.21: Clarified requirements for recording relatedness and/or seriousness associated with an AE or Non-Subject AE. | 13. Addition of a data source for AE relatedness/seriousness, to comply with ISO114155:2020 updates. | | | |

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| | 14. Section 10.1: 'intention to treat' was removed for the analysis of subjects that become pregnant. | 14. This terminology is used for randomized controlled clinical trials. | | | |
| | 15. Section 11.4 -Table 15: Deleted German Definition for SAE. | 15. Not applicable any longer due to MDR. | | | |
| | 16. Section 11.6: Added sentence in the first paragraph that AEs will be reported per EU MDR and MDCG in countries following EU MDR. | 16. Clarification for AE reporting in countries following EU MDR. | | | |
| | 17. Table 17: Updated requirements for Adverse Event reporting at European sites and Singapore. | 17. To align with current requirements. Applies to clinical sites in Europe and Singapore only. | | | |
| | 18. Section 13.2: Clarification of analysis time point associated with second decision point. | 18. To ensure clarity and alignment with the SAP. | | | |
| | 19. Section 13.5.3: Update to Figure 8. | 19. Updated image of RV lead-related major complication-free rates to ensure consistency with image used in other documents. | | | |
| | 20. Section 13.5.3 - Table 20: Update of lead-related complication-free rates. | 20. To ensure consistency with rates used in other documents | | | |
| | 21. Section 14.1: Removed version reference to Japanese GCP. | 21. Previous reference is not up to date. To avoid the need for future updates the reference is removed. | | | |
| | 22. Section 15.2: updated language regarding data retention. | 22. To comply with applicable regulations. | | | |
| | 23. Appendix I: Changed 'Investigator Statement' to 'Investigator Agreement and Signature Page'. EU Legal Representative of the Sponsor was also added. | 23. To align with current Medtronic CIP template and to comply with EU MDR Requirements. | | | |