Medtronic

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Medtronic

# ECG Belt for CRT Response

## Clinical Investigation Plan

Version 5.0

02MAY2019

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|---|---|---|
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| ***Worldwide clinical study leader***<br><br>Dana Wigert, Sr. Prin. Clinical Research Specialist<br>[redacted]<br>**dana.wigert@medtronic.com** | ***Canada***<br><br>Aarthi Kamath, Sr. Clinical Research Specialist<br>[redacted]<br>**aarthi.kamath@medtronic.com** |
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# CRO AND CORE LABS

| Contact Information | Duties Performed |
|---|---|
| *Cognizant Technology Solutions*<br><br>500 Frank W. Burr Blvd.<br>Teaneck, NJ 07666<br>Direct Phone: (201) 801-0233<br>Direct Fax: (201) 801-0243 | • Develop study electronic case report forms, edit checks, and study management reports.<br>• Review of electronic case report forms, management of discrepancies, and coding of medications and deviations. |
| *Echo Core Lab*<br><br>The Ohio State University<br>1960 Kenny Road<br>Columbus, Ohio 43210 | • Provide visual pre-screen of baseline echo for each subject. A 24-hour turnaround is required.<br>• Confirm that all subjects included in the analysis have a readable echo.<br>• Analyze in a blinded fashion all echocardiograms.<br>• Enter data in Oracle Clinical Echo database. |

# STEERING COMMITTEE

Primary function of the Steering Committee is to provide input for development of the protocol and study design, and to develop the publication strategy.

| Committee Member | Contact Information |
|---|---|
| John Rickard, MD-Chair<br>Cleveland Clinic | 9500 Euclid Ave J2-2<br>Cleveland, OH 44195<br>[redacted]<br>Email: rickarj2@ccf.org |
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| Kevin Vernooy, MD<br>Maastricht University Medical Center | Heart and Vascular Centre, Cardiology<br>P. Debyelaan 25<br>6229 HX Maastricht, The Netherlands<br>[redacted] |

Any additions/changes will be distributed under separate cover, upon request.

# 1. SYNOPSIS

**Title**
ECG Belt for CRT Response (**ECG Belt**)

**Purpose**
The purpose is to compare ECG Belt Research System managed cardiac resynchronization therapy (CRT) patients and a control CRT group with respect to left ventricular (LV) remodeling. The ECG Belt Research System will be used at implant and follow-up to help implanters choose a suitable LV pacing site within the recommended locations for LV lead implantation and optimize pacing vector/timing parameters in line with the EHRA/HRS 2012 expert consensus statement.

The first 6 months of follow-up will focus on using the ECG Belt Research System to help choose pacing site, vector and post-implant follow-up pacing programming. From 6 to 9 months the ECG Belt Research System will be used to further investigate more personalized programming at follow-up visits.

**Design**
Prospective, interventional, randomized, multi-center, investigational, pre-market research study.

**Investigational Medical Device**
The medical device under investigation is the investigational ECG Belt Research System that includes hardware and software components.

**Implanted System**
Use of a market-released Medtronic CRT device with AdaptivCRT and a market-released Medtronic quadripolar LV lead is required. Any market-released right ventricular (RV) and right atrial (RA) leads can be used.

**Primary Objective**
Demonstrate benefit of using the ECG Belt Research System on reducing left ventricular end-systolic volume (LVESV) from baseline to 6 months post-implant compared to standard CRT.

ECG Belt arm subjects will be compared with the control arm subjects (combined control arms A and B).

A core lab blinded to randomization and follow up status will analyze the echo data and measure LVESV.

**Subject Population**
The study population is known to have a lower likelihood of response to CRT with typical LV lead placement and device programming without an option for evaluating if pacing resynchronizes the patient's heart. The ECG Belt Research System may serve this unmet medical need.

The study will enroll approximately 500 patients at approximately 48 centers in the US, Europe, and Canada in order to randomize 400 subjects. Each subject in the study

will be enrolled prior to CRT implant and will have 3 follow-ups: post-implant, 6-month, and 9-month.

**Intervention**

Upon screening of the baseline echo, eligible subjects will be randomized 2:1:1 to either the ECG Belt arm, control arm A, or control arm B respectively. The latter two arms are identically treated up until the 6-month follow-up and will be called the control arm as a whole.

→ The ECG Belt arm will undergo ECG Belt Research System management at CRT implant to help choose pacing site and programmed vector. At Post-Implant follow-up and at the 6-month follow-up visit the ECG Belt Research System will be used to guide vector and programming parameters. At the 9-month visit the ECG Belt Research System will be used to collect data for research purposes only.

→ Control arm A will undergo routine implant and blinded ECG Belt Research System data collection at the Post-Implant follow-up. ECG Belt Research System management at the 6-month visit will help choose vector and programming parameters. At the 9-month visit the ECG Belt Research System will be used to collect data for research purposes only.

→ Control arm B will undergo routine CRT implant and blinded ECG Belt Research System data collection at both the Post-Implant and 6-month follow-ups. At the 9-month visit The ECG Belt Research System will be used to collect data for research purposes only.

**Inclusion criteria**

- Indicated for CRT, with QRS duration ≥130 ms, and planned to be implanted with a market-released Medtronic CRT device with AdaptivCRT and a market-released Medtronic quadripolar LV lead.
- Meets *at least one* of the following criteria:
  - QRS duration < 150 ms
  - Prior documented Myocardial Infarction
  - Non-LBBB[a]
- LVEDD ≥ 55 mm, as determined by site

**Exclusion criteria**

- Permanent/persistent atrial fibrillation (AF) or presenting with AF
- Pre-existing or previous LV lead or other confounding devices e.g. Left Ventricular Assist Device, Vagal Nerve Stimulator
- Currently implanted with implantable pulse generator (IPG) or implantable cardioverter defibrillator (ICD) with >10% RV pacing
- Permanent complete atrioventricular (AV) block
- Enrolled in a concurrent study that may confound the results of this study. Pre-approval from the study manager is required for enrollment of a patient that is in a concurrent study.
- Less than 1 year life expectancy

a Does not meet Strauss definition of LBBB[1]: QS or rS in leads V1 and V2 and Mid-QRS notching or slurring in ≥2 of leads V1, V2, V5, V6, I, and aVL

- Vulnerable adults
- Younger than 18 years of age

**Study Duration**

Study duration is approximately 3.5 years representing approximately 32 months of enrollment and 9 months of subject follow-up.

**Clinical Procedures and Data Collection**

- All subjects will undergo the ECG Belt Research System procedure per their randomization assignment (see schedule below). After the 9-month visit subjects will be exited.
- For patients in the ECG Belt arm the implant site, vector and pacing programming will be guided by the ECG Belt Research System data. Through the 6-month visit AdaptivCRT is required off for subjects in the control arms. After 6 months AdaptivCRT is required to stay off for subjects in control arm B. After 6 months subjects in control arm A will have vector and pacing programming guided by the ECG Belt Research System data.
- The following data will be collected for all subjects in all arms:
    - Echocardiogram (Echo) at baseline (pre-implant), and at 6- and 9-month follow-up visits
    - 12-lead ECG at baseline
    - Medical history and demographics at baseline
    - ACE/ARB, beta blockers, diuretics, and anti-arrhythmics use at baseline
    - Implanted CRT system information and characteristics
    - Device interrogations after implant and at the beginning and end of each follow-up visit
    - NYHA Functional Classification at baseline, 6 and 9 months
    - Minnesota Living with Heart Failure questionnaire at baseline, 6 and 9 months
    - Six-Minute Walk Test at baseline and 6 months
    - Patient Global Assessment Score at 6 and 9 months
    - Adverse events (including hospitalizations and death) and system modifications as they occur

## Study Diagram and Schedule

<table>
<tr><th>VISIT</th><th>ECG BELT ARM (N=200)</th><th colspan="2">CONTROL ARM (N=200)</th></tr>
<tr><td>Implant</td><td>ECG Belt: LV Lead Pacing Site<br><br>Final Programming Requirement<br>AdaptivCRT OFF<br>Final Programming Recommendation<br>Best vector per ECG Belt</td><td colspan="2">No ECG Belt<br>Routine Implant<br><br>Final Programming Requirement<br>AdaptivCRT OFF</td></tr>
<tr><td>Post-Implant Follow-up<br>(0-14 days)</td><td>ECG Belt: Programming Management<br><br>Final Programming Recommendation<br>Best vector per ECG Belt<br>AdaptivCRT BiV + LV ON, AdaptivCRT BiV ON, or personalized AV/VV delay based on relative improvement per ECG Belt</td><td colspan="2">ECG Belt: Blinded Data Collection Only<br><br>Final Programming Requirement<br>AdaptivCRT OFF</td></tr>
<tr><td>6-Month Follow-up<br><br>Primary Endpoint, begin Research Phase</td><td>ECG Belt: Less-Restricted Programming Management<br><br>Final Programming Recommendation<br>Best vector and programming per ECG Belt</td><td>Control Arm A (N=100)<br>ECG Belt: Less-Restricted Programming Management<br><br>Final Programming Recommendation<br>Best vector and programming per ECG Belt</td><td>Control Arm B (N=100)<br>ECG Belt: Blinded Data Collection Only<br><br>Final Programming Requirement<br>AdaptivCRT OFF</td></tr>
<tr><td>9-Month Follow-up</td><td colspan="3">ECG Belt for Research Phase Data Collection<br><br>Final Programming per physician discretion</td></tr>
</table>

# 2. INTRODUCTION

## a. Study purpose

Medtronic is sponsoring the ECG Belt for CRT Response (ECG Belt) study, a prospective, interventional, randomized, multi-center, investigational, pre-market research study.

The primary purpose of this study is to evaluate the ECG Belt Research System as an additional diagnostic tool for optimizing CRT therapy. The ECG Belt Research System will be used to inform placement of the LV lead while satisfying the EHRA/HRS published guidelines for LV lead implantation, and for optimizing pacing programming parameters in CRT patients. The ECG Belt Research System will provide real-time on-site feedback on CRT efficacy at the time of implant and follow-up.

The first 6 months of follow-up will focus on using the ECG Belt Research System to help choose pacing site, vector and pacing programming. From 6 to 9 months the ECG Belt Research System will be used to further investigate more personalized programming and post-implant optimization at follow-ups.

The study will focus on CRT patients that are known to have a lower likelihood of response to CRT with typical LV lead placement and device programming. These are CRT-indicated patients with a QRS duration ≥130 ms and LVEDD ≥55 mm who meet at least one of the following criteria:

- QRS duration <150 ms
- Prior documented Myocardial Infarction
- Non-LBBB

## b. Study description

The study is expected to be conducted at approximately 48 centers located in the United States, Europe, and Canada. Centers will be initiated in phases to ensure optimal implementation of the ECG Belt Research System.

Approximately 500 subjects will be enrolled in the study to ensure 400 randomized subjects. Centers are expected to randomize 8 subjects on average during the course of the study. Centers that enroll faster than others will be allowed to do so in order to maintain an adequate enrollment rate, with a maximum of 40 randomized subjects at one center to limit bias.

Study subjects will be followed for 9 months, unless there is a decision by Medtronic or regulatory authority to end the study early. The expected study duration is approximately 3.5 years representing approximately 32 months of enrollment and 9 months of subject follow-up.

# 3. BACKGROUND AND JUSTIFICATION

Implantation of cardiac resynchronization therapy device typically requires three leads, one in right atrium (RA), one in right ventricle (RV) and one in left ventricle (LV). The RV lead is usually implanted first, RA lead is always implanted in patients with sinus rhythm or when there's a chance of resumption of sinus rhythm in patients with atrial fibrillation.

Practice varies regarding placement of right sided lead but pacing threshold and sensing are usually the main factors for deciding lead location as there is no clear evidence on effect of right sided lead location on outcomes[19]. Avoiding phrenic nerve stimulation and having reasonable LV pacing thresholds also play a role in determining where to place the LV lead in the coronary sinus (CS) though several studies have shown that selection of specific LV sites for pacing may improve CRT outcomes. Though initial studies suggested placement of LV lead in the lateral wall, more recent data[19] have shown a broader spectrum of LV pacing site locations may provide good clinical response to CRT. Venography is recommended to evaluate candidate CS tributaries and consideration of fluoroscopic methods are helpful for determining anatomically optimal locations. Smaller studies have shown potential benefit in targeting areas of late electrical activation for placement of LV lead. These were based on timing from ECG QRS-onset to local LV activation (q-LV), intrinsic electrical delay between the RV lead and LV lead or even targeting areas of late mechanical activation identified using echocardiographic methods[19]. However, mostly standard-of-care approaches focus on placing the leads 'anatomically' rather than using more patient-specific physiological approaches that the ECG Belt System may provide. Multipolar leads with more stimulation points provide more pacing options which may also help get a more optimal pacing electrode and/or vector for pacing the LV.

Post-implant follow-up mainly involves routine device interrogation and testing which includes checks on battery status, lead impedances, sensing amplitudes, pacing threshold tests in all three chambers, a percentage of biventricular or left ventricular pacing. Standard-of-care practices for optimization of device timing parameters like choice of pacing vectors, AV delay, VV delay etc. are more variable with some centers using device nominals or automatic optimization routines available with certain manufacturers. Echocardiography and/or 12-lead ECG may be also used to set these parameters though there is not a clear consensus on a programming strategy to maximize the benefit of this therapy.

There are several unmet needs for patients with Heart Failure such as to reduce device complications, improve efficiency of care, and maximize CRT response.

Medtronic CRT features, such as the AdaptivCRT algorithm[2] have succeeded in improving incremental response. Even so, approximately 20-25% of patients still don't appear to improve following CRT implant. LV lead position is an important factor governing CRT response. Based on physician surveys, a key unmet need for CRT implant procedures is a system/means to determine acute response to CRT pacing during the implant procedure. Such feedback may provide physicians the confidence that they are placing the LV lead in a location that will decrease cardiac electrical dyssynchrony while ensuring that all other clinical parameters are met including lead stability, avoidance of phrenic nerve stimulation and reasonable pacing capture thresholds. Such feedback may also be used during implant and/or follow-up to determine the most optimal pacing parameters in case of a multipolar LV lead.

The ECG Belt Research System may provide a solution to this unmet need. The ECG Belt Research System [redacted]y. These maps and metrics are computed during intrinsic rhythm as well as during pacing to determine the changes from intrinsic to pacing rhythm.

Initial feasibility studies have shown that improvement in ECG Belt system metrics of electrical heterogeneity from intrinsic to CRT pacing is a better predictor of LV reverse remodeling than standard ECG-based metrics (baseline QRS, morphology, or changes in paced QRS duration) or echocardiographic measures of radial strain[3]. There is also promise of achieving a better acute hemodynamic response by helping choose an optimal LV lead position, especially in a sub-group of CRT patients. This sub-group, historically known to be more challenging to respond, includes all non-LBBB or ischemic or LBBB patients with QRS duration less than 150 ms. Reduction in the ECG Belt system metrics of electrical heterogeneity from intrinsic rhythm to CRT paced rhythm had much higher accuracy towards identifying LV pacing sites which provided acute hemodynamic improvements than did other parameters like intrinsic interventricular delays (RV-LV timing)[4] measured at different LV pacing sites or reduction in QRS width from intrinsic to CRT pacing. Continuous variable analyses have shown the ECG Belt system metrics of electrical heterogeneity, especially their changes from intrinsic to CRT pacing, exhibited a strong correlation with invasively measured LV pressure gradients obtained acutely by a Millar pressure catheter in the LV[5]. Measurement of acute response has been used previously in a study[6] to identify responsive pacing sites in the LV for improved patient outcomes. But those studies involved invasive instrumentation for measuring LV pressure.

An observational retrospective analysis[7] involving ECG belt data at follow-up in 94 patients, showed that measuring relative change in electrical heterogeneity from the belt at baseline and at optimized programming settings may help to personalize CRT to minimize heterogeneity and potentially maximize response. Optimization potential is similar regardless of pre-CRT QRS morphology or duration. Body surface mapping can therefore possibly improve CRT response by individualizing device programming to minimize electrical dyssynchrony. In another published study[8], device optimization in CRT patients with delayed enhancement (scar) on MRI improved EF and reduced electrical dyssynchrony from ECG Belt.

Since the ECG Belt Research System is a noninvasive tool and its measurements have been shown in previous studies to correlate with invasively measured hemodynamic response, it can be an easy to use noninvasive tool for identifying a potentially adequate LV pacing site without risk of additional invasive equipment (e.g. pressure catheters) during implant. The strategic intent of this study is to gather evidence in support of the ECG Belt Research System as a key tool to maximize CRT response.

A number of studies published in peer-reviewed journals and presented in peer-reviewed scientific sessions have indicated that CRT response is associated with favorable changes in the electrical activation of the heart which may be evaluated from ECG based measures or by direct or non-invasive mapping of electrical activation of the ventricles.

Sweeney et al[9] have shown that analysis of ventricular activation from the routine 12-lead ECG and its changes from intrinsic to CRT pacing can predict reverse LV remodeling in LBBB patients (n=202) with NYHA Class III-IV heart failure and with ejection fraction <35%.

Spatial patterns of ventricular activation during intrinsic rhythm and pacing in CRT patients have been studied with a noninvasive activation mapping technique called

electrocardiographic imaging (or mapping). Electrocardiographic imaging[10,11], based on the inverse problem of electrocardiography, reconstructs epicardial electrical activation based on multi-electrode ECGs (body surface potential mapping) and a thoracic CT scan.

A study of electrocardiographic imaging in ischemic heart failure patients (n=8) with varying degrees of coronary heart disease[12] has shown variable activation patterns characterized by areas of slow conduction and conduction block whose effect on the overall activation of the left ventricle may be a key determinant of CRT response. It also demonstrated the sensitivity of electrical activation maps to device timings, especially during LV only fusion pacing.

Another recent study by Ghosh et al[13] using noninvasive electrocardiographic imaging has shown that CRT response in non-ischemic cardiomyopathy (n=25) is associated with a reduction of LV electrical dyssynchrony from intrinsic to CRT pacing. The study showed presence of lines of functional block in the left ventricle which change position depending on nature of the activation (intrinsic or single V-paced or biventricular-paced) and may affect electrical resynchronization.

Similar metrics of electrical dyssynchrony derived from electrocardiographic imaging, indicative of the spatial heterogeneity in ventricular activation (which may be caused by block or regional slowing of conduction) have been investigated in a study involving narrow or normal QRS heart failure patients (n=9)[14]. Heterogeneities in activation maps and electrical dyssynchrony were observed in this group despite normal QRS duration. The potential of these patients to benefit from CRT was also suggested.

In another abstract[15], several measures of electrical dyssynchrony derived from Electrocardiographic Mapping (ECM) maps in patients (n=50) with wide and normal QRS durations were investigated for their utility in predicting short-term CRT response as identified by acute improvements in LV pressure. ECM metrics were able to successfully identify candidature for CRT, irrespective of QRS duration.

In canine studies of resynchronization pacing in LBBB with and without scar, Rademakers et al[16] have shown that best electrical resynchronization of the ventricles is associated with the best acute hemodynamic response as measured by changes in LV pressure and stroke volume.

There is mounting clinical evidence of the importance of electrical activation in CRT response. The ECG Belt (the ECG Electrode Array component of the ECG Belt Research System) [redacted] ata from internal Medtronic studies[17] show that the ECG Belt system can measure ventricular activation and its changes favorable for acute and chronic CRT response, with higher accuracy than QLV or QRS narrowing[3,5]. The present study evaluates if the ECG Belt Research System metrics can help choose an adequate LV lead pacing site at implant and optimize therapy at follow-up that improves LVESV response, an accepted surrogate for CRT response.

The study will require enrollment of patients planned to be implanted with a device that has the AdaptivCRT feature and a Medtronic quadripolar LV lead. For the primary objective, the benefit of using the ECG Belt Research System to guide personalized

therapy with Medtronic market released CRT solutions, including AdaptivCRT will be investigated. Results of the AdaptivCRT trial show that AdaptivCRT BiV-LV pacing is non-inferior to echo-optimized CRT therapy[18]. Use of a quadripolar LV lead provides the most options in choosing an optimal pacing vector. The research phase of the study will use the ECG Belt Research System to further investigate personalized CRT therapy at follow-ups.

In summary, this clinical research study will focus on maximizing CRT response by applying a non-invasive, diagnostic tool (ECG Belt Research System) at implant that could help implanters choose a suitable LV pacing site within the coronary sinus venous tributaries which are the recommended targets for the LV lead implant according to EHRA/HRS expert consensus[19], and optimize pacing parameters (e.g. timing, pacing vectors) at implant and follow-up.

# 4. SYSTEM DESCRIPTION AND INTENDED USE

## a. Investigational system description

The ECG Belt Research System is intended for research use only. It is a diagnostic tool to provide feedback on the efficacy of CRT pacing at the time of device implant or at device follow-up. The system allows measurement of electrical dyssynchrony during intrinsic rhythm and during CRT pacing and calculates the change in dyssynchrony between these measurements.

Based on the degree of change in dyssynchrony and based on prior clinical research related to the correlation of these dyssynchrony measurements to acute measures of LV dP/dt, the investigational ECG Belt Software Application will give specific feedback to the user. Two metrics of electrical heterogeneity, e.g. SDAT and LVAT, will be computed by the software. SDAT is the Standard Deviation of Activation Times of all electrodes and provides a measure of global electrical heterogeneity. LVAT is the Left Ventricular Activation Time, computed by averaging the activation time of electrodes on the left body surface. Changes in LVAT and SDAT between the intrinsic rhythm and a paced setting (ΔLVAT(%) and ΔSDAT(%), respectively) can be considered the diagnostic mechanism of action of the system. Based on these two metrics, the ECG Belt Software Application will sort the resynchronization effect achieved among all tested pacing configurations from highest to lowest.

When used for CRT management, the user will have the option to evaluate different pacing sites and CRT parameters. The primary goals of the feedback measurements are to provide the implanter with additional confidence that the patient will be a responder to CRT therapy and to provide effective CRT optimization at device follow-up. When used in blinded mode for data collection only, the software will record SDAT and LVAT values, but these will not be shown to the user.

The study will be conducted using the ECG Belt Research System components described in Table 1 and illustrated in Figure 1. Further details (manufacturer, model number etc.) will be maintained in the Investigator's Brochure. Future changes may occur with respect to the ECG Electrode Array, Software Application, Amplifier, and Tablet manufacturer and/or model during the study. A new version of the system may be incorporated that is market-approved in some geographies. Medtronic will ensure that

any future changes to the ECG Belt Research System do not impact the scientific soundness and safety of the study and IRBs/MECs are informed and have approved these changes per local requirement before use in the study.

Instructions for use will be provided in the ECG Belt Research System's User Manual.

The following are body contacting materials found on the ECG Electrode Array (ECG Belt): Polyethylene terephthalate (PET), LOCTITE UV Curable Dielectric Ink and Katecho Adhesive Hydrogel.

Table 1: ECG Belt Research System components information

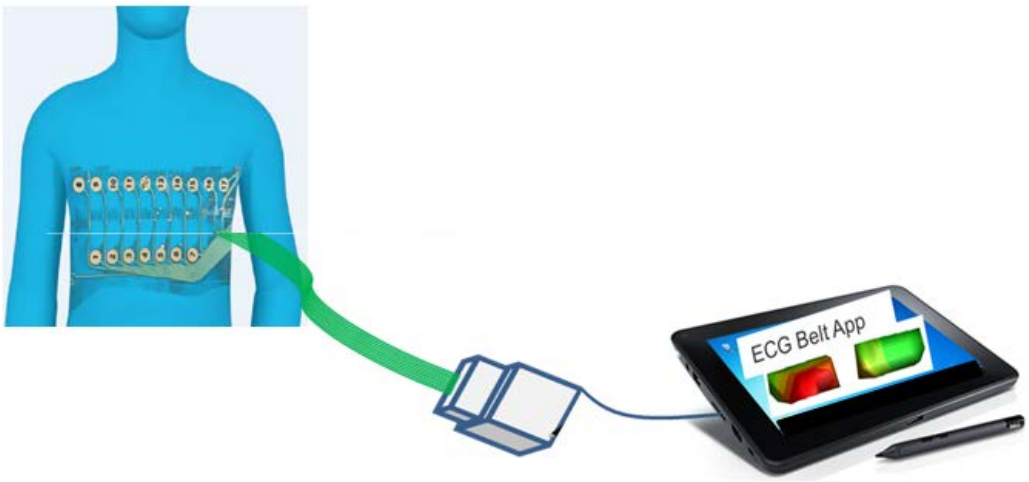
| **System Component** | **Investigational or Market-Released (applies in all regions)** | **Functional Responsibilities** |
|---|---|---|
| ECG Electrode Array (ECG Belt) | Investigational | • Provides multiple electrodes that are in contact with the skin of the patient's torso via the electrode |
| Multi-Channel ECG Amplifier (includes the hardware, firmware, connector/adapter) | Investigational | • [redacted]<br>• Provides amplification, signal processing, A/D conversion and sampling of electrical potentials<br>• [redacted] |
| [redacted] | [redacted] | [redacted] |

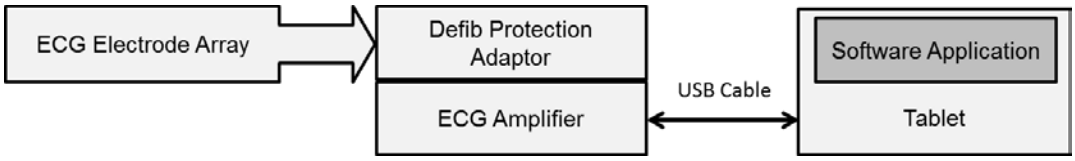
| System Component | Investigational or Market-Released (applies in all regions) | Functional Responsibilities |
|---|---|---|
| | | • Protected by drive level encryption and requires a password |
| Tablet | Market-Released | • Runs the software application<br>• Displays the user interface and accepts user inputs<br>• Stores data<br>• Provides power via USB to the multi-channel ECG amplifier<br>• Provides an output to display to an external monitor<br>• Provides at least three hours of operation when fully charged (must not be connected to wall power when connected to the subject) |

Traceability of all system components shall be achieved during and after the study through the lot numbers, batch numbers or serial number of the component assigned by the manufacturer. If the manufacturer has not assigned such an identifier, Medtronic will assign one. The tablet with pre-installed ECG Belt Software Application will be tracked as one item.

The ECG Electrode Array will be referred to as the ECG Belt. ECG Belts are single use, so each subject in the ECG Belt arm will require 4 ECG Belts and subjects in control arm A and B will require 3 ECG Belts. This will result in the use of approximately 1400 ECG Belts throughout the course of the study. Approximately 55 Multi-Channel ECG Amplifiers/Adaptors and tablets pre-loaded with the ECG Belt Software Application will be available in the study. This will allow for one ECG Belt Research System per site and several backups per region.

Figure 1: ECG Belt Research System






### b. Intended use investigational system

The ECG Belt Research System will be used at implant and device follow-up for CRT indicated patients. The ECG Belt is intended for single use. All other components are reusable.

### c. Other devices and equipment used in the study

For this study patients are selected for which implant of a market-released Medtronic CRT device with AdaptivCRT and a Medtronic quadripolar LV lead is planned. Any market-released RV and RA leads are allowed. Systems will be used within their approved intended use, e.g. off-label use/programming is not allowed.

A commercially available Medtronic CRT device with AdaptivCRT is required which may include (based on geographic availability):

- Viva™ Quad XT CRT-D
- Claria MRI™ Quad CRT-D SureScan™
- Amplia MRI™ Quad CRT-D SureScan™
- Percepta™ Quad CRT-P MRI SureScan™
- Serena™ Quad CRT-P MRI SureScan™
- Any future generation commercially available CRT Quad device with the AdaptivCRT™ algorithm

A commercially available Medtronic quadripolar LV pacing lead is required unless placement is unsuccessful, in which case a commercially available, transvenous, Medtronic bipolar LV pacing lead may be used.

Any compatible commercially available RV lead can be used.

Any compatible commercially available RA lead can be used.

Any market-released Medtronic programmer and analyzer can be used, for example CareLink Model 2090 Programmer with the Model 2290 Analyzer. Adaptors and cables will be used to test the leads during implant.

An optional isolation transformer will be provided with the system in geographies where this is required.

The Medtronic CareLink Model 2090 Programmer and software (or any market-released Medtronic programmer) are used to program the CRT device at implant and follow-ups. The programming head will be needed for communications with this device. Programmers from other manufacturers are not compatible with Medtronic devices.

# 5. REGULATORY COMPLIANCE

This 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 Board/IRB/MEC before initiating a study, continuing review of an ongoing study by an Ethics Boards, and obtaining and documenting the freely given informed consent of a subject before initiating the study.

The ECG Belt study was designed to reflect the GCP principles outlined in ISO 14155:2011 and other international clinical requirements outlined below. These include the protection of the rights, safety and well-being of human subjects, controls to ensure the scientific conduct and credibility of the clinical investigation and the definition of responsibilities of the sponsor and investigators. In accordance with ISO standard, the sponsor shall avoid improper influence on, or inducement of, the subject, monitor, any investigator(s) or other parties participating in, 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.

The ISO standard also informed study design in the areas of device deficiency reporting and risk evaluation, with the exception (to Section 6.4 of the ISO standard) that only those Adverse Events (AEs) considered related to the ECG Belt Research System and all Serious AEs will be collected. This ensures any AEs which could potentially be relevant will be collected.

The study will be conducted in compliance with the Clinical Investigation Plan (CIP), federal, national and local laws, including data protection laws, regulations, standards, and requirements of the countries/geographies where the study is being conducted. The principles of the Declaration of Helsinki have been implemented through the patient informed consent process, Ethics Board/IRB/MEC approval, study training, clinical trial registration, preclinical testing, risk-benefit assessment and publication policy.

In all geographies, the study will be conducted in compliance with 21 CFR Part 54.

In the United States, the study will be conducted in compliance with 21 CFR Parts 11, 50, 56, 812. This study does not require an IDE submission to FDA. However, all requirements in 812.2(b)(1) must be followed. The study will be conducted as a Non-Significant Risk (NSR) study because it does not meet the definition of a significant risk device study.

(1) The ECG Belt Research System does not contain any components intended as an implant. It is non-invasive and will be temporarily wrapped around the subject's upper torso to collect electrical data.

(2) The ECG Belt Research System is not for use in supporting or sustaining human life.

(3) The ECG Belt Research System is not of substantial importance in diagnosing, curing, mitigating, treating disease, or otherwise preventing impairment of human health. Only subjects already planned for CRT implant will be enrolled in the study.

(4) For subjects in the ECG Belt arm, LV lead placement will not be solely based on ECG Belt Research System data. The lead will be placed in a location based on ECG Belt Research System data if the location also satisfies other clinical criteria for lead placement (e.g., appropriate pacing thresholds, lack of

phrenic nerve stimulation, anatomic stability, etc.) according to the expert consensus statement on CRT implant and follow-up[19]. Similarly, the ECG Belt Research System will provide an additional tool for optimizing CRT therapy during follow up for subjects in the ECG Belt arm and control arm A.

(5) The ECG Belt Research System does not otherwise present a potential for serious risk to the health, safety, or welfare of a subject.

In Canada, the study will be conducted in accordance with Canada Medical Device Regulations,1998 (SOR/98-282), and the Guidance document for Mandatory Problem Reporting for Medical Devices, 2011(H164-145/201E).

In Europe, the study will be conducted in compliance with ISO14155:2011 and in accordance with the Declaration of Helsinki version 2013 and local laws and requirements for pre-market research feasibility studies.

Any additional requirements imposed by the regulatory authorities and independent medical ethics committee or institutional review board shall be followed.

The study will be publicly registered prior to first enrollment in accordance with the 2007 Food and Drug Administration Amendments Act (FDAAA) and Declaration of Helsinki on http://clinicaltrials.gov (PL 110-85, Section 810(a)).Approval of the CIP is required from the following groups prior to any study procedures at a study center:

- Medtronic
- Principal Investigators (where required by local law)
- Geography-specific regulatory authorities (if regulatory approval is required)
- An independent medical ethics committee or institutional review board.

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

# 6. METHODOLOGY

The study comprises two phases. The first phase through 6-month follow-up has the purpose to investigate use of the ECG Belt Research System to help choose pacing site, vector and pacing programming.
The second phase of the study from 6 to 9 months follow-up has the purpose to further investigate use of the ECG Belt Research System for more personalized programming at follow-ups.

### a. Primary Objective

Demonstrate benefit of using the ECG Belt Research System on reducing LVESV from baseline to 6 months post-implant compared to standard CRT.

## b. Ancillary Objectives

1. To estimate the benefit of using the ECG Belt Research System on LVEF compared to standard CRT.
2. To estimate the benefit of using the ECG Belt Research System on change in quality of life compared to standard CRT.
3. To estimate the benefit of using the ECG Belt Research System on change in Six-Minute Walk Test distance compared to standard CRT.
4. To estimate the benefit of using the ECG Belt Research System on the Clinical Composite Score compared to standard CRT.
5. To characterize ECG Belt Research System-related AEs.
6. To assess the changes in LVESV from 6-9 months between subjects who have and have not used the ECG Belt Research System at 6 months.
7. To assess the extent of ECG Belt Research System guided programming changes across study visits.

## c. Subject selection criteria and enrollment

Patients will be screened to ensure they meet all of the inclusion and none of the exclusion criteria prior to study enrollment. Ethics Committee approval of the ECG Belt CIP and Informed Consent Form (ICF) must be obtained prior to enrolling patients in the study. The patient is considered enrolled upon signing of the ICF.

### *i. Inclusion criteria*

- Indicated for CRT, with QRS duration ≥130 ms, and planned to be implanted with a market-released Medtronic CRT device with AdaptivCRT and a Medtronic quadripolar LV lead.
- Meets *at least <u>one</u>* of the following criteria:
  - QRS duration < 150 ms
  - Prior documented Myocardial Infarction
  - Non-LBBB[b]
- LVEDD ≥ 55 mm, as determined by site

### *ii. Exclusion criteria*

- Permanent/persistent AF or presenting with AF
- Pre-existing or previous LV lead or other confounding devices e.g. Left Ventricular Assist Device, Vagal Nerve Stimulator
- Currently implanted with IPG or ICD with > 10% RV pacing
- Permanent complete AV block
- Enrolled in a concurrent study that may confound the results of this study. Pre-approval from the study manager is required for enrollment of a patient that is in a concurrent study.
- Less than 1 year life expectancy
- Vulnerable adults
- Younger than 18 years of age

b Does <u>not</u> meet Strauss definition of LBBB[1]: QS or rS in leads V1 and V2 and Mid-QRS notching or slurring in ≥2 of leads V1, V2, V5, V6, I, and aVL

### d. Randomization

Eligible subjects will be randomized 2:1:1 to either the ECG Belt arm, control arm A, or control arm B respectively. The latter two arms are identically treated up until the 6-month follow-up and will be called the control arm as a whole. Randomization schedules will be created for each site by a statistician using randomized blocks and stratified by center to ensure relatively equal randomization within each center.

After verification that a subject meets all inclusion/exclusion criteria and core lab confirmation that LVESV is able to be determined from the subject's echocardiogram, subjects will undergo randomization prior to any implant attempt. Centers will receive each subject's assignment electronically via the study database.

### e. Blinding

Due to the use of the ECG Belt during implant and follow-up, it is difficult to blind subjects or physicians to the treatment assignment. The echo core lab will be blinded to the randomization assignment.

### f. Minimization of Bias

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

- Subjects will be screened to confirm eligibility for enrollment with defined inclusion/exclusion criteria prior to enrollment.
- A maximum of 40 subjects is allowed to be randomized at a single center.
- Subject demographics and other characteristics will be collected at baseline to evaluate any possible differences between ECG Belt and control groups that may affect outcome.
- All clinicians will be trained and required to follow the CIP.
- Clinicians will be encouraged to approach all subjects who meet inclusion/exclusion criteria.
- The primary endpoint, LVESV is a measurement that is not directly controlled by the subject, making it less prone to bias due to placebo effects.
- Individual randomization assignments will only be provided to centers once required data is entered into the database.
- The echo core lab will measure the primary endpoint and will be blinded to the randomization assignment and follow-up status.

When using the ECG Belt Research System in control arm subjects for data collection only, clinicians will be blinded to the ECG Belt Software Application maps and metrics. For subjects in the Control arm, the ECG Belt Research System data will not be collected at Implant and will not be displayed at Post-Implant Follow-up Visits and at the 6 month Follow-up Visit (Control Arm B). In these cases, Investigators will use their standard of care procedure for implant and device programming. This will prevent the

ECG Belt Research System data from influencing their routine decision-making process for implant and device programming. Potential sources of bias that may be encountered in this clinical study have been considered and minimized by careful study design.

# 7. STUDY PROCEDURES

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

### a. Investigator / Investigation site selection

All clinical investigators managing the subject's heart failure must be qualified practitioners and experienced in the diagnosis and treatment of subjects with heart failure. All EP/implanting physicians must be experienced and/or trained in the handling of CRT devices.

The role of the principal investigator is to implement and manage the day-to-day conduct of the clinical investigation as well as to 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/interested in CRT optimization
- During implant, be willing to move the LV lead to a second location (if available and accessible) if the ECG Belt Research System does not indicate an improvement at the first location
- Disclose potential conflicts of interest, including financial, that interfere with the conduct of the clinical investigation or interpretation of results (all geographies)

The principal investigator shall be able to demonstrate that the proposed investigational site:

- Has a reasonable number of eligible subjects within the recruitment period
- Has a coordinator, a qualified investigational site team and adequate facilities for the foreseen duration of the clinical investigation

Center personnel training will be completed prior to participation in this clinical study.

### b. Site activation

During the activation process (prior to subject enrollment), Medtronic will train site personnel on the ECG Belt Research System, clinical investigation plan, relevant standards and regulations, if needed, informed consent, and on data collection and reporting tools. If new members join the study center team, they will receive training on the applicable clinical study requirements relevant to their role before contributing to the clinical study.

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

Prior to performing study related activities, all local regulatory requirements shall be fulfilled, including, but not limited to the following:

- Ethics Committee approval (and voting list, as required by local law) of the current version of the CIP and ICF
- Regulatory authority approval or notification (as required per local law)
- Fully executed Clinical Trial Agreement (CTA)
- Curriculum Vitae (CV) of investigators (all geographies), and key members of the investigation site team (Europe)
    - The signature on the CV must be dated within 3 years prior to the date of activation of the site (Europe).
- Documentation of delegated tasks
- Documentation of study training

Additional requirements imposed by the Ethics Committee and regulatory authority shall be followed, if appropriate.

In addition, all participating site staff must be trained on the current version of the CIP and must be delegated by the principal investigator prior to performing study related activities. Personnel delegated to operate the ECG Belt Research System and perform the implant and/or provide technical support at implant and follow-up must be trained on the use of the ECG Belt Research System.

Medtronic will provide each study center with documentation of study center/investigator readiness; this letter must be received prior to subject enrollment.

### c. Equipment requirements

The following equipment must be available at each center to support study activities:

- Medtronic will provide an ECG Belt Research System and an adequate supply of disposable ECG Belts to each center
- Echocardiographic system
- Any market-released Medtronic programmer and analyzer can be used, for example CareLink Model 2090 Programmer with the Model 2290 Analyzer.
- Medtronic will provide cables and adaptors necessary to test leads with the Analyzer during implant
- Medtronic will provide disposable tape measures to collect chest circumference at the Baseline visit

No arrangements are needed related to the calibration and maintenance of the Medtronic-provided ECG Belt Research System. The echocardiographic system will be calibrated and maintained per hospital policy.

### d. Data collection

Data collection requirements are summarized in Table 2 below.

Table 2: Data collection and study procedure requirements at subject visits

| Study Procedure | Baseline | Rando-mization | Implant | Post-implant Follow-up | 6-month Follow-up | 9-month Follow-up |
|---|---|---|---|---|---|---|
| Patient informed consent | x | | | | | |
| Inclusion/exclusion assessment | x | | | | | |
| Medical history and demographics | x | | | | | |
| NYHA Functional Classification | x | | | | x | x |
| Minnesota living with Heart Failure questionnaire | x | | | | x | x |
| Patient Global Assessment Score* | | | | | x | x |
| Six-Minute Walk Test | x | | | | x | |
| Echocardiogram | x** | | | | x | x |
| Randomization | | x | | | | |
| Collection of CRT implant characteristics and implanted system description | | | x | | | |
| ECG Belt Research System procedure | | | ECG Belt arm: management | ECG Belt arm: management<br><br>Control arm A and B: blinded data collection | ECG Belt arm and Control arm A: manage-ment<br><br>Control arm B: blinded data collection | All subjects: unblinded data collection |
| ECG 12 lead | x*** | | | | | |
| Full CRT device interrogation and save-to-media | | | At end of visit | Pre and post-visit | Pre and post-visit | Pre and post-visit |
| Exits | As they occur | | | | | |
| Adverse events (AEs, including AEs with outcome of death, and hospitalizations) | | | | | | |
| Device deficiencies**** | | | | | | |

| Study Procedure | Baseline | Rando-mization | Implant | Post-implant Follow-up | 6-month Follow-up | 9-month Follow-up |
|---|---|---|---|---|---|---|
| System modifications | | | | | | |
| Study deviations | | | | | | |

* This is needed for Clinical Composite Score
** Echo is acceptable if taken within 2 months of enrollment
*** 12-lead ECG is acceptable if taken within 30 days of enrollment
**** Where “device” refers to the ECG Belt Research System used in this study

### e. Role of the sponsor representatives

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

- Provide study training relevant and pertinent to the involvement of personnel conducting study activities and investigator responsibilities
- Technical support at baseline, implant and follow-up visits under the supervision of a study investigator, but no data entry into the electronic database shall be performed by Medtronic personnel at sites. Medtronic personnel may support completion of the study worksheets.

### f. Patient informed consent process

The ICF is defined as a legally effective documented confirmation of a patient’s voluntary agreement to participate in a particular clinical study after information has been given to the patient on all aspects of the clinical study that are relevant to the patient’s decision to participate. This process includes obtaining an ICF and an Authorization to Use and Disclose Personal Health Information/Research Authorization/other privacy language as required by law (US sites) that has been approved by the study center’s Ethics Committee and signed and dated by the subject. A patient may only consent after information has been given to the patient on all aspects of the clinical investigation that are relevant to the subject’s decision to participate. Patients requiring a Legally Authorized Representative to consent should not be enrolled in the ECG Belt study.

Consistent with the Declaration of Helsinki, vulnerable adults (i.e. those patients mentally incapable of giving consent) are excluded from this protocol. Any patients with mental incompetence (e.g. Alzheimers, dementia, psychiatric disorders, developmental disorders) should be assessed for vulnerable status. This protocol defines vulnerable adult as those patients mentally incapable of giving consent, in the Investigator’s opinion. The Investigator should consider the definition of vulnerable adult per ISO 14155, which defines vulnerable adults as: “vulnerable patients are those patients that could be unduly influenced by the expectation or benefits associated with participation or of retaliatory response from senior members of a hierarchy in case of refusal to participate. For example, this could include Individuals with loss of autonomy due to immaturity or through mental disability, persons in nursing homes, children, impoverished persons, subjects in emergency situations, ethnic minority groups, homeless persons, nomads, refugees, and those incapable of giving informed consent. Other vulnerable subjects could include, for example, members of a group with a hierarchical structure such as university students, subordinate hospital and laboratory

personnel, employees of the sponsor, members of the armed forces, and persons kept in detention."

Prior to enrolling patients, each center's Ethics Committee will be required to approve the ICF. The document(s) must be controlled (i.e. versioned and/or dated) to ensure it is clear which version(s) were approved by the Ethics Committee. Any adaptation of the sample ICF must be reviewed and approved by Medtronic and the Ethics Committee reviewing the application prior to enrolling subjects.

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

Prior to initiation of any study-specific procedures, patient informed consent must be obtained from the subject. Likewise, privacy or health information protection regulation may require subjects to sign additional forms to authorize centers to submit subject information to the study sponsor. The informed consent process must be conducted by the principal investigator or an authorized designee, and the Patient Consent Form and Authorization to Use and Disclose Personal Health Information/Research Authorization/other privacy language (US) must be given to the subject in a language he/she is able to read and understand. The process of patient informed consent must be conducted without using coercion or undue improper influence on or inducement of the subject to participate by the investigator or other center personnel. The informed consent process shall not waive or appear to waive subject's legal right. The language used shall be as non-technical as possible and must be understandable to the subject and the impartial witness, where applicable.

The subject must have ample time and opportunity to read and understand the informed consent form, to inquire about details of the study, and to decide whether or not to participate in the clinical study. All questions about the study should be answered to the satisfaction of the subject.

When the patient decides to participate in the clinical study, the ICF must be signed and personally dated by the patient and investigator or authorized designee, as required by the ICF. If applicable, the witness shall also sign and personally date the ICF to attest that the information in the ICF was accurately explained and clearly understood by the subject, and that informed consent was freely given.

A copy of the ICF and the Authorization to Use and Disclose Personal Health Information/Research Authorization/other privacy language (US), signed and dated as required by law, must be provided to the subject.

If the ICF 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. It is required for the informed consent process to be documented in the patient's case history, regardless of circumstance.

In the event the patient cannot read and/or write, witnessed (impartial third party) patient informed consent will be allowed, provided detailed documentation of the process is recorded in the patient's case history and the witness signs and dates the patient informed consent. The independent witness shall be present throughout the process.

The written informed consent form and any other information shall be read aloud and explained to the patient. The patient should “make his mark” (sign or otherwise physically mark the document so as to indicate consent) on the ICF as well. The ICF should document the method used for communication with the prospective subject and specific the means by which the prospective subject communicated agreement to participate in the study.

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

The ICF and Authorization to Use and Disclose Personal Health Information/Research Authorization/other privacy language as required by law (US) must be available for monitoring and auditing. Any Medtronic Field personnel who support the ECG Belt study must be able to review the subject’s signed and dated Consent Form and verify its completeness prior to proceeding with the implant/download. In the event the Medtronic Field personnel identify patient informed consent as being incomplete, the study specific procedures will not be allowed to occur until the consent of the patient can be adequately and appropriately obtained.

When a patient and the principal investigator or authorized designee, as required have personally signed and dated the ICF, the patient is considered a subject enrolled in the study. The date the subject signed the ICF and data protection authorization must be documented in the subject’s medical records.

### g. Baseline (pre-CRT implant) data collection

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

- Echo recording. Instructions on data transmission to Core Lab will be provided under a separate cover. The echo should be current within the last 2 months of the enrollment date. All echos must be anonymized and labeled with a Medtronic-assigned identification number prior to submission to the Core Lab.
- Baseline ECG (12-lead). The ECG should be current within last 30 days of the enrollment date.
- NYHA Functional Classification
- Minnesota Living with Heart Failure questionnaire
- Six-Minute Walk Test
- Medical history and demographics

An echo will be collected prior to randomization. A standard of care echo is acceptable if taken within 2 months of enrollment. The echo will be sent to the core laboratory for review. The core lab review of the baseline echo will be required to confirm readability of LVESV. If the images are determined unreadable and/or of poor quality by the core lab, the site may try another echo or exit the subject from the study prior to randomization.

Additionally, a 12-lead ECG will be collected if no 12-lead ECG has been performed within 30 days of enrollment. For subjects being considered for an upgrade from pacemaker/ICD, their rhythm will be tested. For subjects with a single chamber device, program to VVI 40. For subjects with a dual chamber device, program to AAI mode or extend the AV delays to the maximum setting. If the subject receives ventricular pacing from the device under the setting, the subject will be exited from the study.

### h. Randomization

Centers will receive each subject's randomization assignment electronically via the Oracle Clinical database upon confirmation of the subject's inclusion/exclusion criteria and baseline echo readability.

### i. Implant

Use of market released Medtronic CRT device with AdaptivCRT and a market released Medtronic quadripolar LV lead is required.

Physicians are expected to follow the recommendations of the 2012 EHRA-HRS expert consensus statement[19]. These recommendations include "venography to evaluate candidate venous tributaries and consideration of electrical and fluoroscopic methods to help select optimal sites; The final position of the LV pacing lead depends on the anatomy of the cardiac venous system, the performance and stability of the pacing lead, and the absence of PNS [Phrenic Nerve Stimulation]". Furthermore, the consensus also states that "recent trials evaluating long-term response to CRT show a good clinical response with a range of LV lead locations".

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

- CRT implant characteristics and implanted system details
- For control arms A and B, methods used to determine LV lead placement and programming settings
- For subjects randomized to the ECG Belt arm, ECG Belt Research System data will be collected for the following situations:
    - intrinsic rhythm
    - during intra-procedural biventricular pacing
    - final device programming
- A full interrogation of the implanted device with final programmed parameters.

In case the final implanted system differs from what was planned according to the inclusion criteria (a market-released Medtronic CRT device with AdaptivCRT and a Medtronic quadripolar LV lead), continue to collect data and follow the protocol as closely as possible.

#### *i. ECG Belt arm: CRT device implant and recommended programming*

For subjects enrolled in the ECG Belt arm of the study, the ECG Belt will be applied on the subject's chest and back just before he or she is prepped for the CRT implant procedure. The right heart leads should be implanted per standard of care. After evaluation of a venogram, the quadripolar LV lead will be placed in the implanter's preferred site. The ECG Belt Research System will obtain measurements of the baseline intrinsic rhythm and during pacing.

If the ECG Belt Software Application does not indicate an improvement in electrical dyssynchrony during pacing at available electrodes without inducing phrenic nerve

stimulation, it is recommended that the implanter move the lead to another candidate site (e.g. other vein or side branch) if such a site is available and accessible. An improvement in dyssynchrony will be considered a relative improvement in SDAT by ≥10% with pacing or an improvement in LVAT by ≥30% without a worsening of SDAT by more than 10%. If the lead is placed at another location, the ECG Belt Research System measurements will be repeated during pacing at available electrodes in this new site.

The final LV lead implant site will be determined by the maximum resynchronization effect achieved as long as it satisfies other clinical criteria for lead placement (reasonable pacing thresholds, lack of phrenic nerve stimulation at target LV pacing site(s), anatomic stability of lead location) per physician discretion.

After the CRT device is implanted and the pocket is closed per standard of care, the LV pacing vector is expected to be programmed to provide the best electrical resynchronization, as indicated by the ECG Belt Software Application, after clinical factors such as phrenic nerve stimulation, reasonable pacing thresholds, etc. have been considered. AdaptivCRT and multiple point pacing (MPP) should be OFF. MPP is intended for non-responders who cannot be identified at implant. Additionally, MPP results in a decrease to longevity that may be avoided with the personalized programming offered by the ECG Belt system.

Upon completion of the CRT implant procedure, the ECG Belt Software Application results will be saved and submitted to Medtronic, the System will be disconnected, and the ECG Belt will be removed from the subject.

See Figure 2 for an overview of the study workflow at implant for subjects in the ECG Belt arm.

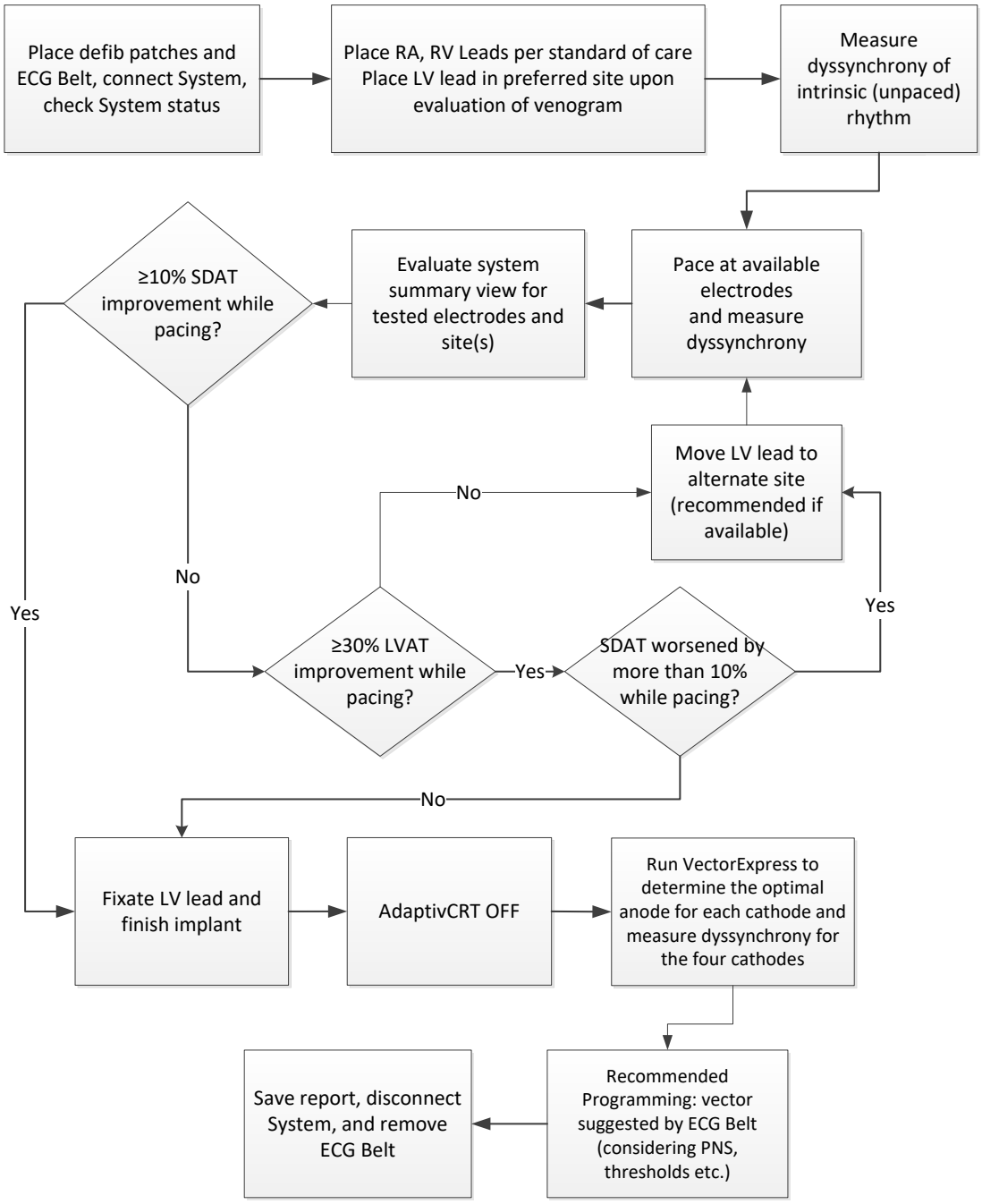
*ii. Control arms A and B: CRT device implant and programming*

For subjects in control arms A and B, the final position of the LV pacing lead must be determined per physician routine standard of care.

The LV pacing vector and other CRT settings must be programmed per physician routine standard of care.

AdaptivCRT and MPP should be OFF. MPP is intended for non-responders who cannot be identified at implant. Additionally, MPP results in a decrease to longevity that may be avoided with the personalized programming offered by the ECG Belt system.

Figure 2: ECG Belt management workflow diagram at Implant



### j. Scheduled Follow-up Visits

After receiving electronic notice of implant in the Oracle Clinical database, the database system will provide the windows for each visit. 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 will 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. Follow-up visit windows are listed in Table 3 and are based on days post-implant.

Table 3: Data collection and study procedure requirements at subject visits

| **Study Follow-up Visit** | **Window (Calculated days post-implant)** | |
|---|---|---|
| | Window Start (days post-implant) | Window End (days post-implant) |
| Post-Implant follow-up | 0 | 14 |
| 6-month Follow-up | 182 | 196 |
| 9-month Follow-up | 274 | 288 |

### k. Post-Implant Follow-Up

The following information is required to be collected at post-implant follow-up. This can be pre-discharge after the CRT implant or a standalone visit, whichever aligns best with standard CRT practice at each site:

- A full interrogation of the implanted device with programmed parameters at start of visit (save to media)
- All subjects will require the ECG Belt to be temporarily applied to the chest and back. A separate ECG Belt is suggested to be used for the Implant and Post-Implant workflows to ensure consistent application conditions in the Post-Implant workflow. If the Post-Implant Follow-up visit occurs on the same day as Implant and the same ECG Belt will be used, ensure the signal quality does not diminish compared to Implant and that the total wear time does not exceed 8 hours. Use a new ECG Belt if these conditions cannot be met.
- For the ECG Belt arm, ECG Belt Research System data will be collected without pacing (e.g. intrinsic rhythm) and with pacing with a subset of vectors and various pacing parameters in order to manage CRT therapy (see Figure 3 for the workflow, details will be provided in the Case Report Forms (CRFs) and in a controlled handbook).
- For control arms A and B, ECG Belt Research System data will be collected without pacing (e.g. intrinsic rhythm) and at final programming settings. Pacing configurations, A-V and V-V delays will be temporarily programmed to collect blinded ECG Belt Research System data, data collection is optional. These data will not be used to determine the final programming settings.

- Control arms A and B: methods used to determine programming settings will be collected.
- A full interrogation of the implanted device with programmed parameters at end of visit (save to media)

*i. ECG Belt arm: Post-Implant Follow-Up CRT programming*

The ECG Belt arm will require ECG Belt Research System management. Changes in dyssynchrony will be measured with AdaptivCRT Bi-V + LV, AdaptivCRT Bi-V and more personalized A-V and/or V-V delays. The optimal LV pacing vector will also be reassessed.

Adaptive LV-only pacing, as provided by AdaptivCRT BiV + LV ON has been shown to improve clinical outcome[20]. However, patients included in this study may benefit from a more personalized, ECG Belt Research System-guided A-V and/or V-V delays that maximally decrease dyssynchrony[c].

The recommended programming will be determined by the relative change in ECG Belt Research System metrics while pacing compared to the intrinsic rhythm.

Recommendations for using an ECG Belt Research System guided A-V and/or V-V delay or AdaptivCRT Bi-V settings:

1) >15% improvement in SDAT with AdaptivCRT BiV+LV ON

   AdaptivCRT BiV+LV is recommended be programmed ON unless an ECG Belt suggested personalized A-V and/or V-V setting or AdaptivCRT Bi-V setting have an additional SDAT improvement of at least 10%. For example, if AdaptivCRT BiV+LV ON offers an 18% improvement in SDAT, a personalized A-V and/or V-V setting should have at least a 28% improvement in SDAT to be used instead of AdaptivCRT BiV+LV.

2) 0-15% improvement in SDAT with AdaptivCRT BiV+LV ON

   AdaptivCRT BiV+LV is recommended be programmed ON unless an ECG Belt suggested A-V and/or V-V setting or AdaptivCRT Bi-V settings offer an additional 5% absolute improvement in SDAT.

3) The SDAT with AdaptivCRT is worse than the intrinsic SDAT

   When no improvement in SDAT can be achieved with AdaptivCRT BiV+LV ON, the ECG Belt suggested A-V and/or V-V setting or AdaptivCRT Bi-V-like settings with the best SDAT are recommended.

The recommended programming settings account for potential variability in SDAT measurements and favor AdaptivCRT over standard BiV CRT because it may be associated with additional improvement in clinical response compared with standard CRT[21].

The recommended LV pacing vector will be the vector that provides the maximum resynchronization based on the ECG Belt Research System metrics, after consideration of other clinical factors (phrenic nerve stimulation, pacing

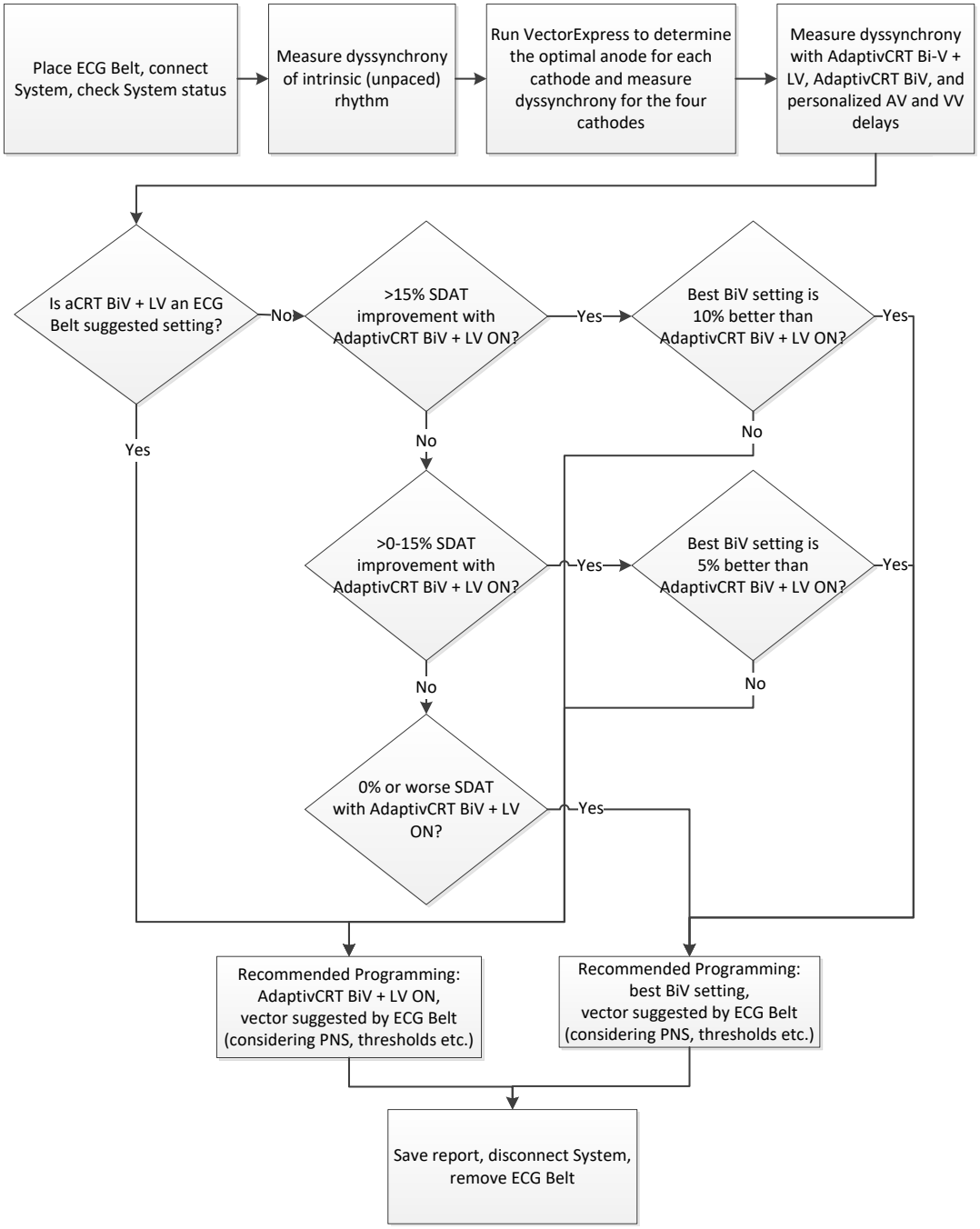
c Note: The V-V delay is not programmable in some currently available versions of AdaptivCRT. This capability will be added in the future.

thresholds, etc.). MPP should be OFF. MPP is intended for non-responders who cannot be identified at the post-implant follow-up. Additionally, MPP results in a decrease to longevity that may be avoided with the personalized programming offered by the ECG Belt system.

Once study testing is complete, the ECG Belt Research System results will be saved and submitted to Medtronic, the System will be disconnected, and the ECG Belt will be removed from the subject.

See Figure 3 for an overview of the ECG Belt management workflow and recommended programming at Post-Implant follow-up for subjects in the ECG Belt arm.

Figure 3: ECG Belt management workflow and recommend programming at Post-Implant Follow-Up



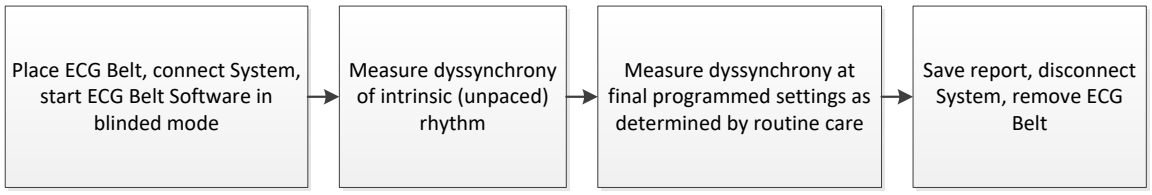

### *ii. Control arms A and B: Post-Implant Follow-Up CRT programming*

For subjects in the control arms, the ECG Belt Research System data is collected blinded and not visible for the physician or operator. Once study testing is complete, the ECG Belt Research System results will be saved and submitted to Medtronic, the System will be disconnected, and the ECG Belt will be removed from the subject.

The LV pacing vector and other CRT settings will be programmed per the physician's routine standard of care. Pacing configurations, A-V and V-V delays will be temporarily programmed to collect blinded ECG Belt Research System data, data collection is optional. These data will not be used to determine the final programming settings. AdaptivCRT and MPP should be OFF. MPP is intended for non-responders who cannot be identified at the post-implant follow-up. Additionally, MPP results in a decrease to longevity that may be avoided with the personalized programming offered by the ECG Belt system.

See Figure 4 for an overview of the ECG Belt data collection workflow for subjects in control arm A and B.

Figure 4: Blinded ECG Belt data collection workflow diagram at Post-implant and 6 Months Follow-Ups




## I. 6-Month Follow-up Visit

The following information is required to be collected at the 6-month follow-up visit:

- Echocardiogram images with CRT on (should be taken prior to ECG Belt use). All echos must be anonymized and labeled with a Medtronic-assigned identification number prior to submission to the Core Lab.
- NYHA Functional Classification
- Patient Global Assessment Score
- Minnesota Living With Heart Failure questionnaire
- Six-Minute Walk Test
- A full interrogation of the implanted device with programmed parameters at start of visit (save to media)
- All Subjects will require the ECG Belt to be temporarily applied to the chest and back.
- For the ECG Belt arm and control arm A, ECG Belt Research System data will be collected without pacing (e.g. intrinsic rhythm) and with pacing with a subset of vectors and various pacing parameters in order to manage CRT therapy (see Figure 5 for the workflow, further details will be provided in the CRFs and in a controlled handbook).

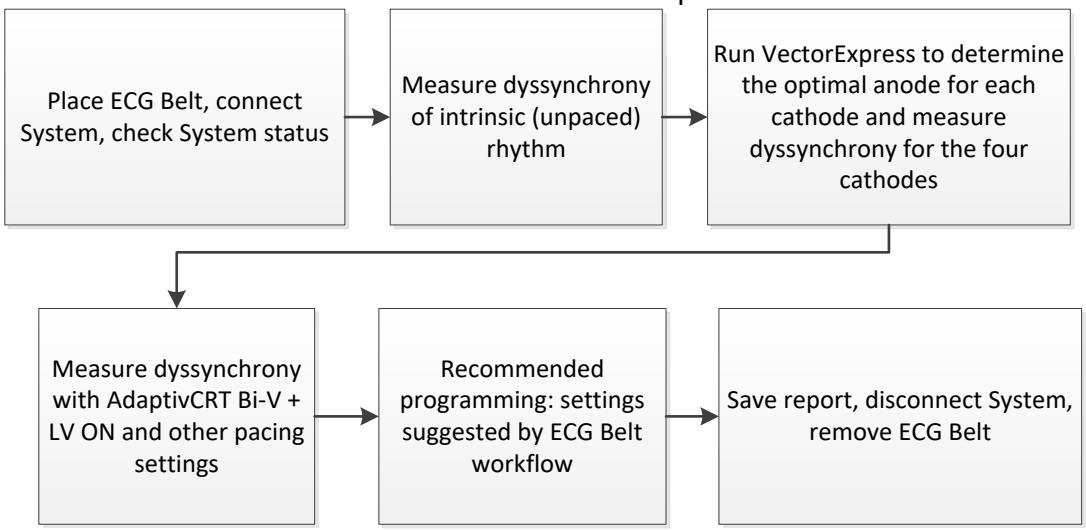
- For control arm B, ECG Belt Research System data will be collected only without pacing (e.g. intrinsic rhythm) and at final programming settings. Pacing configurations, A-V and V-V delays will be temporarily programmed to collect blinded ECG Belt Research System data, data collection is optional. These data will not be used to determine the final programming settings.
- For control arm B, methods used to determine programming settings will be collected
- A full interrogation of the implanted device with programmed parameters at end of visit (save to media)

*i. ECG Belt arm and control arm A: 6 month follow-up CRT programming*

The ECG Belt arm and control arm A will require ECG Belt Research System management. From 6 to 9 months the ECG Belt Research System will be used to further investigate personalized programming. Changes in dyssynchrony will be measured with AdaptivCRT BiV + LV ON, AdaptivCRT Bi-V-like settings, and selected A-V and V-V delays (see Figure 5 for the workflow and programming recommendations). This may further optimize pacing vector and pacing parameters, especially if there are parameters that provide a distinctively large improvement in resynchronization compared to the pacing parameters/settings to which the patient was programmed before the follow-up.

Once study testing is complete, the ECG Belt Research System results will be saved and submitted to Medtronic, the System will be disconnected, and the ECG Belt will be removed from the subject.

Figure 5: ECG Belt management workflow and programming recommendations at 6 Months Follow Up



*ii. Control arm B: 6 month follow-up CRT recommended programming*

For subjects in the control arm B, the ECG Belt Research System data is collected blinded and not visible for the physician or operator. Once study testing is complete, the ECG Belt Research System results will be saved and submitted to Medtronic, the System will be disconnected, and the ECG Belt will be removed from the subject.

The LV pacing vector and other CRT settings will be programmed per physician's routine standard of care. AdaptivCRT will be turned OFF. Pacing configurations, A-V and V-V delays will be temporarily programmed to collect blinded ECG Belt Research System data, data collection is optional. These data will not be used to determine the final programming settings.

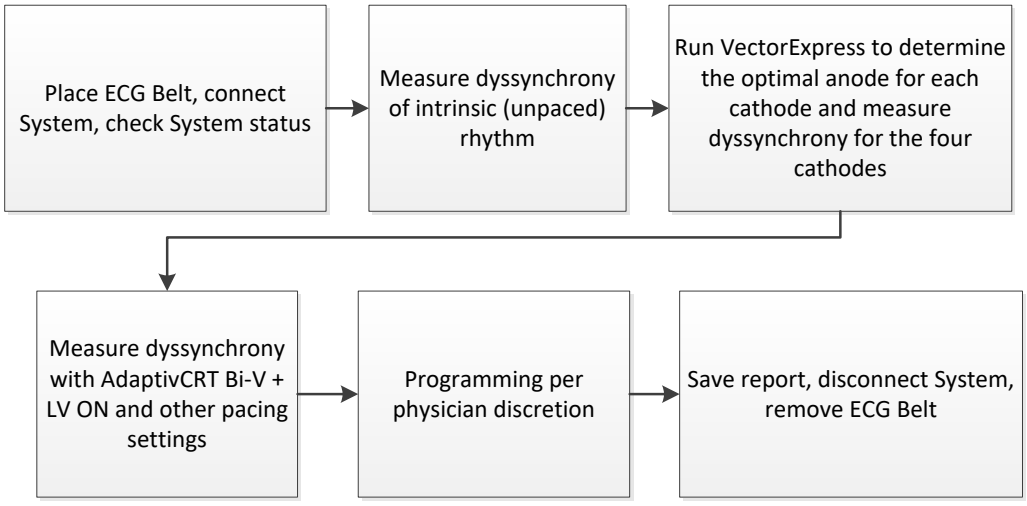
See Figure 4 for an overview of the ECG Belt data collection workflow for subjects in control arm B.

### m. 9-Month Follow-up Visit

The following information is required to be collected at the 9 month follow-up visit:

- Echocardiogram images with CRT on (should be taken prior to ECG Belt use). All echos must be anonymized and labeled with a Medtronic-assigned identification number prior to submission to the Core Lab.
- NYHA Functional Classification
- Patient Global Assessment Score
- Minnesota Living With Heart Failure questionnaire
- A full interrogation of the implanted device with programmed parameters at start of visit (save to media)
- All subjects will require the ECG Belt to be temporarily applied to the chest and back. ECG Belt Research System data will be collected without pacing (e.g. intrinsic rhythm), with AdaptivCRT BiV LV ON, and for selected pacing settings (see Figure 6 for the workflow).
- Once ECG Belt Research System data has been collected, all programming will occur per physician discretion
- A full interrogation of the implanted device with programmed parameters at end of visit (save to media)
- Make sure that a final status of any open Adverse Events is collected
- After the visit the subject is considered exited from the study

Figure 6: ECG Belt data collection workflow diagram at 9 Months Follow-Up




### n. Device Interrogation

For implant and follow-up visits, an initial (not at implant) and final full "Interrogate ALL" final device interrogation file (pdd) must be obtained and saved in a digital format (e.g., USB). The original file will be stored at the site and a copy provided electronically to Medtronic. Device data should not be cleared at any time. In case a device interrogation file was not obtained on site, but the subject is remotely followed per standard of care, Medtronic may obtain remote CareLink files of that subject from the CareLink server if available for the follow-up period of the subject.

### o. Healthcare Utilization

Health Care Utilization information will be collected as part of the Adverse Event Form, if applicable. A hospitalization due to worsening heart failure will be determined by the site and defined as an event that occurred primarily because of the documented presence of:

- Use of additional or increased pharmacologic or mechanical interventions directed at the treatment of heart failure including:
  - Initiation of intravenous diuretic, inotropic, or vasodilator therapy
  - Significant addition or increase in oral heart failure therapy
  - Up-titration of intravenous therapy, if already on therapy
  - Initiation of mechanical or surgical intervention (mechanical circulatory or ventilatory support, heart transplantation or ventricular pacing to improve cardiac function), or the use of ultrafiltration, hemofiltration, or dialysis that is specifically directed at treatment of heart failure.

In addition, at least 1 of the following 2 criteria must be documented:

- Clinical manifestations of heart failure including the following new or worsening signs or symptoms:
  - Dyspnea
  - Orthopnea
  - Paroxysmal nocturnal dyspnea
  - Edema

- Pulmonary rales
- Jugular venous distension
- New or worsening third heart sound or gallop rhythm
- Hypotension or cardiogenic shock not occurring in the context of an acute myocardial infarction or as the consequence of an arrhythmia, or
- Other clinical evidence of new or worsening heart failure, eg, weight gain, or confinement to bed predominantly due to heart failure symptoms

- Biomarker or radiographic evidence consistent with heart failure
  - Biomarker results consistent with heart failure include documented increased or increasing levels of a natriuretic peptide (BNP or NTproBNP).
  - Radiographic evidence consistent with heart failure includes documented worsening pulmonary congestion or pulmonary edema on chest X-ray or other generally recognized imaging pattern.

Hospitalizations due to worsening heart failure will also be confirmed by Medtronic and an attempt will be made to resolve any discrepancies with the site determination.

### p. System Modification

A system modification will be reported in the event the device and/or leads require invasive modification (e.g., generator or lead explant, generator or lead replacement, lead repositioning) or CRT is turned off. In the event of a system modification, the follow-up schedule for the subject will remain unchanged. For a system modification the following activities are required:

- Perform a device interrogation before and after the system modification.
- If the subject is in the ECG Belt arm, use the ECG Belt Research System to place the lead in a suitable pacing site (if applicable) and for device programming optimization.

The reason for the system modification must be recorded on the CRF, including whether it was due to worsening heart failure, treatment failure, or lack of/insufficient therapeutic response.

If the device is taken out of service (e.g. explanted or capped) and a replacement will not be implanted, keep the subject in the study and collect data as scheduled through the 6 month visit. ECG Belt Research System data collection at 6 months is optional. After the 6 month visit, subjects with an out of service device should be exited from the study.

All explanted product (device, leads, etc.) should be returned to Medtronic for analysis when permissible by local laws and regulations.

In the event that a subject has a re-attempt after a previous unsuccessful system modification, the subsequent attempt(s) must be reported via CRF as separate system modifications.

### q. Study Exit

Once the 9-month follow-up is completed, the subject is considered exited from the study, unless there are unresolved system related AEs with further actions or treatments

planned. No exit CRF is required. The exit date is collected on the 9-month visit CRF. No data should be collected after the 9-month follow-up, except for updates and resolutions to AEs that started during or prior to the 9-month follow-up.

A study exit CRF is required for all subjects exiting the study prior to the 9-month follow-up, except in the case of death. Prior to exiting a subject from the study, it is recommended to follow the subject until all unresolved system related AEs are resolved or unresolved with no further actions planned. Following exit, subjects will continue to receive standard medical care. Upon exiting from the study, no further study data will be collected or study visits will occur for the subject. Investigators will request for permission to follow-up patients outside the clinical study in case of withdrawal due to problems related to investigational device safety or performance.

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 lost to follow-up
- Subject did not meet inclusion/exclusion criteria and was not randomized
- Subject has unreadable echo at baseline (prior to randomization)
- Subject did not provide consent or data use protection authorization
- Subject implant not attempted
- Subject implanted prior to being randomized
- Subject chooses to withdraw (e.g., consent withdrawal, relocation to another geographic location)
- Investigator deems withdrawal necessary (e.g., medically justified, inclusion/exclusion criteria not met, failure of subject to maintain adequate study compliance)

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

- Reason for exit (indicated on CRF)
- Date of study exit. This should be the date that data was last collected from the subject, including vital status
- A full interrogation of the implanted device (save to media) (Except if lost to follow up or not yet implanted)
- In the case that the subject is determined to be lost to follow-up, details of a minimum of two attempts and the method of attempt (e.g., one letter and one phone record or two letters) to contact the subject must be recorded. In addition, follow the regulations set forth by the governing Ethics Committee.

### r. Medications

Medication data collection will be limited to collecting whether or not the subjects were on ACE/ARB, beta blockers, diuretics, and anti-arrhythmics at baseline.

# 8. INVESTIGATIONAL DEVICE/SOFTWARE STORAGE, HANDLING AND TRACEABILITY

The ECG Belt Research System, with the exception of the tablet, is considered investigational in US, Canada, and Europe. The investigational system will be distributed to a center only when Medtronic has received all required documentation and has notified the center of center activation. Distribution of the investigational products to study centers during the clinical study will be managed by Medtronic and can only be ordered by Medtronic personnel. Investigational product, once received at the site, must be stored in a secure location at the site. It is the responsibility of the investigator to correctly handle, store, and track the investigational products maintained at the site. Investigational products will be used only in the study according to the CIP.

In the future, a new version of the system may be incorporated that is market-approved in some geographies. In this case, investigational product distribution and tracking will only apply in geographies in which the product is investigational.

A Device Disposition Log is available to the center in the Oracle Clinical database and will be used for tracking of all investigational ECG Belt Research System components provided by Medtronic during and after the study. The logs must be maintained at each study center and updated when an ECG Belt Research System component is received, opened (as applicable), (re)used, disposed of or returned to Medtronic. The disposition log tracks product information including, but not limited to: component name, serial number/lot number/batch number, date received from Medtronic, dates of use and subject identification, date returned to Medtronic, components not returned to Medtronic (if applicable), and name of person responsible for return or destruction/disposal (if applicable). Successfully used ECG Belts can be destroyed/disposed of according to local laws and regulations. Any ECG Belts that came into contact with a subject and were found deficient should be returned to Medtronic in a Medtronic-provided biohazard kit. Unused ECG Belts and reusable system components should be returned to Medtronic after the study.

Medtronic will perform periodic reconciliation of investigational product to ensure traceability.

# 9. STUDY DEVIATIONS

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

Investigators are not allowed to deviate unless it is necessary to protect the safety, rights or well-being of a subject in an emergency or in unforeseen situations beyond the investigator’s control (e.g. subject failure to attend scheduled follow-up visits, inadvertent loss of data due to computer malfunction, inability to perform required procedures due to subject illness). If nevertheless the investigator anticipates, contemplates, or makes a conscious decision to deviate, in other situations, Medtronic should be notified and asked for approval in advance.

All study deviations must be reported on the Case Report Form regardless of whether medically justifiable, pre-approved by Medtronic, an inadvertent occurrence, or taken to protect the subject in an emergency. The explanation for the deviation must be documented. Multiple deviations of the same type at the same visit may be reported on

one case report form in the following situations: multiple device interrogations missing for same visit. In the occurrence of a corrupted device interrogation file, Medtronic may request a deviation to document that a readable interrogation file is unavailable.

In the event the deviation involves 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, the deviation must be reported to the Ethics Committee as well as Medtronic within five (5) working days. Reporting of all other study deviations should comply with Ethics Committee policies and/or local laws and must be reported to Medtronic as soon as possible upon the center becoming aware of the deviation. Reporting of deviations must comply with Ethics Committee policies, local laws, and/or regulatory agency requirements. Refer to Table 9, Table 10 and Table 11 for Investigator Reports, geography-specific deviation reporting requirements and timeframes for reporting to Medtronic and/or regulatory bodies.

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

Study deviation waivers for the Clinical Investigation Plan are prohibited.

A study deviation is not required if additional data collection for the pacing configurations, A-V and V-V delays is not collected at the Control Post-Implant Follow-up visit and the 6 month Follow-up visit for Control B subjects.

# 10. ADVERSE EVENTS AND DEVICE DEFICIENCIES

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

For the ECG Belt study, AE CRF's will be collected for all AEs that are potentially ECG Belt Research System-related and all serious AEs regardless of their relationship to the ECG Belt Research System and/or application procedure.

## a. Adverse Event and Device Deficiency definitions

Where the definition indicates "device", it refers to the ECG Belt Research System used in this study.

Table 4: Adverse Event definitions

| General | |
|---|---|
| Adverse Event (AE)<br>(ISO 14155:2011, 3.2) | 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<br><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.<br>NOTE 3: For users or other persons, this definition is restricted to events related to investigational medical devices. |
| Adverse Device Effect (ADE)<br>(ISO 14155:2011, 3.1) | Adverse event related to the use of an investigational medical device<br><br>NOTE 1: This definition includes adverse events 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 an error use or from intentional misuse of the investigational medical device. |
| Device Deficiency (DD)<br>(ISO 14155:2011, 3.15) | Inadequacy of a medical device with respect to its identity, quality, durability, reliability, safety or performance.<br><br>NOTE: Device deficiencies include malfunctions, use errors and inadequate labeling |
| **Relatedness** | |
| System related | An adverse event that results from the presence, application or performance (intended or otherwise) of the ECG Belt Research System |
| 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>▪Harms to the subject are not clearly due to use error;<br><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 were relatedness cannot be assessed or no information has been obtained should also be classified as possible. |
| Probable | The relationship with the use of the investigational device seems relevant and/or the event cannot reasonably 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;<br>▪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)<br>(ISO 14155:2011, 3.37) | Adverse event that<br>a) led to death,<br>b) led to serious deterioration in the health of the subject, that either resulted in<br>1) a life-threatening illness or injury, or<br>2) a permanent impairment of a body structure or a body function, 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) led to foetal distress, foetal death or a congenital abnormality or birth defect<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. |

| | |
|---|---|
| Serious Adverse Device Effect (SADE)<br>(ISO 14155:2011, 3.36) | Adverse device effect that has resulted in any of the consequences characteristic of a serious adverse event. |
| Unanticipated Adverse Device Effect (UADE)<br>(21 CFR 812) | 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)<br>(ISO 14155:2011, 3.42) | Serious adverse device effect which by its nature, incidence, severity or outcome has not been identified in the current version of the risk analysis report<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 analysis report. |

## b. Adverse Event and Device Deficiency Assessment

### *i. Adverse Events*

All ECG Belt Research System related and all Serious Adverse Events will be collected throughout the study duration, starting at the time of signing the ICF.

Reporting of these events to Medtronic will occur on an Adverse Event (AE) Form, 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. Each AE must be recorded on a separate AE Form. Subject deaths are also required to be reported. Refer to Section 10.e. for Subject Death collection and reporting requirements. In addition, AEs impacting users or other persons, Non-subject Adverse Events, (reportable per ISO 14155) will be collected.

Documented pre-existing conditions are not considered AEs unless the nature or severity of the condition has worsened.

For AEs that require immediate reporting, initial reporting may be done by phone, fax, email (see Sponsor Contact Information) or on the CRF completing as much information as possible. The AE CRF must be completed as soon as possible.

### *ii. Device Deficiencies*

Device deficiency information for the ECG Belt Research System will be collected throughout the study and reported to Medtronic. Note that device deficiencies that result in an adverse device effect (ADE) to the subject should be captured as an Adverse Event only.

Device deficiencies that did not lead to an AE but could have led to a Serious Adverse Device Effect (SADE) (i.e., if suitable action had not been taken, if intervention had not been made, or if the circumstances had been less fortunate) require immediate reporting (see Table 6).

### *iii. Processing Updates and Resolution*

For any changes in status of a previously reported adverse event (i.e. change in actions taken, change in outcome, change in relatedness), an update to the original AE must be

completed. All reported AEs must be followed until the AE has been resolved, is unresolved with no further actions planned, the subject dies or exits the study, or until study closure, whichever occurs first.

In the event that a subject is exited from the study prior to study closure, all efforts should be made to continue following the subject until all unresolved system related AEs, as classified by the investigator, are resolved or they are unresolved with no further actions planned.

At the time of study exit, all collected AEs with an outcome of “Unresolved, further actions or treatment planned” must be reviewed and an update to the original AE must be reported. At a minimum, if there are no changes to the description, relatedness, test and procedures or actions taken, the outcome must be updated to reflect “Unresolved at time of study closure.”

### c. Adverse Events and Deficiency Classification

All reported AEs and device deficiencies will be reviewed by a Medtronic representative. AEs will be classified according to the definitions provided.

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 adverse event based on the information provided by the investigator.

Regulatory reporting of AEs and device deficiencies that could have led to an SADE will be completed according to local regulatory requirements. Refer to Table 9 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 Foreseeable Adverse Event List (FAL), please refer to the Investigator’s Brochure. This is a list of AEs related to the ECG Belt Research System or application procedure that have been observed in previous studies and may be experienced by subjects. This list may help to assess if an AE is unexpected in nature. For emergency contact regarding a UADE, SAE and/or SADE, contact a clinical study representative immediately (refer to the study contact list provided in the center’s study documents binder/investigator site file or refer to the contact information provided on the title page).

Adverse Events and Deaths will be classified according to the standard definitions as outlined below:

Table 5: Adverse Event classification responsibilities

| What is classified? | Who classifies? | Classification Parameters |
|---|---|---|
| Relatedness | Investigator | ECG Belt Research System (Belt, amplifier, software, tablet, application procedure), heart failure related hospitalizations |
| | Sponsor | ECG Belt Research System (Belt, amplifier, software, tablet, application procedure), heart failure related hospitalizations |
| Severity | Investigator | SAE |
| | Sponsor | SAE, UADE/USADE, Device Deficiency with SADE potential |
| Diagnosis | Investigator | Based on presenting signs and symptoms and other supporting data |
| | Sponsor | MedDRA term assigned based on the data provided by Investigator |
| Death Classification | Investigator | Sudden Cardiac, Non-sudden Cardiac, Non-Cardiac, Unknown |

Medtronic will review and trend AEs and if necessary, take any actions considered appropriate to protect subject safety. Medtronic has documented procedures for suspending a study in the event the safety or the welfare of the subjects is endangered.

### d. Adverse Event and Device Deficiency Reporting Requirements

Regulatory reporting of AEs/device deficiencies will be completed according to local regulatory requirements. Refer to Table 6 for a list of required investigator reporting requirements and timeframes, and of required Medtronic reporting requirements and timeframes.

The investigator is required to report all SAE's to Medtronic immediately, and to the Ethics Committee per local requirements. Medtronic is also required to report these events to the local regulatory authority based on their requirements. It is the responsibility of the investigator to abide by any additional AE/device deficiency reporting requirements stipulated by the Ethics Committee responsible for oversight of the study.

For AEs/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.

Regulatory reporting of AEs/device deficiencies that could have led to an SADE will be completed according to local regulatory requirements. Refer to Table 6: Reporting Requirements for a list of required investigator and Medtronic reporting requirements and timeframes. Each geography has the responsibility to follow current local reporting requirements.

Table 6: Adverse Event reporting requirements

| Serious Adverse Events (SAEs) | |
|---|---|
| **Investigator submit to:** | |
| Medtronic | **Europe:** Immediately after the investigator first learns of the event or new information in relation with an already reported event. (ISO14155 and local law)<br>**All other geographies:** Submit in a timely manner after the investigator first learns of the event. |
| Ethics Committee, | **Europe:** Submit to Ethics Board per local reporting requirement<br>**All other geographies:** Submit per local EC requirement. |
| Regulatory authorities | **Europe:** Submit to regulatory authorities per local reporting requirement<br>**All other geographies:** Submit per local reporting requirement. |
| **Sponsor submit to:** | |
| Regulatory authorities | **Europe:** Submit to Competent Authority per local reporting requirement.<br>**All other geographies:** Submit per local reporting requirement. |
| Ethics Committee | **Europe:** Submit to Ethics Board per local reporting requirement.<br>**All other geographies:** Submit per local reporting requirement. |
| **Serious Adverse Device Effects (SADEs)**<br><br>**Note: in this study 'device' refers to the ECG Belt Research System** | |
| **Investigator submit to:** | |
| Medtronic | **Canada:** Investigators are required, per the TPD Investigator Agreement, to report any incident that is related to a failure of the device or deterioration in its effectiveness, or any inadequacy in its labeling or directions for use leading to death or serious deterioration in a subject's health within 72 hours after the occurrence. (Canada Medical Device Regulations, SOR/98-282; 77, 59)<br>**Europe:** Immediately after the investigator first learns of the event or of new information in relation with an already reported event. ((ISO 14155 and local law).<br>**All other geographies:** Immediately after the investigator first learns of the event or of new information in relation with an already reported event. |
| Ethics Committee | **Europe:** Submit to Ethics Board per local reporting requirement<br>**All other geographies:** Submit per local EC requirement. |
| **Regulatory authorities** | **Canada:** Investigators are required, per the TPD Investigator Agreement, to report any incident that is related to a failure of the device or deterioration in its effectiveness, or any inadequacy in its labeling or directions for use leading to death or serious deterioration in a subject's health within 72 hours after the occurrence. (Canada Medical Device Regulations, SOR/98-282; 77, 59)<br>**All other geographies:** Immediately after the investigator first learns of the event or of new information in relation with an already reported event. |
| **Sponsor submit to:** | |

| | |
|---|---|
| Regulatory authorities | **Canada:** Preliminary and final reporting to the Canadian Ministry of Health of events occurring inside (always) or outside Canada (in case of corrective actions) that is related to a failure of the device or a deterioration in its effectiveness, or any inadequacy in its labeling or its directions for use and has led to the death or a serious deterioration in the state of health of a patient, user or other person or could do so were it to recur. Report a) within 10 days after awareness, if incident has led to death or a serious deterioration in the state of health of a patient, user or other person b) within 30 days, if incident has not led to led to death or a serious deterioration in the state of health of a patient, user or other person, but could do so were it to recur c) as soon as possible, if incident occurred outside of Canada and is related to a corrective action. (Canada Medical Device Regulations, SOR/98-282; Mandatory Problem Reporting 59(1) , 59(2), 60 (1))<br>**All other geographies:** Submit per local reporting requirement. |
| Ethics Committee | **Europe:** Submit to Ethics Board per local reporting requirement.<br>**All other geographies:** Submit per local reporting requirement. |
| **Unanticipated Adverse Device Effects (UADEs) and Unanticipated Serious Adverse Device Effects (USADEs)**<br><br>**Note: in this study 'device' refers to the ECG Belt Research System** | |
| **Investigator submit to:** | |
| Medtronic | **Canada:** Investigators are required, per the Therapeutic Products Directorate Investigator Agreement, to report any incident that is related to a failure of the device or deterioration in its effectiveness, or any inadequacy in its labeling or directions for use leading to death or serious deterioration in a subject's health within 72 hours after the occurrence. (Canada Medical Device Regulations, SOR/98-282; 77, 59)<br>**US:** Submit as soon as possible, but no later than within 10 working days after the investigator first receives notice of the effect. (21 CFR 812.150(a)(1))<br>**Europe:** Immediately after the investigator first learns of the event or of new information in relation with an already reported event (ISO 14155 and local law). |
| Ethics Committee | **US:** Submit as soon as possible, but no later than within 10 working days after the investigator first receives notice of the effect. (21 CFR 812.150(a)(1))<br>**All other geographies:** Submit per local reporting requirement. |
| Regulatory authorities | **Canada:** Investigators are required, per the TPD Investigator Agreement, to report any incident that is related to a failure of the device or deterioration in its effectiveness, or any inadequacy in its labeling or directions for use leading to death or serious deterioration in a subject's health within 72 hours after the occurrence. (Canada Medical Device Regulations, SOR/98-282; 77, 59)<br>**Europe:** Submit per local reporting requirement. |
| **Sponsor submit to:** | |
| Investigator | **All geographies:** 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)(1)) |

| | |
|---|---|
| Regulatory authorities | **Canada:** Preliminary and final reporting to the Canadian Ministry of Health of events occurring inside (always) or outside Canada (in case of corrective actions) that is related to a failure of the device or a deterioration in its effectiveness, or any inadequacy in its labeling or its directions for use and has led to the death or a serious deterioration in the state of health of a patient, user or other person or could do so were it to recur. Report a) within 10 days after awareness, if incident has led to death or a serious deterioration in the state of health of a patient, user or other person b) within 30 days, if incident has not led to led to death or a serious deterioration in the state of health of a patient, user or other person, but could do so were it to recur c) as soon as possible, if incident occurred outside of Canada and is related to a corrective action. (Canada Medical Device Regulations, SOR/98-282; Mandatory Problem Reporting 59(1) , 59(2), 60 (1))<br>**US:** Notification as soon as possible to FDA, but not later than 10 working days after the sponsor first receives notice of the effect. (21 CFR 812.150(b)(1))<br>**Europe**: Submit per local reporting requirement. |
| Ethics Committee | **US:** Notification as soon as possible, but not later than 10 working days after the sponsor first learns of the effect. (21 CFR 812.150(b)(1))<br>**All geographies:** Submit USADE to IRB/MEC per local reporting requirement. |
| **Device Deficiencies with SADE potential**<br><br>**Note: in this study 'device' refers to the ECG Belt Research System** | |
| **Investigator submit to:** | |
| Medtronic | **Canada:** Investigators are required, per the TPD Investigator Agreement, to report any incident that is related to a failure of the device or deterioration in its effectiveness, or any inadequacy in its labeling or directions for use leading to death or serious deterioration in a subject's health within 72 hours after the occurrence. (Medical Devices Regulations, SOR/98-282; 77, 59)<br>**Europe:** Immediately after the investigator first learns of the deficiency or of new information in relation with an already reported deficiency.<br>**All other geographies:** Submit or report as required per local reporting requirements |
| Ethics Committee | **All geographies:** Submit per local EC requirement |
| Regulatory authorities | **All geographies:** Submit per local reporting requirement. |
| **Sponsor submit to:** | |
| Regulatory authorities | **Canada**: Preliminary and final reporting to the Canadian Ministry of Health of events occurring inside (always) or outside Canada (in case of corrective actions) that is related to a failure of the device or a deterioration in its effectiveness, or any inadequacy in its labeling or its directions for use and has led to the death or a serious deterioration in the state of health of a patient, user or other person or could do so were it to recur. Report a) within 10 days after awareness, if incident has led to death or a serious deterioration in the state of health of a patient, user or other person b) within 30 days, if incident has not led to death or a serious deterioration in the state of health of a patient, user or other person, but could do so were it to recur c) as soon as possible, if incident occurred outside of Canada and is related to a corrective action. (Canada Medical Device Regulations, SOR/98-282; Mandatory Problem Reporting 59(1) , 59(2), 60 (1))<br>**All geographies:** Submit per local reporting requirement |
| Ethics Committee | **All geographies:** Submit per local EC requirement. |

| All other Device Deficiencies<br><br>Note: in this study 'device' refers to the ECG Belt Research System | |
|---|---|
| **Investigator submit to:** | |
| Medtronic | **All geographies**: Submit in a timely manner after the investigator first learns of the deficiency. |
| Regulatory Authorities | **All geographies**: Submit or report as required per local reporting requirement. |
| Ethics Committee | **All geographies**: Submit per local EC requirement. |

## e. Subject Death

### *i. Death data collection*

When a subject dies during the study, the death must be reported using an Adverse Event CRF with an outcome of death as soon as possible after the investigator first learns of the death. There should be only one AE CRF with an outcome of death.

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

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

### *ii. Death classification and reporting*

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

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

Sudden Cardiac Death (SCD): Natural death due to cardiac causes, indicated by abrupt loss of consciousness within one hour of the onset of acute symptoms; preexisting heart disease may have been known to be present, but the time and mode of death are unexpected. If time of onset cannot be determined, SCD will

alternatively be defined as any unexpected cardiac death occurring out of the hospital or in the emergency room as dead on arrival.

Non-sudden Cardiac Death: All cardiac deaths that are not classified as sudden deaths, including all cardiac deaths of hospitalized subjects on inotropic support.

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

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

Regulatory reporting of Subject Deaths will be completed according to local regulatory requirements. Refer to Table 6 for a list of required investigator and sponsor reporting requirements and timeframes.

### f. Clinical event review

Medtronic will review and trend AEs and if necessary, take any actions considered appropriate to protect subject safety. Medtronic has documented procedures for suspending a study in the event the safety or the welfare of the subjects is endangered. Since anticipated risks and AEs related to the ECG Belt Research System are minor, a Clinical Events Committee and Data Monitoring Committee are not planned.

### g. Product Complaint Reporting

In geographies where devices are market-released, product complaint reporting is applicable. This includes when an AE is related to a market-released device during the study. The reporting of product complaints is not part of the clinical study and should be done in addition to the Adverse Event reporting requirements. Refer to local regulations for reporting requirements.

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

It is the responsibility of the investigator to report all product complaint(s) associated with a medical device distributed by Medtronic, regardless 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.

Medtronic will notify the regulatory authorities (e.g. Competent Authority) as applicable for the following incidents immediately upon learning of them:

- Any malfunction or deterioration in the characteristics and/or performance of the investigational 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.
- An adverse event that led to death.
- An adverse event that led to a serious deterioration in the state of heath that either resulted in:

- 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.

- An adverse event that led to fetal distress, fetal death or any congenital abnormality or birth defects.

# 11. RISK ANALYSIS

Medtronic follows rigorous Risk Management procedures throughout the life of the research system, from the research and development phase through the study phase. The risk management process for the ECG Belt Research System is being performed in accordance with ISO 14971, and will ensure that the level of risk has been reduced as low as possible and is acceptable prior to starting the clinical study. A summary of the risk analysis and risk assessment is provided in the Investigator Brochure. Critical changes impacting the overall risk of the study will be documented through update of the Investigator Brochure and disclosed to subjects as needed.

If changes are made to components of the ECG Belt Research System throughout the course of the study, Medtronic will ensure these changes do not impact the scientific soundness and safety of the study. The risk analysis and risk assessment summaries will be updated in the Investigator Brochure, and IRBs/MECs will be informed and approve these changes per local requirement before use in the study.

For more details on the risk analysis of the ECG Belt Research System, refer to the ECG Belt Risk Management Report. The Risk Analysis in this report only addresses ECG Belt Research System risks.

Use of the ECG Belt Research System introduces a small duration impact to the procedure which it is being added to. The set-up of the ECG Belt Research System is estimated to take approximately 10 minutes. At implant, this set-up time takes place outside of the sterile portion of the CRT procedure.

For ECG Belt arm subjects, the contribution to the implant procedure is estimated to be approximately 40 minutes when two pacing locations are evaluated. For follow-up usage, the incorporation of the ECG Belt Research System is estimated to take approximately 40 minutes for both ECG Belt and control arm subjects.

Note that eligible patients are already planned for a standard CRT system implant. Inherent CRT system and implant related risks and risks related to standard X-ray procedures as part of CRT implantation are therefore not in scope as study risks. These include, but are not limited to the following: valve damage; puncture of the heart muscle, vein, artery or lung; infection; a blood or air embolism in the heart, lung, arteries or veins; bleeding; hematoma; seroma; hemothorax; pneumothorax; swelling/bruising; stimulating muscles or nerves outside the heart; induction of an irregular heartbeat or arrhythmia; damage to a central vein or epicardial vein including dissection and perforation; arteriovenous fistula; pseudo-aneurysm; or localized pain where the incision is made to insert the catheters and CRT device and leads and radiation burden, skin reaction and slight increase in cancer risk.

Possible risks specific for participating in this study include the following (other unforeseen risks may also be possible):

- **ECG Belt Research System related risks**:
    - **At Implant (ECG Belt arm only)**: The non-invasive ECG Belt Research System is investigational but has been qualified for human use and tested for safety similar to standard ECG recording systems. There may be allergenic reaction, skin redness or irritation or discomfort from the additional ECG Belt electrodes, minor pain or discomfort while attaching and detaching multiple electrodes to the skin, and discomfort due to lying on the ECG Belt. Since a larger surface is covered by the ECG Belt, the area of irritation skin redness or irritation may be larger than with standard ECG electrode systems. Use of the ECG Belt Research System during the LV lead implant procedure may add to the length of sterile procedure time. ECG Belt Research System testing at the first location is estimated to take approximately 10 minutes. If the implanter moves the lead to a second location based on the ECG Belt Research System metrics, this could add approximately 20 minutes to move the lead plus 10 minutes for ECG Belt Research System testing at the second location.
    - **At follow-ups (all subjects)**: The non-invasive ECG Belt Research System is investigational but has been qualified for human use and tested for safety similar to standard ECG recording systems. There may be skin redness or irritation from the additional ECG Belt electrodes, minor pain or discomfort while attaching and detaching multiple electrodes to the skin, and discomfort due to lying on the ECG Belt. Since a larger surface is covered by the ECG Belt, the area of skin redness or irritation may be larger than with standard ECG electrode systems. The use of the ECG Belt Research System may add approximately 40 minutes of time to follow-up visits for testing various CRT parameters, plus 10 minutes for application of the ECG Belt and System setup.
    - **During the study (for ECG Belt arm and control arm A):** There is a potential risk that errors, omissions or inaccuracies of ECG Belt Research System may provide feedback that results in suboptimal LV location and/or suboptimal programming and reduced CRT response.

  There may be additional risks related to use of the ECG Belt Research System that are unknown at this time.

**Other risks related to participation in the study:**

- All study subjects will have to undergo a higher number of echocardiogram procedures than in normal practice (e.g. echo at baseline, 6 month and 9 month follow-up). The placement of the ultrasound probe may cause discomfort, but the echocardiogram imaging procedure itself does not pose any additional risk to the subject.

### a. Risk Minimization

The potential risks associated with the ECG Belt Research System and other potential risks of study participation were identified and risk control measures were defined. Any potential risks associated with this study are further minimized by selecting qualified investigators and training study personnel on the Clinical Investigation Plan. In the event that subjects do not respond to CRT during the study, the required use of quadripolar LV leads will provide investigators more options to improve CRT response after the study has ended.

In addition, investigators will be actively involved in the implantation and follow-up of the subjects implanted with the CRT systems.

Risks will be minimized by careful assessment of each subject prior to, during, and after implant of the indicated CRT implant. Investigators will continuously monitor, assess and document risks.

Medtronic has further minimized the possibility of risks by providing guidelines for subject selection and evaluation, and will provide adequate instructions and labeling.

Table 7: Potential risks and risk minimization strategy

| Potential risk | Risk Control Strategy |
|---|---|
| Bioincompatibility (including toxicity, sensitivity and allergenic reactions): *Characteristics of the ECG Belt materials (electrodes, and surface electrode gel) may introduce an undesirable physiological response when a patient/ user is exposed to it.* | • The ECG Belt complies with the Biological evaluation of medical device standard, EN ISO 10993. |
| Misleading/ Misinformation causing insufficient/ inappropriate medical intervention: *Errors, omissions or inaccuracies of ECG Belt Research System may provide feedback that results in suboptimal LV location and/or suboptimal programming and reduced CRT response* | • Study population are those patients that are known to have lower likelihood of response to typical LV lead placement and device programming.<br>• Implanters are expected to follow the EHRA/HRS guidelines for CRT implant and will be instructed to stay within the recommended locations for LV lead implantation and optimize pacing vector/timing parameters (during implant and follow-up) in line with EHRA/HRS expert consensus[19].<br>• Efficacy data from pre-clinical ECG Belt system studies support the use of ECG Belt system LV lead placement during this study[5].<br>• Functional testing will be performed to ensure product integrity and safe performance when exposed to surrounding environment.<br>• The User Manual will include instructions and precautions to be considered regarding system operation. |

| Potential risk | Risk Control Strategy |
|---|---|
| Precursor to infection:<br>*The use of the ECG Belt Research System or procedural designs of the research study may increase the risk of patient infection, due to lengthened CRT procedure duration.* | • The ECG Belt Research System workflow steps are designed to have a minimal duration impact to the baseline sterile portion of the CRT implant procedure (approximately 40 minutes if two lead locations are tested). |
| Precursor to acute tissue trauma:<br>*The use of electrical equipment in contact with the patient introduces the potential for harmful currents to be applied.* | • Basic/electrical safety testing will be performed to ensure product safety as a human contacting device. |

There is a negligible impact to the implantable device's longevity with the ECG Belt study. The interrogations included at implant and follow-up visits are part of standard of care for CRT patients and they have a negligible impact on the device's longevity.

### b. Potential Benefits

The ECG Belt Research System may offer benefit. Medtronic data on file has demonstrated that ECG Belt system metrics have superior sensitivity and specificity for finding the best LV pacing location (compared to QLV or QRS narrowing). While these data are based on retrospective analysis, the potential benefit to subjects is that CRT response rate and magnitude of CRT response may be improved through use of the ECG Belt Research System.

Additionally, information collected from this study may assist in the design of new product(s)/therapy(ies) and/or instructions for use.

### c. Risk-benefit rationale

The study population is known to have a lower likelihood of response to CRT with typical LV lead placement and device programming without an option for evaluating if pacing resynchronizes the patient.

The use of ECG Belt Research System during implant would help the implanter with this information and may help confirming a suitable implant site and choosing the most optimal pacing settings which resynchronize the heart, in addition to satisfying other criteria (lead stability, clinically acceptable thresholds, no phrenic stimulation). The ECG Belt application and evaluation may add time to the implant procedure of approximately 40 minutes when two lead locations are tested, but may result in better response to CRT therapy.

The use of ECG Belt Research System for management during follow-up would help the physician with this information and may help choose the most optimal pacing settings which resynchronize the heart, in addition to satisfying other criteria (clinically acceptable thresholds, no phrenic stimulation). The ECG Belt Research System setup and evaluation may add approximately 40 minutes to the follow up procedure but may result in better response to CRT therapy.

The ECG Belt Study risks have been analyzed, evaluated and controls put in place to address all identified risks. The individual risks have been reduced as low as

possible, the risks are outweighed by the potential benefits, and the overall residual risk evaluated and disclosed via the ICF.

# 12. PLANNED STUDY CLOSURE, EARLY TERMINATION OF STUDY OR STUDY SUSPENSION

## a. Planned study closure

Study Closure is a process initiated by distribution of a study closure letter. Study closure is defined as closure of a clinical study that occurs when Medtronic and/or regulatory requirements have been satisfied per the CIP and/or by a decision by Medtronic or regulatory authority, whichever occurs first. The study closure process is complete upon distribution of the Final Report or after final payments, whichever occurs last. Ongoing Ethics Committee oversight is required until the overall study closure process is complete. Refer to Section 7q for additional information regarding study exit procedures.

## b. Early termination or suspension

Early Termination is the closure of a clinical study or single site that occurs prior to meeting defined endpoints. Suspension is a temporary postponement of study activities related to enrollment and distribution of the product. This is possible for the whole study or a single center.

### *i. Study-wide termination or suspension*

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

- Adverse events associated with the system or product under investigation which might endanger the safety or welfare of the subject
- Observed/suspected performance different from the product's design intent
- Decision by Medtronic or regulatory body (where the study is operating under regulatory body authority)
- Technical issues during the manufacturing process
- When the risks are found to outweigh the potential benefits or when there is conclusive proof of definitive outcomes, investigators must assess whether to continue, modify or immediately stop the study.

### *ii. Investigator/center termination or suspension*

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

- Failure to obtain initial Ethics Committee approval or annual renewal of the study

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

### c. Procedures for termination or suspension

*i. 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 MEC/IRB/Head of Medical Institution approval lapse, the investigator will promptly inform the MEC/IRB/Head of Medical Institution
- 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

*ii. Investigator-initiated*

- The investigator will 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 MEC/IRB/Head of Medical Institution
- 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

*iii. Ethics committee-initiated*

- The investigator will inform Medtronic and provide a detailed written explanation of the termination or suspension within 5 business days

- Subject enrollment must stop until the suspension is lifted
- Subjects already enrolled should continue to be followed in accordance with MEC/IRB/Head of Medical Institution policy or its determination that an overriding safety concern or ethical issue is involved
- The investigator will inform his/her institution (where required per local requirements)
- The investigator will promptly inform the subjects and/or the personal physician of the subjects, with the rationale for the study termination or suspension

# 13. STATISTICAL METHODS AND DATA ANALYSIS

## a. Sample size determination

The sample size of the study will be 400 randomized subjects. It will require approximately 500 enrolled to acquire 400 randomized, but enrollment will end once 400 are randomized. It is allowable to go over 400 randomized if the final randomizations occur within a week. As this is a research study, the sample size was based on budget, however power calculations can be found in the primary objective below.

## b. General considerations

Data analysis will be performed by Medtronic-employed statisticians or designees. Data analysis will occur after 6-month follow-up data is collected and once final study data is collected. A modified intention-to-treat analysis will be performed and will serve as the primary analysis for all objectives in this study. The modified intention-to-treat cohort will include all CRT-implanted randomized subjects in the group to which they were randomized. Since this is a research study, there are no sample size requirements for these data analyses.

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

The Statistical Analysis Plan (SAP) will be developed prior to data analysis and will include a comprehensive description of the statistical methods and reports to be included in the final study report. Any change to the data analysis methods described in the CIP will require an amendment only if it changes a principal feature of the CIP. Any other change to the data analysis methods described in the CIP, and the justification for making the change, will be described in the clinical study report.

The primary objective will be analyzed once the final 6-month follow-up is collected. Ancillary objectives may or may not be reported on at that time. The analysis of all objectives will appear in the study's final report.

## c. Primary Objective

Demonstrate benefit of using the ECG Belt Research System on reducing LVESV from baseline to 6 months post-implant compared to standard CRT.

*i. Hypothesis*

$H_0$: $\Delta$ $LVESV_{ECG\ Belt} = \Delta$ $LVESV_{control}$
$H_A$: $\Delta$ $LVESV_{ECG\ Belt} \neq \Delta$ $LVESV_{control}$

Where $\Delta$ LVESV is the relative (%) change in LVESV from baseline to 6 months post-implant calculated as 100 x (6-month LVESV – baseline LVESV) / baseline LVESV.

*ii. Performance Requirements*

The null hypothesis will be rejected if the p-value is less than 0.05. This is a research study, therefore if the ECG Belt arm has a better change in LVESV than the control arm, even if it is not statistically significant, the results could be interpreted as positive.

*iii. Rationale for Performance Criteria*

A reduction in LVESV has been shown to predict lower mortality rates in CRT patients[22], and changes are seen soon after implant. An alpha level of 0.05 is a standard statistical criterion.

*iv. Analysis Methods*

The relative change in LVESV from baseline to 6 months will be calculated and compared using a two-sided, two-sample t-test. Subjects exiting, dying, or with missing LVESV at baseline or 6 months will not be included, and their data will not be imputed.

If more than 10 randomized subjects fail to get implanted with an AdaptivCRT device and a Medtronic quadripolar LV lead, then a secondary analysis including only subjects successfully implanted with an AdaptivCRT device and a Medtronic quadripolar LV lead will be conducted.

*v. Determination of Subjects for Analysis*

All randomized subjects with paired LVESV data will be included.

*vi. Sample Size*

The sample size of approximately 200 subjects in the ECG Belt arm and 200 in the control arm was chosen based on budget considerations. Table 8 shows data from previous studies. The first row of the table shows that, among the patients meeting this study's inclusion criteria, the mean relative change in LVESV at 6 months is -7.1 ± 27.5.

So, it can be assumed that the control group without ECG Belt Research System management will decrease by a mean 7.1% over 6 months, with a standard deviation of 27.5%.

Table 8: LVESV Results from Previous CRT Studies' CRT Patients

| Study | n | Mean ± S.D. Relative Change at 6 months in LVESV (%) |
|---|---|---|
| All studies | 583 | -7.1 ± 27.5 |

| Study | n | Mean ± S.D. Relative Change at 6 months in LVESV (%) |
|---|---|---|
| MIRACLE | 125 | -9.2 ± 22.8 |
| MIRACLE ICD | 142 | -5.1 ± 25.1 |
| REVERSE | 124 | -8.2 ± 28.0 |
| Adaptive CRT control | 62 | -9.2 ± 32.3 |
| Adaptive CRT aCRT | 130 | -5.0 ± 31.3 |

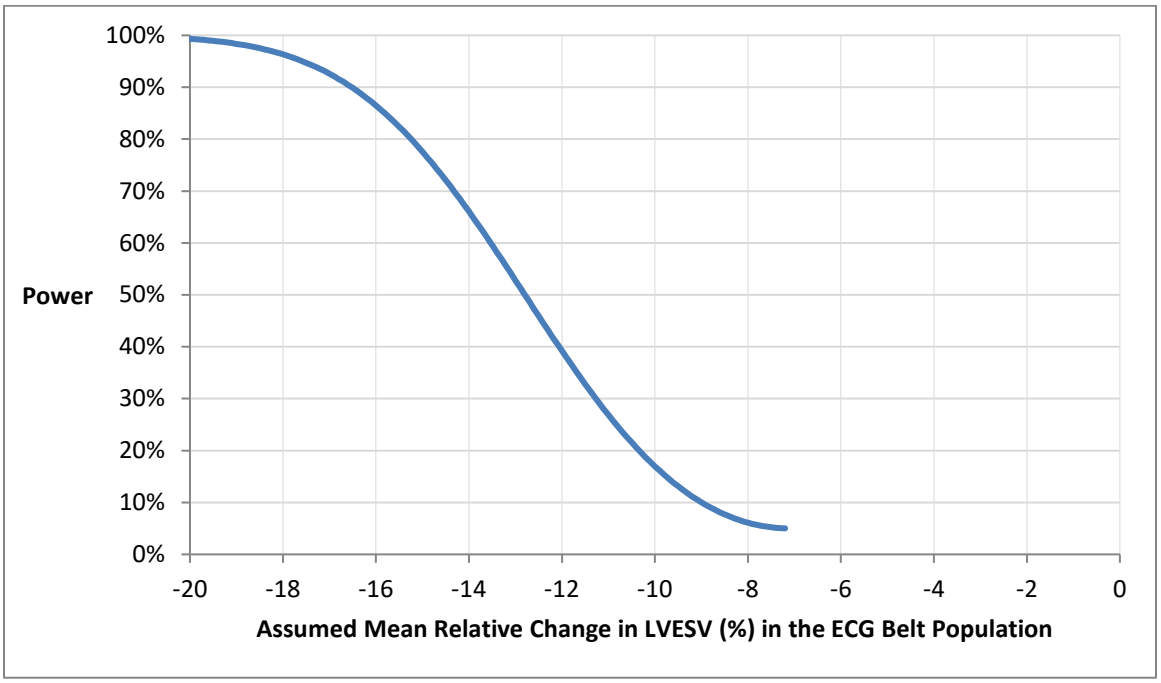
Note: To be included in the table, subjects must meet current indications for CRT (NYHA II with LVEF≤30% or NYHA III/IV), and have QRS≥130, LVEDD≥55, and (QRS<150 or Ischemic or non-LBBB)

Figure 7 shows the power of the study under various values of improvement in LVESV due to the ECG Belt Research System under the following assumptions:

- Alpha=0.05
- Mean LVESV change in control population at 6 months is –7.1 ± 27.5%
- ECG Belt Research System population subjects also have a standard deviation of 27.5%
- 180 subjects in the ECG Belt arm will have paired LVESV data, along with 180 subjects in the control arm (10% attrition primarily due to deaths and unreadable echos at 6 months)

The graph shows that the power of the study is 80% under the assumptions above if the ECG Belt Research System population reduces its mean LVESV by 15.3% (a 8.2% increase over the assumed control population mean relative change of 7.1%). As another example, if the ECG Belt Research System population has a mean reduction of 14%, then the power of this objective is 66%.

Figure 7: Primary Objective #1 Power Curve




### d. Ancillary Objectives

Though the following ancillary objectives have hypotheses to be tested, they are primarily intended to estimate various effects of the ECG Belt Research System.

### e. Ancillary Objective #1

To estimate the benefit of using the ECG Belt Research System on LVEF compared to standard CRT.

#### *i. Endpoint Definition*

Absolute LVEF change from baseline to 6 months.

#### *ii. Analysis Methods*

The mean changes in LVEF will be compared between ECG Belt arm and control arm using a two-sided, two-sample t-test.

#### *iii. Determination of Subjects for Analysis*

All randomized subjects with paired LVEF data.

### f. Ancillary Objective #2

To estimate the benefit of using the ECG Belt Research System on change in quality of life compared to standard CRT.

*i. Endpoint Definition*

Quality of life will be measured using the Minnesota Living with Heart Failure Questionnaire. The endpoint is change from baseline to 6 months. Questionnaires with less than 11 questions answered will not be included.

*ii. Analysis Methods*

The mean changes in quality of life will be compared between ECG Belt arm and control arm using a two-sided, two-sample t-test.

*iii. Determination of Subjects for Analysis*

All randomized subjects with paired Minnesota Living with Heart Failure Questionnaire data.

### g. Ancillary Objective #3

To estimate the benefit of using the ECG Belt Research System on change in Six-Minute Walk Test distance compared to standard CRT.

*i. Endpoint Definition*

Six-Minute Walk Test distance will be measured at baseline and 6 months. The endpoint is change from baseline to 6 months. If the test at either time point was not done due to heart failure reasons, the distance will be considered to be 0.

*ii. Analysis Methods*

The mean changes in Six-Minute Walk Test distance will be compared between ECG Belt arm and control arm using a two-sided, two-sample t-test.

*iii. Determination of Subjects for Analysis*

All randomized subjects with paired Six-Minute Walk Test distances, including those with a 0 distance on either or both the baseline and six-month visit due to heart failure.

### h. Ancillary Objective #4

To estimate the benefit of using the ECG Belt Research System on the Clinical Composite Score compared to standard CRT.

*i. Endpoint Definition*

Clinical Composite Response[23] will be evaluated at both 6 and 9 months post-implant. The description below is for 6 months, 9 months is analogous, but using 274 days instead of 182.

A subject will be considered “worsened” if he/she experiences any of the following between randomization and the earlier of 182 days post-implant or his/her 6-month follow-up:

- Death from any cause.
- Hospitalization >24 hours due to or associated with worsening heart failure.

- Discontinues CRT due to or associated with worsening heart failure, treatment failure, or lack of/ insufficient therapeutic response.

A subject will also be considered “worsened” if either of the following occurs:

- A worsening in NYHA class at 6 months (as compared to baseline.
- Moderate or marked worsening of the subject global assessment score at 6 months.

A subject will be considered “improved” if he/she is not “worsened” and one of the following is true:

- An improvement in NYHA class at 6 months (as compared to baseline.
- Moderate or marked improvement of the subject global assessment score at 6 months.

If a subject is neither “worsened” nor “improved”, and the subject has a 6-month follow-up, then he/she will be considered “unchanged”.

*ii. Analysis Methods*

Clinical Composite Response results will be reported at 6 months by randomization arm and compared using a chi-squared test.

*iii. Determination of Subjects for Analysis*

All randomized subjects who either worsen, or have a 6-month follow-up will be included.

### i. Ancillary Objective #5

To characterize ECG Belt Research System related AEs.

*i. Endpoint Definition*

An AE will be considered related to the ECG Belt Research System if it is classified as system-related.

*ii. Analysis Methods*

The percentage of ECG Belt Research System uses with an AE related to them will be reported. The denominator for this calculation will be the number of times the ECG Belt Research System was used. For example, this is expected to be 4 times (during implant, post-implant, 6 months, and 9 months) for a subject randomized to the ECG Belt arm and completing the study. The numerator will be the number of ECG Belt Research System uses with at least one adverse event. A 95% confidence interval will be applied to the estimate as well using GEE methods with patient as a repeated variable.

In addition, similar methods will be used to calculate the percentage of ECG Belt Research System uses with a serious adverse event related to the use of the ECG Belt Research System.

*iii. Determination of Subjects for Analysis*

All ECG Belt Research System uses will be included.

### j. Ancillary Objective #6

To assess the changes in LVESV from 6-9 months between subjects who have and have not used the ECG Belt Research System at 6 months.

*i. Endpoint Definition*

Relative LVESV change from 6 months to 9 months.

*ii. Analysis Methods*

The relative change in LVESV from 6 months to 9 months will be calculated and compared between control groups A and B using a two-sided, two-sample t-test.

*iii. Determination of Subjects for Analysis*

Only subjects in the control arm with paired LVESV data at 6 and 9 month follow up visits will be included.

### k. Ancillary Objective #7

To assess the extent of ECG Belt Research System guided programming changes across study visits.

*i. Endpoint Definition*

Any change in programming due to use of the ECG Belt Research System. This includes vector selection, Adaptive CRT programming mode, and A-V and V-V timing.

*ii. Analysis Methods*

The percentage of subjects whose programming is changed due to the ECG Belt Research System will be reported at each visit where the ECG Belt Research System is used. Additionally, frequencies of types of changes (e.g., vectors, V-V timing) will be reported.

*iii. Determination of Data for Analysis*

All subject visits where the ECG Belt Research System was used post-implant will be included.

# 14. DATA AND QUALITY MANAGEMENT

Data will be collected using an electronic data management system for clinical studies. CRF data will be stored in a secure, password-protected database which will be backed up nightly. Data will need to be saved complete upon entry by the centers to make it available for review. Data review, database cleaning and issuing and resolving data queries will be done according to Medtronic internal Standard Operating Procedures.

Data will be reviewed using programmed and manual data checks. Data queries will be made available to centers for resolution. Sign-off of CRFs is required at the end of the study upon database closure. Study management reports may be generated to monitor data quality and study progress. At the end of the study, the data will be locked and will be retained indefinitely by Medtronic.

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

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

The investigator will clearly mark clinical records to indicate that the subject is enrolled in this study. Where copies of the original source document as well as print outs of original electronic source documents are retained, these shall be signed and dated by a member of the investigation site team with a statement that it is a true reproduction of the original source document.

The data reported on the CRFs shall be derived from source documents and be consistent with these source documents, and any discrepancies shall be explained in writing. The CRF must be signed by the investigator. The CRF may be considered source for the following data collection elements:

- LV Lead placement decisions
- ECG Belt Research System measurements
- CRT programming decisions
- Device Tracking
- Randomization assignment
- The following Administrative information:
    - Date of baseline assessment
    - Date of most recent inclusion/exclusion criteria assessment
    - Date Medical History was assessed
    - Date study center became aware of the Adverse Event

Hard copy data (if applicable) such as Echo (uploaded to a disk/USB) or 12-lead ECG (paper or uploaded to disk/USB) that is collected at Implant and/ or follow-up visits will be sent to Medtronic. Upon receipt, hard copy data will be maintained in a secure location and retrieved for analysis and reporting.

The sponsor or a regulatory authority may audit or inspect the study center to evaluate the conduct of the study. The clinical investigator(s)/institution(s) shall allow study related monitoring, audits, Ethics Board review and regulatory inspection by providing direct access to source data/documents.

# 15. INSURANCE INFORMATION

**US and Canada:**

Medtronic 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.

**Europe:**

Medtronic Bakken Research B.V 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 Ethics Committee.

# 16. 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 center in order to ensure that the study is conducted in accordance with the CIP, Medtronic Standard Operating Procedures, the Clinical Trial Agreement, and applicable regulatory and local requirements. Medtronic, or delegates, must therefore be allowed access to the subjects' case histories (clinic and hospital records, and other source data/documentation) upon request as per the ICF, Research Authorization (where applicable) and Clinical Trial Agreement. The principal investigator should also be available during monitoring visits.

## a. Monitoring Visits

Frequency of monitoring visits may be based upon subject enrollment, duration of the study, study compliance, number of AEs, number of deviations, findings from previous monitoring visits and any suspected inconsistency in data that requires investigation. Regulatory documents may be reviewed at each study center. Monitoring for the study, including site qualification visits, site initiation visits, interim monitoring visits, and closeout visits, and extent of source data verification will be done in accordance to the ECG Belt Monitoring Plan.

Monitoring visits may be conducted periodically to assess site study progress, the investigator's adherence to the CIP, regulatory compliance including but not limited to IRB/Ethics Committee approval and review of the study, maintenance of records and reports, and review of source documents against subject CRFs. Monitors review site regulatory and study compliance by identifying findings of non-compliance and communicating those findings along with recommendations for preventative/corrective actions to site personnel. Monitors may work with study personnel to determine

appropriate corrective action recommendations and to identify trends within the study or at a particular center.

# 17. REQUIRED RECORDS AND REPORTS

## a. Investigator records

The investigator is responsible for the preparation and retention of the records cited below. All of the below records, with the exception of case history records and case report forms, should be kept in the Investigator Site File (i.e., the study binder provided to the investigator) or Subject Study Binder. 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 the date on which the investigation is terminated.

- All correspondence between the IRB/MEC, sponsor, monitor, regulatory authority and the investigator that pertains to the investigation, including required reports.
- Subject's case history records, including:
    - Signed and dated informed consent form
        - In U.S. and Canada, signed by subject.
        - In Europe, signed and dated by subject and investigator.
    - Observations of AEs/adverse device effects/device deficiencies
    - Medical history
    - Implant and follow-up data
    - Documentation of the dates and rationale for any deviation from the protocol
- List of investigation sites
- All approved versions of the CIP, ICF, and Investigator's Brochure (as applicable)
- Signed and dated Clinical Trial Agreement
- Current curriculum vitae of principal investigators (all geographies), and key members of investigation site team (Europe)
- Financial Disclosures
- Documentation of delegated tasks
- IRB/MEC approval documentation. Written information that the investigator or other study staff, when member of the IRB/MEC, did not participate in the approval process. Approval documentation must include the Ethics Board composition, where required per local law.
- Regulatory authority notification, correspondence and approval, where required per local law
- Study training records for site staff
- Insurance certificates (Europe)

- Device tracking log
- Randomization list
- Subject ID list
- Any other records that FDA and local regulatory agencies require to be maintained
- Final Study Report including the statistical analysis.

### b. Investigator reports

The investigator is responsible for the preparation (review and signature) and submission to the sponsor of all CRFs, AEs 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 IRB/MEC with respect to this clinical study, copies of all pertinent documentation must be forwarded to Medtronic in a timely manner. Reports are subject to inspection and to the retention requirements as described above for investigator records.

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

Table 9: Investigator reports applicable for all geographies per Medtronic requirements

| Report | Submit to | Description/Constraints |
|---|---|---|
| Withdrawal of IRB/MEC approval | Sponsor and Relevant Authorities | The investigator must report a withdrawal of approval by the reviewing IRB/MEC of the investigator's part of the investigation within 5 working days. |
| Study Deviations | Sponsor and IRB/MEC | Any deviation from the clinical investigational plan shall be recorded together with the explanation of the deviation. Notice of deviations from the CIP to protect the life or physical well-being 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. |
| Final Report | IRBs/MECs and Relevant Authorities | This report must be submitted within 3 months of study completion or termination. |

Table 10: Additional Investigator reports applicable to the United States per FDA regulations

| Report | Submit to | Description/Constraints |
|---|---|---|
| Withdrawal of IRB/MEC approval (either suspension or termination) | Sponsor | The investigator must report a withdrawal of approval by the reviewing IRB/MEC of the investigator's part of the investigation within 5 working days. *(21 CFR 812.150(a)(2))* |
| Progress report | Sponsor and IRB/MEC | The investigator must submit this report to the sponsor and IRB/MEC at regular intervals, but in no event less than yearly. *(21 CFR 812.150 (a)(3))*. |
| Study deviations | Sponsor and IRB/MEC | 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 IRB/MEC, 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 IRBs/MECs | 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 IRBs/MECs 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 | IRB/MEC and FDA | An investigator shall, upon request by a reviewing IRB/MEC, FDA or any other regulatory agency, provide accurate, complete, and current information about any aspect of the investigation. *(21 CFR 812.150(a)(7))* |

Table 11: Additional Investigator reports applicable to Europe per ISO14155

| Report | Submit to | Description/Constraints |
|---|---|---|
| Progress Report | Sponsor and IRB/MEC | Provide if required by local law or IRB/MEC. |
| Study Deviations | Sponsor and IRB/MEC | Any deviation from the CIP shall be recorded together with an explanation for the deviation. Deviations shall be reported to the sponsor who is responsible for analyzing them and assessing their significance.<br>Note: When relevant, ethics committees, competent authorities or the appropriate regulatory bodies should be informed. *(ISO 14155:2011)* |
| Failure to obtain informed consent | Sponsor and IRB/MEC | Informed consent shall be obtained in writing and documented before a subject is enrolled into the clinical investigation. *(ISO 14155:2011)* |

## c. Sponsor records

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

- All correspondence which pertains to the investigation
- Investigational device traceability record

- Software traceability records
- All approved informed consent templates, and other information provided to the subjects and advertisements, including translations
- Copies of all IRB/MEC approval letters and relevant IRB/MEC correspondence and IRB/MEC voting list/roster/letter of assurance
- Names of the institutions in which the clinical study will be conducted
- Regulatory authorities correspondence, notification and approval as required by national legislation
- Insurance certificates
- Names/contact addresses of monitors
- Statistical analyses and underlying supporting data
- Final report of the clinical study
- All approved versions of Clinical Investigation Plan, Investigator's Brochure and study related reports, and revisions
- Study training records for site personnel and Medtronic personnel involved in the study
- Signed Investigator Trial Agreements, and current signed and dated curriculum vitae of principal investigator and key members of the investigation site team, signed delegated task list and dated case report forms submitted by investigator, including reports of AEs, ADEs and Device Deficiencies
- Any other records that local regulatory agencies require to be maintained

### d. 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 IRB/MEC, regulatory agency or FDA, provide accurate, complete and current information about any aspect of the investigation. Safety data Medtronic reporting requirements are listed in the Adverse Event section.

Table 12: Sponsor reports for Canada

| Report | Submit to | Description/Constraints |
|---|---|---|
| Premature termination or suspension of the clinical investigation | Investigators, IRB/MEC, Relevant authorities, and Head of the Institution | Provide prompt notification of termination or suspension and reason(s). (ISO 14155:2011) |

| Report | Submit to | Description/Constraints |
|---|---|---|
| Recall and device disposition | Investigators, Head of Institution, IRB/MEC, relevant authorities, and FDA | Notification within 30 working days and will include the reasons for any request that an investigator return, repair, or otherwise dispose of any devices. |
| Study deviation | Investigators | Ensure that all deviations from the Clinical Investigation Plan are reviewed with the appropriate clinical investigator(s), are reported on the case report forms and the final report of the clinical investigation. (ISO 14155:2011)<br>Site specific study deviations will be submitted to investigators periodically. |
| Device Deficiency (DD) | Health Canada | Any DD that:<br>a. has resulted in any of the consequences characteristic of an SAE on the patient, the user or any other person; These must be reported by Medtronic to the Regulator within 10 days from the date Medtronic becomes aware.<br>or<br>b. could do so were it to reoccur. These must be reported by Medtronic to the Regulator within 30 days from the date Medtronic becomes aware. |

Table 13: Sponsor reports for Europe

| Report | Submit to | Description/Constraints |
|---|---|---|
| Premature termination or suspension of the clinical investigation | Investigators, IRB/MEC, Relevant authorities and Head of the Institution | Provide prompt notification of termination or suspension and reason(s). |
| Withdrawal of IRB/MEC approval | Investigators, Head of Institution, IRB/MEC and relevant authorities | Investigators, IRBs/MECs will be notified only if required by local laws or by the IRB/MEC. |
| Withdrawal of CA approval | Investigators, Head of Institution, IRB/MEC, and relevant authorities | Investigators, IRBs/MECs will be notified only if required by local laws or by the IRB/MEC. |
| Progress Reports | IRB/MEC and regulatory authorities | This will be submitted to the IRB/MEC only if required by the IRB/MEC. |

| Report | Submit to | Description/Constraints |
|---|---|---|
| Final report | Investigators, IRB/MEC, and Regulatory authorities upon request | 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). |
| Study deviation | Investigators | Site specific study deviations will be submitted to investigators periodically. |

Table 14: Sponsor reports for the United States

| Report | Submit to | Description/Constraints |
|---|---|---|
| Withdrawal of IRB/MEC approval | Investigators, IRB/MEC, FDA, and relevant authorities | Notification within five working days. *(21 CFR 812.150(b)(2))* |
| Progress Reports | IRB/MEC | 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, IRB/MEC, 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. *(21 CFR 812.150(b)(6))* |
| Failure to obtain informed consent | IRB/MEC | Investigator's report will be submitted to FDA within five working days of notification. *(21 CFR 812.150(b)(8))* |
| Final report | Investigators, IRB/MEC, Regulatory authorities upon request | Medtronic will notify IRB/MEC within 30 working days of the completion or termination of the investigation. A final report will be submitted to IRB/MEC, investigators, and IRBs/MECs within six months after completion or termination of this study. *(21 CFR 812.150(b)(7))* |
| Study deviation | Investigators | Ensure that all deviations from the Clinical Investigation Plan are reviewed with the appropriate clinical investigator(s), are reported on the case report forms and the final report of the clinical investigation.<br>Site specific study deviations will be submitted to investigators periodically. |
| Other | IRB | Accurate, complete, and current information about any aspect of the investigation. (21 CFR 812.150(b)(10)) |

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

After closure of the study Medtronic will archive records and reports for the Life of Product, with Life of Product defined as End of Production plus 15 years or the Life of Medical Device plus 1 year, whichever is longer.

# Appendix A. Draft data collection elements (Case Report Forms)

Draft Case Report Forms for the ECG Belt study may be provided under separate cover upon request. Final CRFs 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 ECG Belt study will be handled according to Medtronic Standard Operating Procedures and as indicated in the Clinical Trial Agreement and the Publication Plan.

**Publication Committee**

Medtronic may form the ECG Belt Publication Committee from steering committee members and study investigators. Medtronic personnel may serve as members of the committee. This committee will manage study publications with the goal of publishing findings from the data. The Publication Committee will develop the final Publication Plan as a separate document.

The Publication Committee's role is to: 1) manage elements addressed in the publication plan as outlined in this appendix, 2) develop the final Publication Plan under separate cover, 3) execute the Publication Plan, 4) oversee the publication of primary, secondary and ancillary study results (as applicable), 5) review and prioritize publication proposals, 6) provide input on publication content, and 7) determine authorship. In addition, the committee will apply and reinforce the authorship guidelines set forth in the Publication Plan.

Membership in the Publication Committee does not guarantee authorship. The committee will meet as needed.

**Management of Primary, 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 Clinical Investigation Plan.

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

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

### Criteria for Determining Authorship and Contributorship

Publications will adhere to authorship and contributorship criteria defined by the International Committee of Medical Journal Editors (ICMJE, Uniform requirements for manuscripts submitted to biomedical journals, www.icmje.org). Individual authorship and contributorship 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 contribution to conception and design, or acquisition of data, or analysis and interpretation of data
- Drafting the article or revising it critically for important intellectual content
- Final approval of the version to be published
- 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.

Contributors, Medtronic personnel or Health Care Provider (HCP), may be considered for inclusion in an Acknowledgement section of the publication. Depending on degree, these contributions might merit contributorship in the publication.

Decisions regarding authorship and contributorship 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.

All investigators not listed as co-authors will be acknowledged as the “Medtronic ECG Belt Clinical Study Investigators” and will be individually listed according to the guidelines of the applicable scientific journal when possible and affiliation. Any other contributors will be acknowledged by name with their specific contribution indicated.

### Transparency

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

- a final report, describing the results of all objectives and analysis, will be distributed to all investigators, ECs and Competent Authorities of participating countries when required by local law
- registering and posting the study results on ClinicalTrials.gov based on the posting rules stipulated
- 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 centers study data accessible to the corresponding investigator after the completion of the study, if requested

# Appendix C. Patient Informed Consent template

Patient ICF template will be provided under separate cover

# Appendix D. Participating investigators and institutions

A complete list of participating investigators and institutions where study activities will be conducted and the emergency contact details will be distributed under a separate cover when available.

# Appendix E. IRB/MEC and Competent Authority list

A complete list of participating IRB/MECs and the Chairperson(s) will be distributed under a separate cover when available.

# Appendix F. Labeling

Labeling and package for all products used in this study will follow the local regulatory requirements. In geographies where the market released products are commercially available, original device labeling will be used unless local regulations require otherwise.

For components that are not market released or not commercially available and in geographies where investigational labeling is required for market released product used outside of approved indications, investigational labelling will be done as per local regulations.

The various investigational components of the ECG Belt Research System used in this study, or their immediate package, shall bear a label with the following information: the name and place of business of the manufacturer, packer, or distributor, and the quantity of contents, as appropriate.

Labeling will be provided according to local law which may require translation to the local language.

Product information (e.g. the ECG Belt Research System User Manual) will be provided in English unless required per local legislation to provide local language.

**United States**

The labeling of the investigational products shall include the statement: “CAUTION - Investigational Device. Limited by Federal law (U.S.A.) to investigational use” and describe all relevant contraindications, hazards, adverse effects, interfering substances or devices, warnings, and precautions.

**Canada**

The labeling of the investigational products shall include the statements: “Investigational Device” / “Instrument de recherche” and “To Be Used by Qualified Investigators Only” and “Réservé uniquement à l’usage de chercheurs compétents”, or any other statements, in English and French, that convey that meaning.

**Europe**

The labeling of the investigational products shall include the statement: “Exclusively for clinical investigations”, as applicable per local law. English labeling will be used for investigational devices unless otherwise required by local regulation. Labeling of CE-Marked devices must follow local language requirements.

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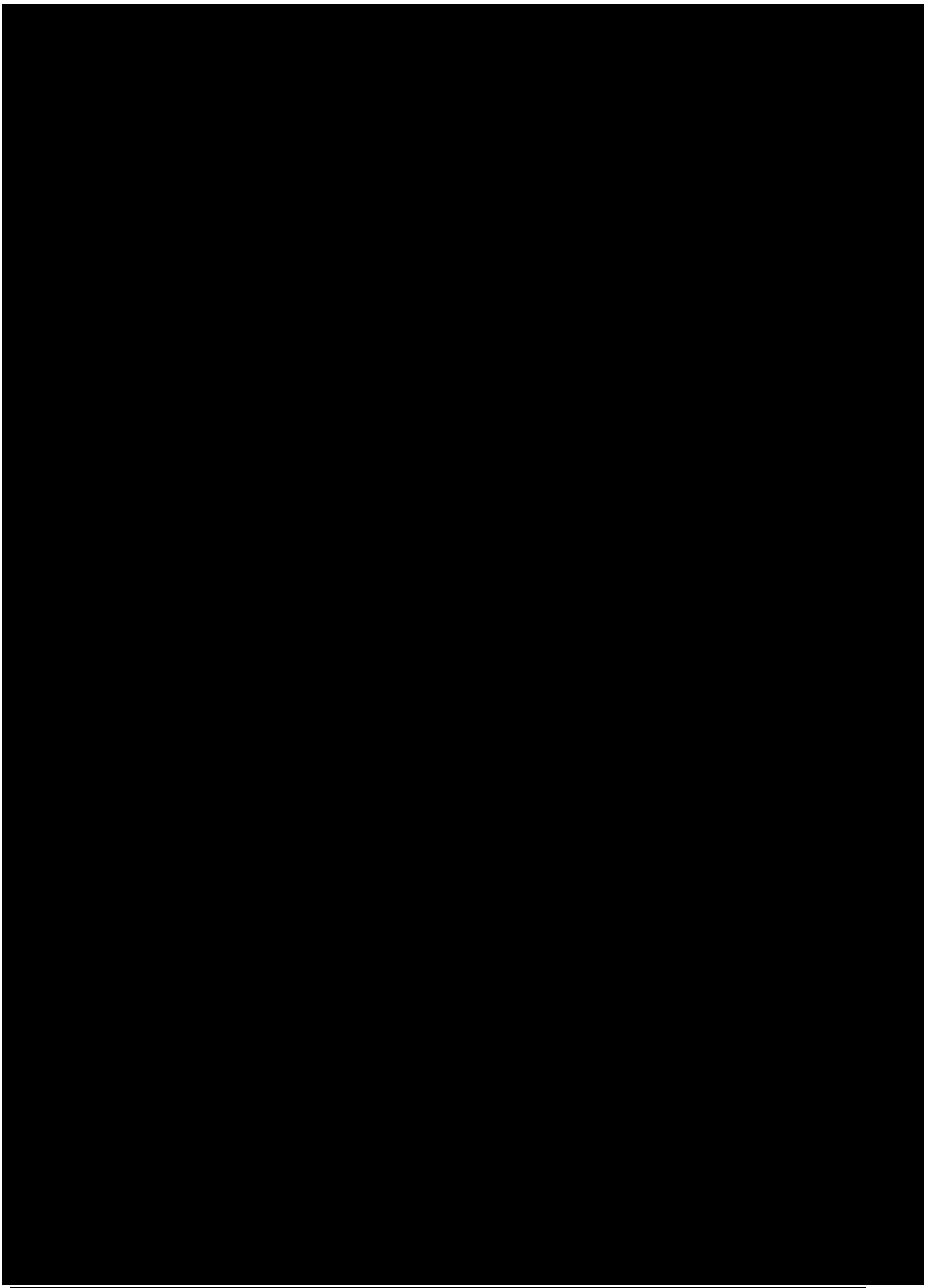

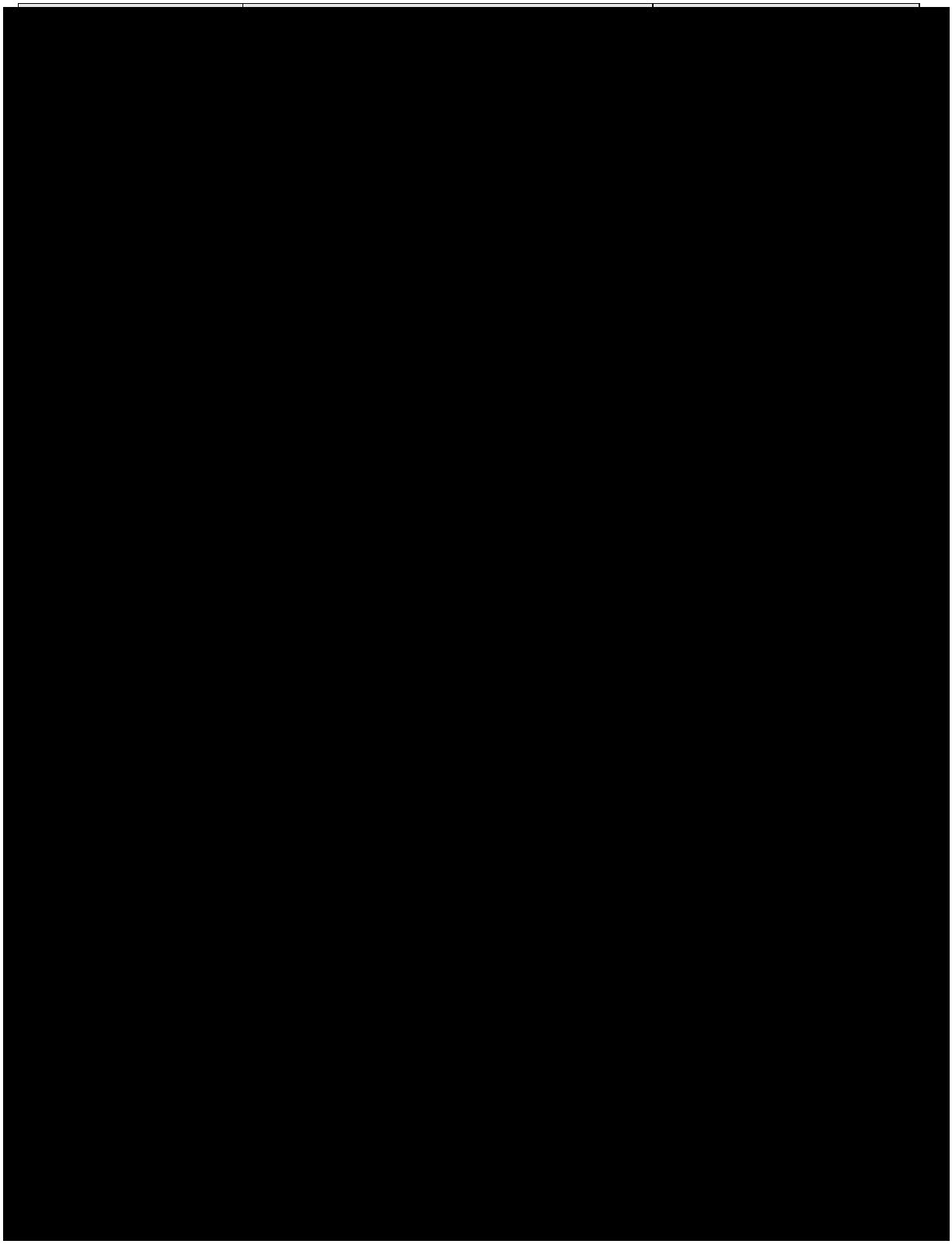

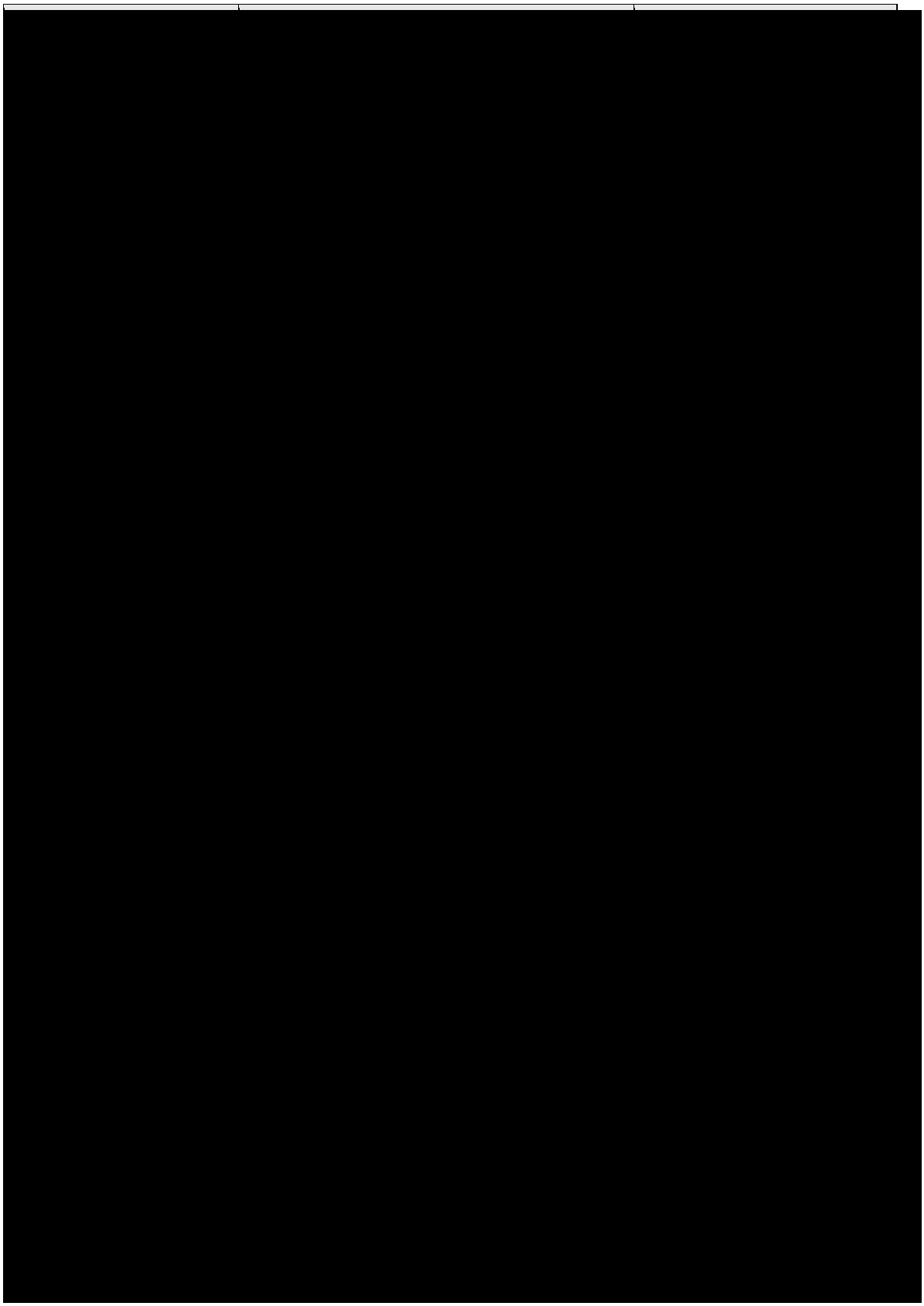

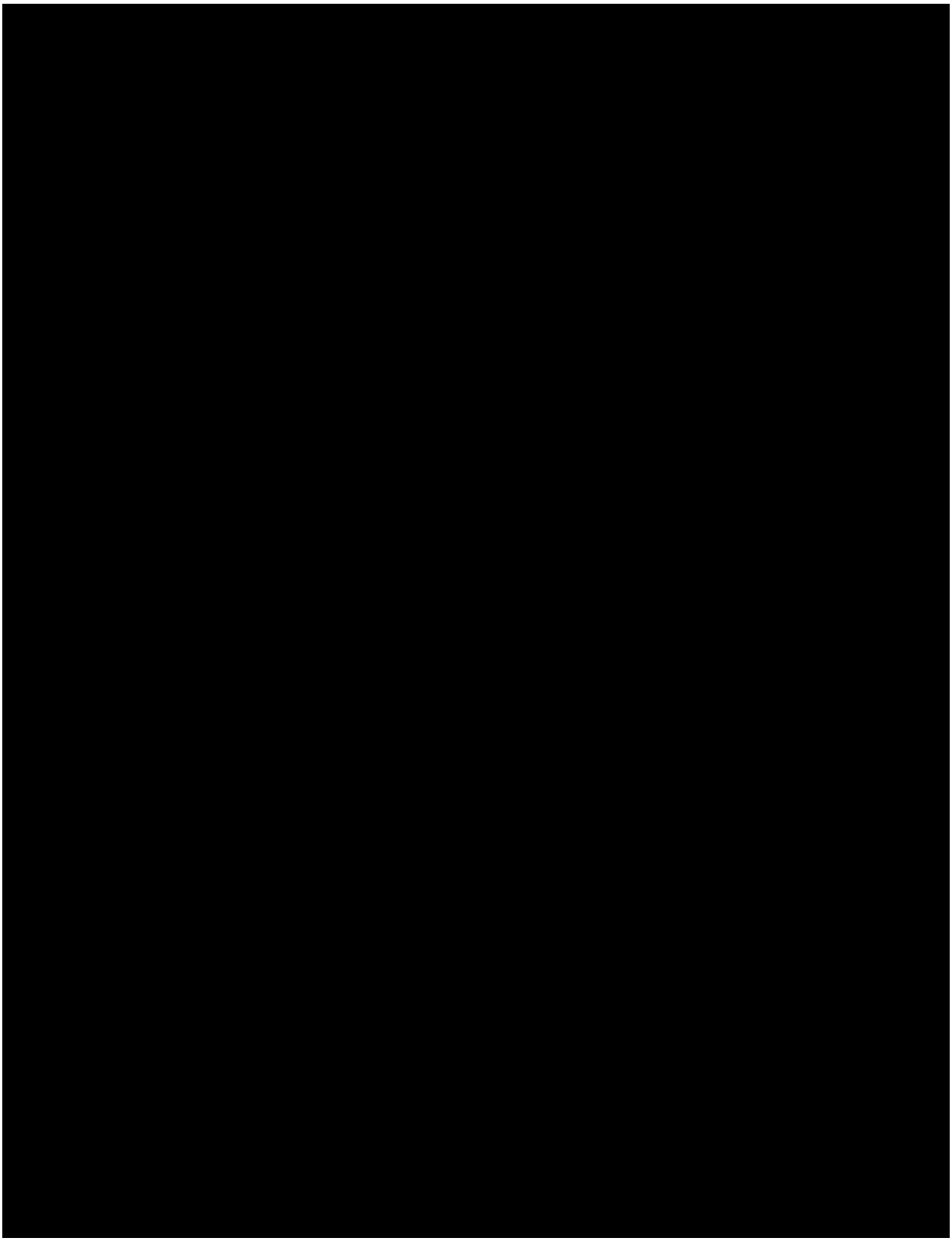

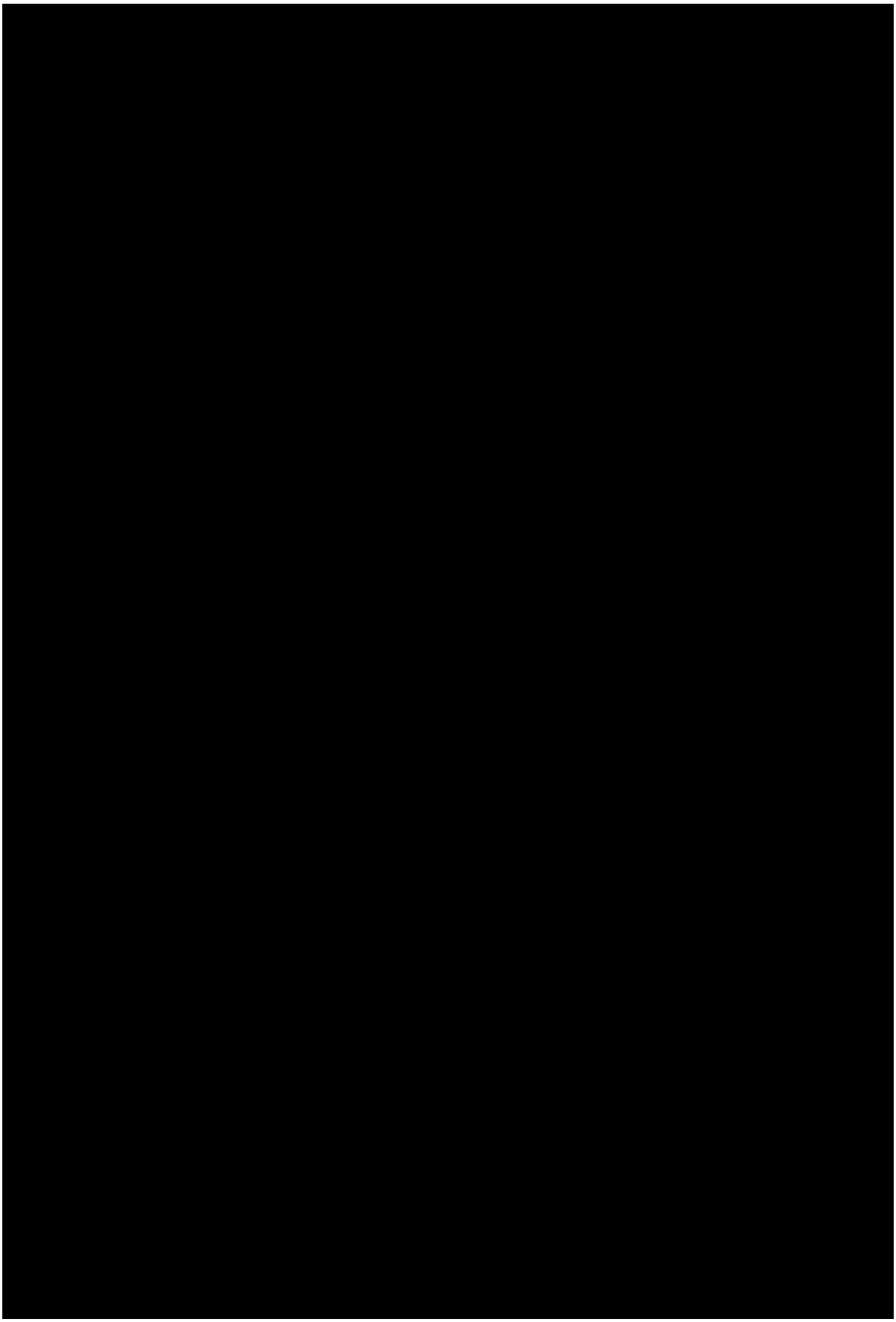

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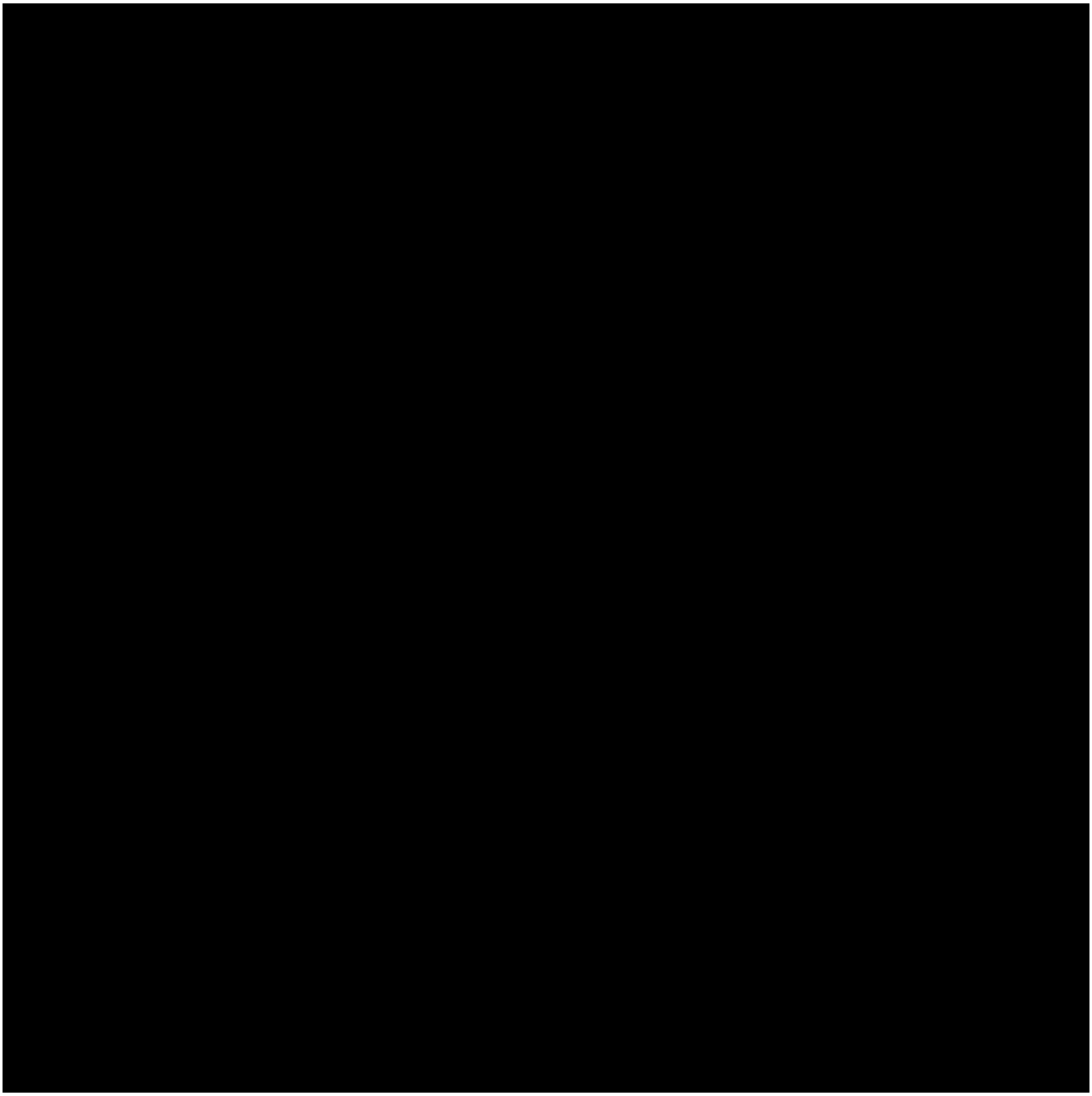

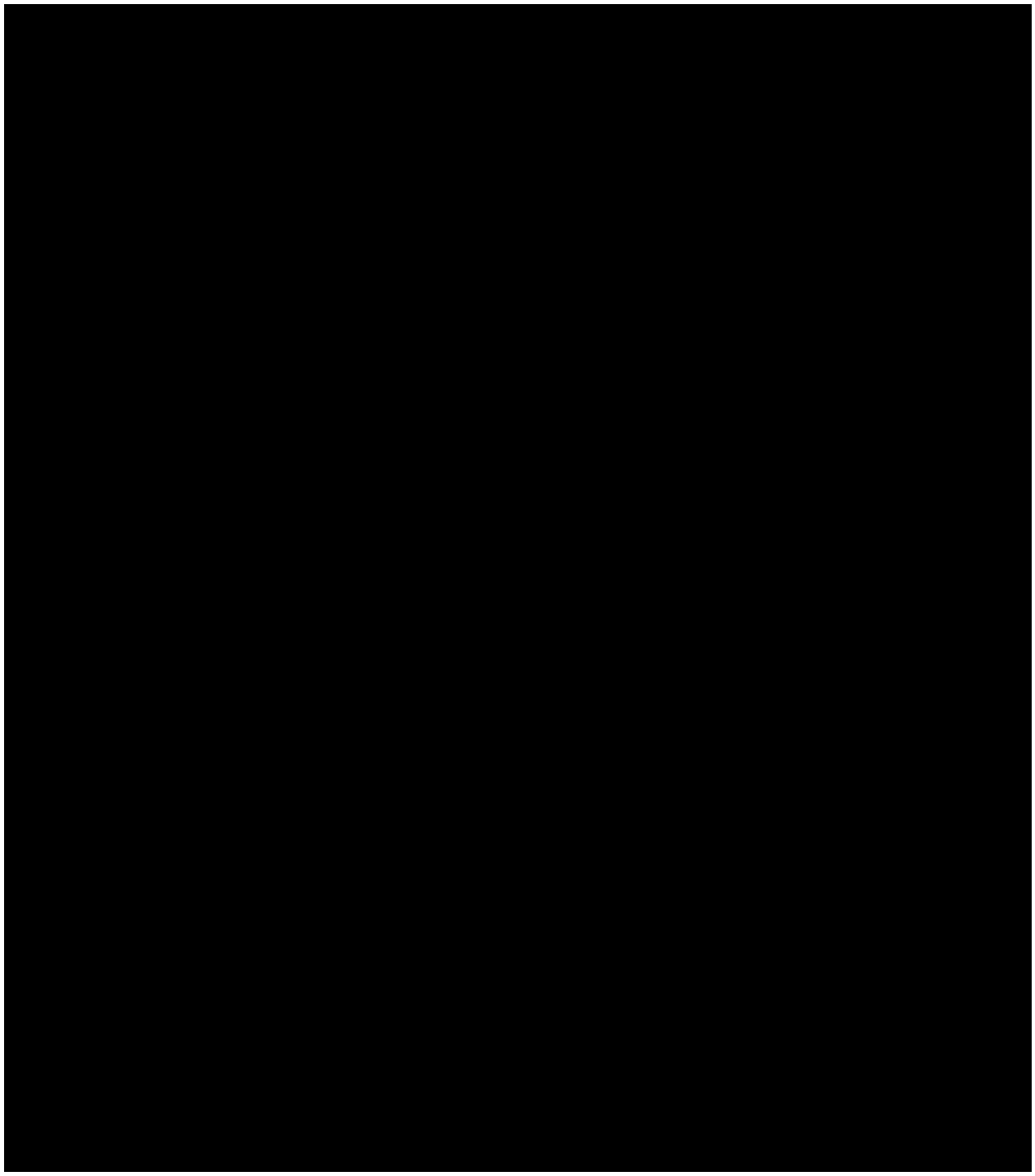

# Appendix H. Clinical investigation plan signature page

**ECG Belt for CRT Response**

The ECG Belt study is a prospective, randomized (2:1:1), multi-center, investigational, research study. The study is being conducted to compare ECG Belt managed CRT patients and standard CRT with respect to chronic outcomes. ECG Belt will be used at implant and/or follow-up to guide LV lead placement (at implant) optimize pacing vector/timing parameters (during follow-up).

Clinical Investigation Plan Version 5.0 – 02MAY2019

I/we acknowledge that I/we have read, understood and agreed to abide by all conditions, instructions and restrictions contained in the above mentioned Clinical Investigation Plan. I/we agree to carry out all of its items in accordance with applicable regulations and in full compliance with the guidelines.

| **Hospital** | **City** | **Country** |
|---|---|---|
| | | |
| **Title, First and last Name** | **Signature** | **Date (dd/MMM/yyyy)** |
| | | |
| | | |

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