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Title	CSPOT SAP Version 1

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Medtronic

Statistical Analysis Plan

Clinical Investigation Plan Title	Conduction System Pacing Optimized Therapy (CSPOT)
Clinical Investigation Plan Identifier	MDT20029
Clinical Investigation Plan Version	4.0, 29-Apr-2022
Sponsor/Local Sponsor and EU Legal representative	Medtronic, Inc US 8200 Coral Sea Street NE Mounds View, MN U.S.A. 55112 Phone: 1-800-328-2518 Medtronic, Bakken Research Center B.V. Endepolsdomein 5, 6229 GW Maastricht, The Netherlands Phone: +31 43 3266566

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1. Version History

Version	Summary of Changes	Author(s)/Title
1.0	• New Document	Pat Zimmerman, Principal Biostatistician
2.0	• Updated Objectives to measure percent change from baseline at implant • [redacted]	James Burrell, Senior Statistician

2. Glossary

Term	Definition
ADE	Adverse Device Effect
AE	Adverse Event
ASADE	Anticipated Serious Adverse Device Effect
AF	Atrial Fibrillation
AFL	Atrial Flutter
AV Block	Atrioventricular Block
AV Delay	Atrioventricular Delay
CA	Competent Authority
CEC	Clinical Events Committee
CFR	Code of Federal Regulation
CIP	Clinical Investigation Plan
CRO	Contract Research Organization
CRT-D	Implantable Cardioverter Defibrillator with Cardiac Resynchronization Therapy
CRT-P	Implantable Pulse Generator with Cardiac Resynchronization Therapy
CRF	Case Report Form
CSP	Conduction System Pacing
CSPOT	Conduction System Pacing, Optimized Therapy
CTA	Clinical Trial Agreement

Term	Definition
CV	Curriculum Vitae
DD	Device Deficiency
DMC	Data Monitoring Committee
DoH	Declaration of Helsinki
DTL	Delegated Task List
eCRF	Electronic Case Report Form
EC/IRB/HREB/Ethics Board/Head of Medical Institution	Ethics Committee
ECG Belt	Electrocardiogram Belt
FAL	Foreseeable Adverse Events List
FD	Financial Disclosure
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act
GCP	Good Clinical Practice
HIPAA	Health Insurance Portability and Accountability Act
IB	Investigator Brochure
IC	Informed Consent
ICD	Implantable Cardioverter Defibrillator
ICH	International Conference of Harmonization
IDE	Investigational Device Exemption
IFU	Instructions For Use
IPG	Implantable Pulse Generator
IVCD	Intraventricular Conduction Delay
LBBB	Left Bundle Branch Block
LBBP	Left Bundle Branch Pacing
LV	Left Ventricle
LVEF	Left Ventricular Ejection Fraction
LVESV	Left Ventricular End Systolic Volume
MDD	Medical Device Directive
MDR	Medical Device Regulation (EU)
MedDRA	Medical Dictionary for Regulatory Activities

Term	Definition
MHRA	Medicines and Healthcare products Regulatory Agency (UK)
MI	Myocardial infarction
PHI	Protected Health Information
RA	Right Atrium
RBBB	Right Bundle Branch Block
RPI	Report of Prior Investigations
RV	Right Ventricle
SADE	Serious Adverse Device Effect
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SC	Steering Committee
SID	Subject Identification
UAE	Unavoidable Adverse Event
UADE	Unanticipated Adverse Device Effect
USADE	Unanticipated Serious Adverse Device Effect
VV-Delay	Ventricle to Ventricle Delay

3. Introduction

3.1 Background

The current standard-of-care therapy for heart failure patients with wide QRS is cardiac resynchronization therapy (CRT), which is commonly accomplished through biventricular pacing. His Bundle pacing may benefit some CRT patients as a replacement for biventricular pacing [3-6]. However, His Bundle pacing will not resynchronize some CRT patients that have conduction block distal to the His Bundle pacing location. In an effort to increase the benefit of His Bundle pacing for CRT patients, three studies suggested that the combination of His Bundle pacing with LV pacing (sometimes called "HOT-CRT") provided improved clinical outcome [7-9]. Nevertheless, His Bundle pacing frequently suffers from high and unstable pacing thresholds and remains a challenging procedure.

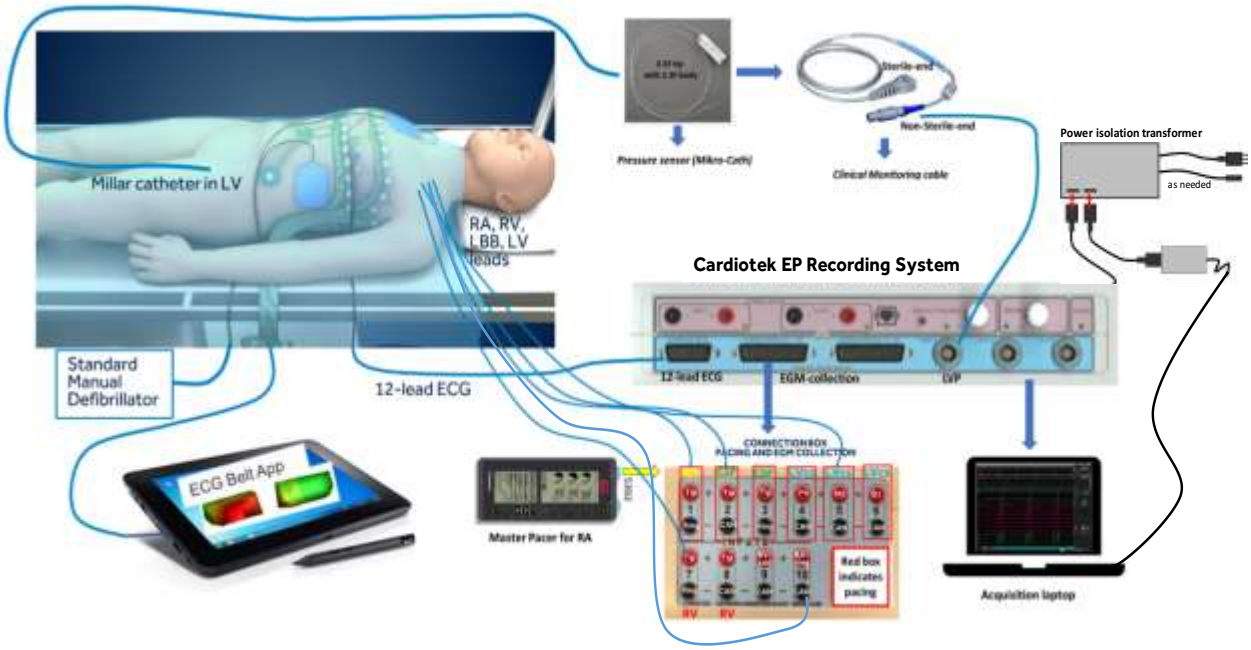
A different form of conduction system pacing (CSP), left bundle-branch pacing (LBBP), was introduced in 2017 [10]. LBBP has lower and more stable pacing thresholds than His Bundle pacing

and is generally considered to be a simpler procedure. Several studies have shown that LBBP is promising as an alternative to BiV pacing in CRT patients [11-13]. However, it appears that, like His pacing, some CRT patients will not receive adequate resynchronization from LBBP alone. These CRT patients may have more diffuse conduction disease, such as a combination of left bundle-branch block (LBBB) and intraventricular conduction delay (IVCD). Two studies have provided pilot data that the combination of LBBP and LV pacing (now referred to as "CSPOT" pacing) may improve resynchronization in some LBBP patients [12, 13]. These studies encourage further study of LBBP and CSPOT pacing in CRT patients, with emphasis on comparing the degree of resynchronization from each kind of pacing therapy and on determining the types of patients that benefit from each kind of pacing therapy. A summary/evaluation of the results of the pre-clinical testing can be found in the IB (Investigator Brochure).

The CSPOT study therefore aims to compare three modes of resynchronization pacing: 1) traditional CRT (BiV or LV-only pacing), 2) LBBP, and 3) CSPOT (CSP+LV). The study will collect three acute measures of resynchronization: 1) Mechanical measures of resynchronization via LV pressure, 2) Electrical measures of resynchronization via the ECG Belt, and 3) Electrical measures of resynchronization via the 12-lead ECG.

The schematic below provides an overview of the CSPOT system.

Figure 1: CSPOT Research System



3.2 Purpose

Medtronic, Inc is sponsoring the CSPOT study, a prospective, non-randomized, multi-center, global, feasibility clinical study in the CRT patient population. The purpose of this study is to determine the best mode of CRT pacing for different populations of CRT patients, comparing traditional CRT (BiV or LV-only pacing), CSP-only, and CSPOT pacing.

The CSPOT (Conduction System Pacing Optimized Therapy) Research System is being developed to support pre-market research comparing the acute effects of several different modalities of cardiac resynchronization pacing and to collect data for use in future algorithm development. CSP, specifically LBBP, may provide superior resynchronization compared to traditional CRT pacing. A subset of patients may further benefit from the combination of traditional LV pacing and CSP. The CSPOT Research System will allow collection of ECG, EGM, LV pressures and ECG Belt dyssynchrony metrics during periods of traditional CRT pacing (BiV or LV-only pacing), CSP-only (i.e. LBB) pacing and CSP+LV pacing. Findings from this feasibility study may be used as design inputs in developing a new system based on this technology. No long-term data using the research system will be collected. The CSPOT Research System is investigational and not intended for market release.

3.3 Documents

This Statistical Analysis Plan (SAP) details the methods used to analyze the study's objectives. The SAP has been designed to document, before data are analyzed, the rationale for the study design, and the planned analyses that will be included in study reports for the CSPOT clinical study. This SAP does not limit the analysis in reports. Additional analysis of the study data beyond this plan may be needed.

The following documents were used to create this SAP:

CIP CSPOT Version 4.0, version date: 29-APR-2022.

4. Study Objectives

4.1 Objectives

This prospective, non-randomized, multi-center, global, feasibility clinical study is designed to assess augmentation of electrical resynchronization as measured by ECG-belt metrics and 12-lead ECG, and to assess augmentation of contractility as measured by positive LV dP/dt max across LV pacing site(s) in patients indicated for CRT.

Thereto, the SDAT metric from ECG Belt and the force of contraction during CSP or CSPOT pacing will be compared to that of standard CRT pacing. Also, the EGM from the different cardiac electrodes will be collected for development of a device-based algorithm for optimized pacing. In addition, the chronic electrical and clinical response will be investigated. Rationale for study design

is to aim for maximizing the acute electrical and hemodynamic response on a per-patient basis, therefore the primary endpoint is written to satisfy comparing the response of CSPOT, the investigational system to traditional CRT pacing.

4.1.1 Primary Objective(s)

The primary objectives of the study are:

1. Compare the electrical synchronization response of CSPOT pacing configuration to CSP-only and traditional CRT (See section 10.7.1 of CIP) in patients undergoing a CRT implant, using the SDAT ECG-belt metric.
2. Compare the hemodynamic response of a CSPOT pacing configuration to CSP-only and traditional CRT in patients undergoing a CRT implant, using the contractility parameter positive LV dP/dt max.

4.1.2 Secondary Objective(s)

The secondary objectives of the study are:

1. For each pacing configuration (CSP-only, traditional CRT, and CSPOT), summarize the improvement in the ECG Belt SDAT measurement relative to baseline at implant, for the following subpopulations:
    a. Subjects with QRS width < 150ms and those with QRS width >= 150ms, as measured by 12-lead ECG at implant
    b. Subjects with pure LBBB and those with other conduction disorders
    c. Subjects with ischemic cardiomyopathy and those with non-ischemic cardiomyopathy
2. For each pacing configuration (CSP-only, traditional CRT, and CSPOT), summarize the improvement in the contractility parameter positive LV dP/dt max relative to baseline at implant, for the following subpopulations:
    a. Subjects with QRS width < 150ms and those with QRS width >= 150ms, as measured by 12-lead ECG at implant
    b. Subjects with pure LBBB and those with other conduction disorders
    c. Subjects with ischemic cardiomyopathy and those with non-ischemic cardiomyopathy
3. Characterize the chronic clinical response from CSPOT pacing by comparing LVEF measured at baseline to that measured at 6 months
4. Characterize the chronic clinical response from CSPOT pacing by comparing LVESV measured at baseline to that measured at 6 months
5. Characterize the chronic clinical response from CSPOT pacing by determining the Clinical Composite Score [1, 2] at 6 months.

4.1.3 Ancillary Objective

The Ancillary objective of the study is:

[redacted]

5. Investigation Plan

5.1 Study Design

CSPOT is a prospective, non-randomized, multi-center, global, feasibility clinical study designed to assess different approaches to resynchronization in CRT-indicated patients and to support pre-market research comparing the acute effects of several different modalities of cardiac resynchronization pacing and to collect data for use in future algorithm development. The study may enroll up to 60 subjects at up to 12 sites in the US, UK, and Europe with no more than 15 subjects enrolled per site. Study subjects will be followed for 6 months or until official study closure, defined as satisfaction of Medtronic and/or regulatory requirements (per the Clinical Investigation Plan) and/or by a decision by Medtronic or regulatory authority, whichever occurs first. [redacted]. All adverse events (AEs) and device deficiencies will be collected throughout the study duration of a subject's participation in the study, beginning at the time of informed consent.

Following consent, subjects will undergo a baseline assessment followed by the CSPOT lead placement procedure, which will include the CSPOT Study Protocol. Each subject will serve as their own control. This will be considered the acute phase. As part of the CSPOT Study Protocol, the primary outcome variables describe in Section 4.1 (SDAT and LV dP/dt max) will be measured at multiple delay settings for each pacing configuration being considered (CSPOT, Traditional CRT, CSP only). [redacted]

[redacted]

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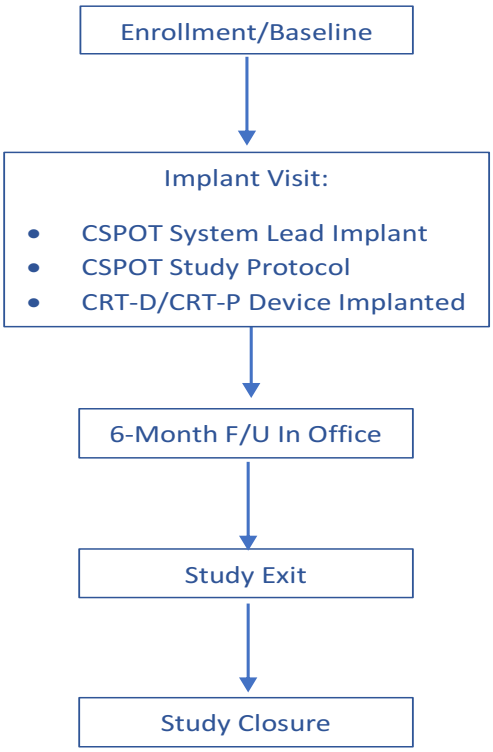
Following the CSPOT study protocol procedure, the CRT-D/CRT-P device will be implanted. Each subject will be programmed to their subject specific CSPOT (CSP+LV) configuration and subjects will be followed for 6 months. At the 6-month time point, electrical characterization will be performed via a 12-lead ECG and clinical endpoints will be collected to assess the chronic efficacy of CSPOT. [redacted] Subjects will be exited upon the completion of the 6-month visit. A study flowchart is shown in Figure 3.

Figure 3: Study Flowchart



5.2 Duration

[redacted] Study subjects will be followed for 6 months or until official study closure, defined as satisfaction of Medtronic and/or regulatory requirements (per the Clinical Investigation Plan) and/or by a decision by Medtronic or regulatory authority, whichever occurs first.

5.3 Rationale

The CSPOT feasibility study employs a prospective, non-randomized, multi-center, global, design aimed at optimizing cardiac resynchronization pacing. This study is intended to contribute to our understanding of optimal electrical synchrony and hemodynamics from different pacing configurations in patients who are indicated and implanted with a CRT-D/CRT-P. The study will also collect device EGM data for future development of automated optimization of pacing settings.

The CSPOT study will focus on optimizing pacing while posing minimal risk to the patient.

[redacted]

After completion of this risk management activity and incorporation of the appropriate mitigations called out in this document, all identified risks have been mitigated to an acceptable level.

5.4 Study Limitations

[redacted]

5.5 Minimization of Bias

Selection of subjects, treatment of subjects, and evaluation of study data are potential sources of bias. [redacted]

- [redacted]

[redacted]n

5.5.1.1 Inclusion Criteria

- Subject is willing and able to provide written informed consent
- Subject is at least 18 years of age
- Subject is willing and able to comply with the protocol, including follow-up visits
- The subject's medical records must be accessible by the enrolling site over the follow-up period
- Standard CRT-D or CRT-P indications, with a preference for IVCD and non-LBBB patients, where LBBB is defined according to Strauss criteria.
- De-novo CRT implant, including upgrade from pacemaker or ICD

5.5.1.2 Exclusion Criteria

- Subject has persistent or permanent AF (Atrial Fibrillation)/AFL (Atrial Flutter)
- Subject has 2nd or 3rd degree AV (Atrioventricular) Block
- Subject has RBBB with no additional conduction block
- Subject has intrinsic (non-paced) QRS width less than or equal to 120 ms
- Subject experienced MI within 40 days prior to enrollment
- Subject underwent valve surgery, within 90 days prior to enrollment
- Subject is post heart transplantation or is actively listed on the transplantation list
- Subject is implanted with a LV assist device
- Subject has severe renal disease
- Subject is on continuous or uninterrupted infusion (inotropic) therapy for heart failure
- Subject has severe aortic stenosis (with a valve area of <1.0 cm or significant valve disease expected to be operated within study period)
- Subject has severe aortic calcification or severe peripheral arterial disease
- Subject has complex or repaired congenital heart disease
- Subject has mechanical heart valve
- Pregnant or breastfeeding woman (pregnancy test required for woman of child-bearing potential and who are not on a reliable form of birth regulation method or abstinence)
- Subject is enrolled in another study that could confound the results of this study without documented pre-approval from Medtronic study manager

6. Determination of Sample Size

Because this is an exploratory feasibility study, sample size has been determined by the number of possible sites, enrollment rates and timing for completion.

The study is expected to be conducted at up to 12 sites in the United States and Europe and up to 60 subjects will be enrolled with no more than 15 subjects enrolled per site.

[redacted]

[redacted]

[redacted]

[redacted]

7. Statistical Methods

7.1 Study Subjects

7.1.1 Disposition of Subjects

Subject disposition will be summarized by a CONSORT flow diagram, based on the subject flow diagram shown in Figure 3, but providing additional details on subject attrition.

Study exits will be summarized according to exit reasons, e.g., lost-to follow-up, death, study completion, unsuccessful procedure etc. This summary will be valuable for assessing reasons for premature study exits and to assess the impact of premature study exits on study results. Violation of inclusion and exclusion criteria at baseline will be summarized for all enrolled subjects.

The following tables will be created to summarize subject disposition:
1. Number (%) of subjects per center
2. Number (%) of subjects by visit/procedure
3. Visit window compliance
4. Study exit summary

7.1.2 Clinical Investigation Plan (CIP) 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. If an infringement remains unresolved, multiple deviations need not be completed. The use of waivers is prohibited for deviating from the CIP.

Prior approval by Medtronic is expected in situations where the investigator anticipates, contemplates, or makes a conscious decision to deviate. Prior approval is not required when a deviation is necessary to protect the safety, right 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).

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

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

All study deviations must be reported on the study deviation e-CRF regardless of whether medically justifiable, pre-approved by Medtronic, an inadvertent occurrence, or taken to protect the subject in an emergency. The deviation description and reason for deviation must be recorded. Multiple deviations of the same type at the same visit may be reported on one e-CRF.

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 IRB/EC as well as Medtronic within five (5) working days. Reporting of all other study deviations must comply with IRB/EC policies and/or local laws and/or regulatory agency requirements and must be reported to Medtronic as soon as possible upon the site becoming aware of the deviation. Refer to CIP section 16.8 for geography specific deviation reporting requirements and timeframes for reporting to Medtronic and/or regulatory bodies.

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

7.1.3 Analysis Sets

All subjects who signed the informed consent document will be defined as the Enrolled Cohort. The Analysis Cohort is defined as subjects who are enrolled and do not violate any inclusion or exclusion criteria and successfully complete baseline measurements, CSPOT lead implant, and the CSPOT protocol. This may include patients that do not successfully complete CRT implant or the 6-month follow-up visit. The Analysis Cohort will be used for the primary analysis approach for all objectives unless otherwise noted. Subjects in the Enrolled Cohort but not the Analysis Cohort will not be included in the primary analyses of the objectives described here because they will not provide the data required for evaluating the hypothesis tests or statistical summaries related to these objectives, but will be reported in a subject disposition table, and may be included in some secondary analysis approaches.

7.2 General Methodology

Data analysis will be performed by Medtronic statisticians or designees.

Data summaries for categorical data will be summarized as count, e.g., number of subjects, and/or number of events, and a percentage relative to the total number of subjects/events. The denominator will be explicitly identified when not clear from the context. For continuous variables, standard deviation, median, quartiles, minimum and maximum will be provided as applicable.

Variable used for objectives evaluation are the SDAT ECG-Belt metric, contractility parameter positive LV dP/dt max, LVEF, LVESV at baseline and LVEF, LVESV at 6 months.

Data analysis may be carried out throughout the study without having all enrolled subjects completing study required follow-ups.

7.3 Center Pooling

Data will be pooled across centers. Standard outlier detection at both individual and center level will be performed to insure poolability.

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

No imputation of missing data for outcomes is planned, but missingness will be summarized as a binary variable. In addition, if the positive dP/dt max or SDAT measurements meant to be observed during the CSPOT protocol are missing for some subjects, additional analysis to characterize baseline factors associated with missing data may be considered.

Imputation of day or month for partially missing dates may be used.

As described in Section 7.9, the SDAT and LV dP/dt max data collected for some delay settings in the CSPOT pacing configuration will not be used in the main approach to evaluating the primary objectives in an effort to mitigate bias associated with analyzing observed extrema. However, Section 7.9.4 prescribes a planned sensitivity analysis to assess the potential impact of any unused data on the results.

7.5 Adjustments for Multiple Comparisons

No adjustments will be made for multiple testing because of the exploratory nature of this study.

7.6 Demographic and Other Baseline Characteristics

Descriptive statistics will be used to summarize the subject demographic and clinical characteristics at baseline. Data for qualitative variables will be presented as incidence rates (total

number of subjects, number of events, and percent). Data for continuous variables will be summarized using measures of central tendency and dispersion.

7.7 Treatment Characteristics

Descriptive statistics will be used to summarize implant procedure information collected.

7.8 Interim Analyses

No interim analyses of the objectives for this study are planned. An FDA annual report will be created in 2022 but will include only descriptive summaries, so no type I error correction is needed.

7.9 Evaluation of Objectives

7.9.1 Primary Objectives

This study has two primary objectives, both based on data collected at implant. One compares electrical synchronization among pacing configurations using SDAT, measured by the ECG belt, and one compares hemodynamic response among configurations using LV dP/dt max, measured by the pressure catheter. [redacted]

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7.10 Safety Evaluation

See Section 12 of CIP [redacted]

All adverse events will be collected throughout the study duration, starting at the time of signing the ICF. For purposes of reporting, events shall be captured on an AE eCRF. In addition, AEs impacting users or other persons will be collected on a Non-subject Adverse Event eCRF.

The study will utilize an Independent Clinical Events Committee (CEC) to adjudicate a subset of all the adverse events collected in the study for an unbiased assessed of those related to the device or system. At regular intervals, an independent CEC will conduct a medical review at a minimum all CRT-D/CRT-P system and procedure-related adverse events, all CSPOT system related, cardiovascular related AEs, all SAEs and all AEs with a fatal outcome of participants in the study.

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

Results will be summarized using descriptive statistics. Number of events, number and percentages of subjects experiencing system and/or procedure-related adverse events will be reported, as well as, in the case of system-related events, the specific component of the system to which the event was related to describe adverse device effects. The seriousness of adverse events and type of event (complication/observation) will also be summarized as well as whether events were unanticipated adverse device effects or unanticipated serious adverse device effects. Details of individual adverse events including MedDRA key term, actions, outcome, relatedness and seriousness will be listed.

The prevalence of adverse events will further be summarized by MedDRA (Medical Dictionary for Regulatory Activities) key term. The Preferred Term (PT) term will be used. The number of events

and the number of subjects and the percentage of subjects with an event will be summarized per each PT Term.

A listing of deaths will be provided with cardiac relatedness (cardiac death, sudden cardiac-death, etc). All subject deaths must be reported by the investigator to Medtronic on an AE eCRF (AE with fatal outcome).

Additionally, any device deficiencies will be collected. Device deficiency information will be collected throughout the study and reported to Medtronic. An eCRF should be completed for each device deficiency that did not lead to an Adverse Event. The term and center description of individual device deficiencies and whether they could have led to a serious adverse device effect will be reported in a listing.

7.11 Changes to Planned Analysis

This Statistical Analysis Plan does not deviate from the planned statistical analysis in the CIP. Any change to the data analysis methods described in the Clinical Investigational Plan will require an amendment only if it changes an objective of the Clinical Investigational Plan. Any other change to the data analysis methods described in the Clinical Investigational Plan and this Statistical Analysis Plan, and the justification for making the change, will be described in an updated version of the Statistical Analysis Plan or the clinical study report. Additional exploratory analyses of the data will be conducted as deemed appropriate.

8. Validation Requirements

Primary objectives will use level I validation (double-coding). Other analysis to be shared externally will use at least level II validation (peer review).

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13. Wang, Y., et al., The efficacy of left bundle branch area pacing compared with biventricular pacing in patients with heart failure: A matched case-control study. J Cardiovasc Electrophysiol, 2020. 31(8): p. 2068-2077.

10. Statistical Appendix

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