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Document Name	RAD Version
CSPOT Clinical Iinvestigation Plan V4.0 29APR2022	1.0

Title	CSPOT Clinical Iinvestigation Plan V4.0 29APR2022

APPROVALS

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Medtronic

Clinical Investigation Plan

Clinical Investigation Plan/Study Title	Conduction System Pacing Optimized Therapy (CSPOT)
Clinical Investigation Plan Identifier	MDT20029
Study Product Name	CSPOT Research System (an un-modified CRT device with off-label use lead placement)
Sponsor/Local Sponsor and EU Legal representative	Medtronic, Inc 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
Document Version	4.0, 29-Apr-2022

Confidentiality Statement

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1. Administrative Information

1.1. Sponsor Contact Information

Medtronic contact information is provided below. This information is subject to change during the clinical study. Periodic updates to study contact information will be sent to the sites as needed.

Table 1: Sponsor Contact Information

Study Manager Contacts
Worldwide clinical study leader/US contact Rachael Rose, Pr. Clinical Research Specialist [redacted] *Europe clinical study leader/OUS contact* Fabio Pradella, Clinical Research Specialist [redacted]
Monitoring Contacts
Worldwide monitoring leader/US contact Taryn Randall, Clinical Monitoring Manager [redacted] *Monitoring leader Europe* Anja Hesse, Prin. Clinical Research Monitor [redacted]

1.2. Contract Research Organizations

CRO information is provided below. This information is subject to change during the clinical study. Periodic updates to CRO information will be sent to the sites as needed.

Table 2: CRO Information

Contact Information	Duties performed
Cognizant Technology Solutions 500 Frank W. Burr Blvd. Teaneck, NJ 07666 United States Direct Phone: +1 201 801-0233 Direct Fax: +1 201 801-0243	• Development of study electronic case report forms, edit checks, and study management reports. • Review of electronic case report forms, management of discrepancies of data collection, and coding of deviations.

1.3. Principal Investigator

Overall study Principal Investigator and Steering Committee member contact information is provided below. Periodic updates to Principal Investigator information will be sent to the sites as needed.

Table 3: Overall Study Principal Investigator Contact Information

Name	Contact Information
Gaurav Upadhyay, MD	University of Chicago 119th E 18th St Chicago, IL 60605 United States [redacted]

2. Glossary

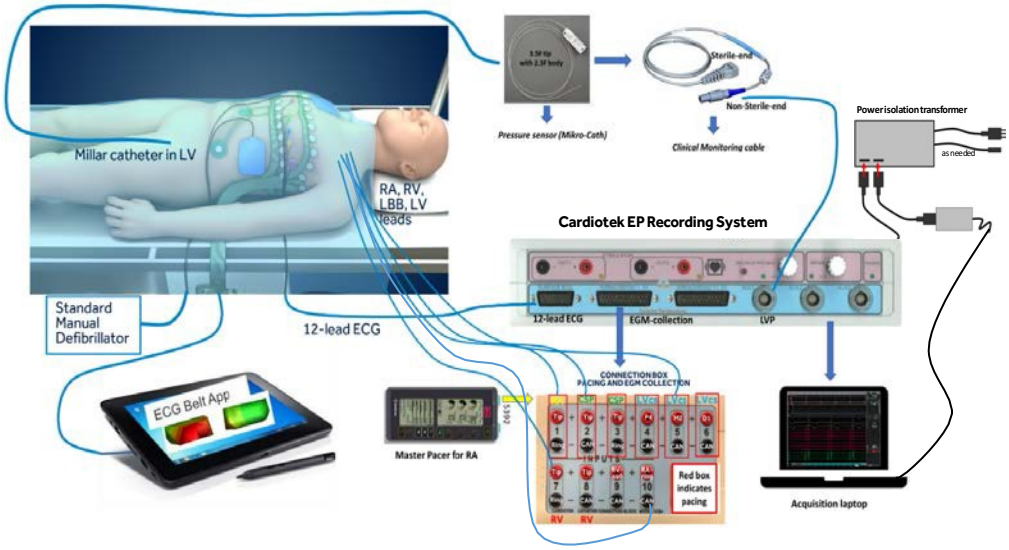
Term	Definition
ADE	Adverse Device Effect
AE	Adverse Event
ASADE	Anticipated Serious Adverse Device Effect
AF	Atrial Fibrillation
AFL	Atrial Flutter
AV Block	Atrioventricular Block
AV Delay	Atrioventricular Delay
CA	Competent Authority
CEC	Clinical Events Committee
CFR	Code of Federal Regulation
CIP	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
CV	Curriculum Vitae
DD	Device Deficiency
DMC	Data Monitoring Committee

Term	Definition
DoH	Declaration of Helsinki
DTL	Delegated Task List
eCRF	Electronic Case Report Form
EC/IRB/HREB/Ethics Board	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

Term	Definition
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
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. Synopsis

Title	Conduction System Pacing Optimized Therapy (CSPOT)
Clinical Study Type	Prospective, non-randomized, multi-center, global, feasibility clinical study
Product Name	CSPOT Research System (an un-modified CRT device with off label use lead placement)
Sponsor	**Sponsor:** Medtronic, Inc 8200 Coral Sea Street NE Mounds View, MN U.S.A. 55112 Phone: +1 800 328 2518 **Local Sponsor:** Medtronic, Bakken Research Center B.V. Endepolsdomein 5, 6229 GW Maastricht, The Netherlands Phone: +31 43 3266566
External Organizations	*Cognizant Technology Solutions* 500 Frank W. Burr Blvd. Teaneck, NJ 07666 United States Direct Phone: +x 201 801 0233 Direct Fax: +x 201 801 0243
Indication under investigation	The CSPOT pacing system is utilizing a market approved CRT device and market approved leads to compare off-label methods of pacing: CSP (LBBP) and the combination of CSP +LV.
Investigation Purpose	The purpose of the CSPOT study is to determine the best mode of CRT pacing for different populations of CRT patients, comparing traditional BiV, CSP-only, and CSPOT (CSP+LV) pacing. Additionally, safety of the system will be assessed.

Product/System	
Study Objective	**Primary Objectives:** 1. Compare the electrical synchronization response of CSPOT pacing configuration to CSP-only and traditional CRT (See section 10.7.1) 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. **Secondary Objectives:** 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

	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
Study Design	The CSPOT study is a prospective, non-randomized, multi-center, global, feasibility clinical study. All enrolled subjects will undergo the CSPOT system protocol to obtain patient-specific optimal CRT therapy and then implanted with a market approved CRT device. Each subject will be programmed in their patient-specific CSPOT (CSP+LV) configuration and patients will be followed up for 6 months or until official study closure, defined as when Medtronic and/or regulatory requirements have been satisfied per the Clinical Investigation Plan and/or by a decision by Medtronic or regulatory authority, whichever occurs first. [redacted] All adverse events (AEs) will be collected throughout the study duration of a subject's participation in the study, beginning at the time of informed consent.
Sample Size	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.
Inclusion/Exclusion Criteria	**Inclusion Criteria** • Patient is willing and able to provide written informed consent • Subject is at least 18 years of age • Patient is willing and able to comply with the protocol, including follow-up visits • The patient'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

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

Study Procedures and Assessment

STUDY PROCEDURE	Baseline (occur within 30 days prior to enrollment)	Implant (occur within 30 days after enrollment)	6 month follow up and Study Exit
Patient Informed Consent	X		
Inclusion/Exclusion Assessment	X		
Demographics	X		
Medical History	X		
Physical Exam	X		X

	Medication Assessment	X		X
	Baseline 12-Lead ECG (within 60 days prior to enrollment/consent)	X		
	Baseline Echocardiography including LVEF and LVESV (within 60 days prior to enrollment/consent)	X		
	NYHA	X		X
	ECG Belt		X	
	Lead Placement		X	
	CSPOT Research System Protocol		X	
	Insertion procedure information		X	
	Fluoroscopic Images of final LBBP lead placement		X	
	Patient Global Assessment			X
	6 Month Echocardiography including LVEF and LVESV (within 30 days prior to visit)			X
	6 Month 12-Lead ECG (within 30 days prior to visit)			X
	Final device programming		X	X
	Initial and Final Device Interrogation (with either initial or final interrogate ALL) and collect .pdd file		X	X
	Adverse Events	As they occur		
	Hospitalizations			
	Death			
	Device Deficiency			
	System Modification			
	Study Deviations			
Safety Assessments	All adverse events (AEs) and device deficiencies will be collected throughout the study duration of a subject's participation, beginning at the time of informed consent. An independent Clinical Event Committee (CEC) will conduct a medical review and adjudicate at a minimum all CRT-D/CRT-P system and procedure-related adverse events, all CSPOT system and procedure-related adverse events, all cardiovascular related AEs (regardless of seriousness), all SAEs and all AEs with a fatal outcome. The CEC will consist of non-Medtronic employed physicians that are not participating investigators for the study.			
Statistics	A sample size of up to 60 subjects will be enrolled to determine the pacing configuration that provides better acute electrical synchrony and hemodynamic response. Additional sub-analyses will be performed to assess whether sub-populations derive benefit from different configurations.			

4. Introduction

4.1 Background

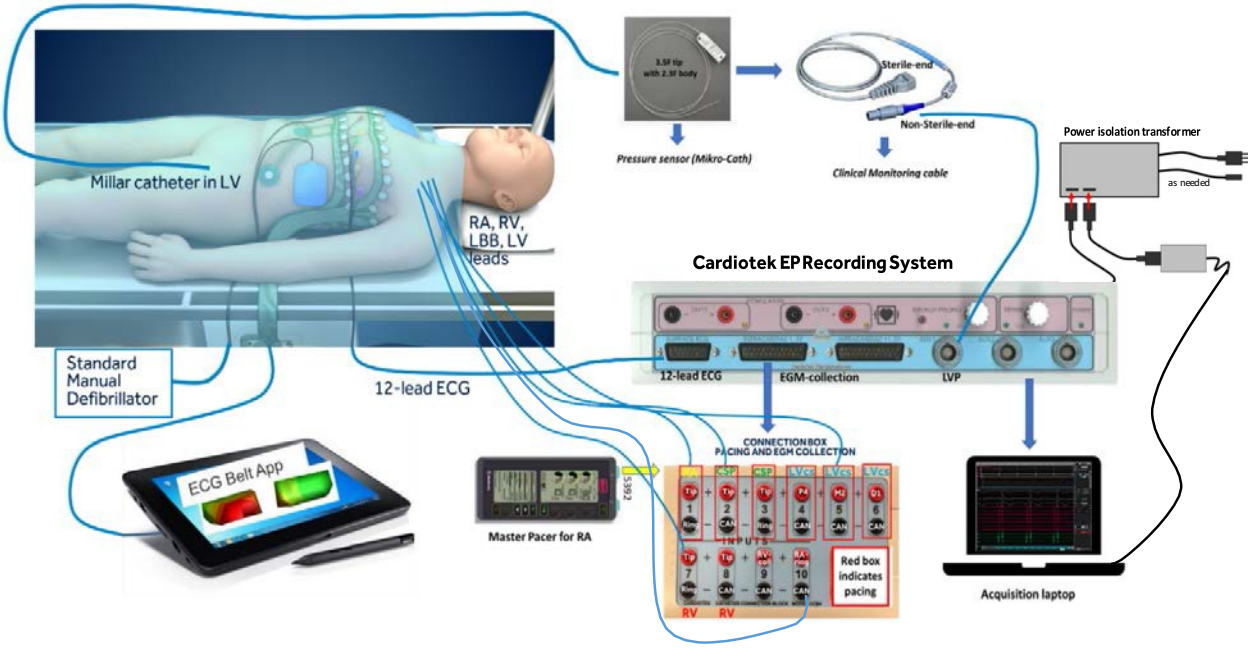
The current standard-of-care therapy for heart failure patients with wide QRS is cardiac resynchronization therapy (CRT), which is commonly accomplished through biventricular pacing. His Bundle pacing may benefit some CRT patients as a replacement for biventricular pacing [3-6]. However, His Bundle pacing 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



4.2 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.

5. Objectives and/or Endpoints

5.1 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. [redacted] 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.

5.1.1 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) 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.

5.1.2 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.

5.1.3 Ancillary Objective

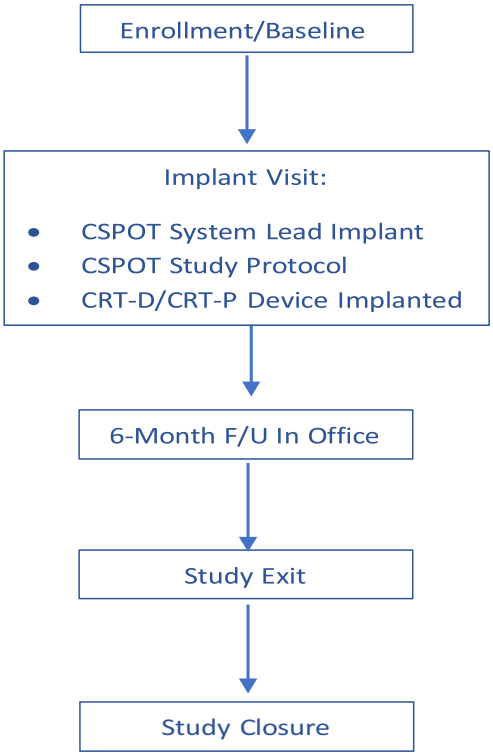
[redacted]

6. 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 patient will serve as their own control. This will be considered the acute phase. Following the CSPOT study protocol procedure, the CRT-D/CRT-P device will be implanted. Each subject will be programmed to their patient specific CSPOT (CSP+LV) configuration and patients 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 2.

Figure 2: Study Flowchart



6.1 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.

6.2 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. [redacted]

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.

6.3 Minimization of Bias

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

[redacted]

7. Product Description

7.1 General

The CSPOT Research System will include both market approved and investigational components that will allow collection of ECG, EGM, LV pressure and electrical dyssynchrony metrics during periods of CRT pacing, CSP-only pacing, and CSP+LV pacing.

Table 4 below identifies the market approved Medtronic devices that are compatible with the CSPOT Research System. All CRT-P/CRT-D devices will be considered investigational during the

course of the study. The CSPOT system also includes several components that include both market approved, and investigational components identified in Table 5.

Instructions for intended use, maintenance and calibration detail (if applicable), including indications and contraindications of the devices and components used in this study, as well as medical procedures and information regarding material in contact with tissues or body fluids, are provided in their respective manuals.

Table 4: CSPOT System Compatible Devices

Device Name	Model Number(s)	Market Released
Percepta™ Quad CRT-P MRI SureScan™	W4TR01	Market released
	W4TR04 (available in Europe)	Market released
Serena™ Quad CRT-P MRI SureScan™	W4TR02	Market released
	W4TR05 (available in Europe)	Market released
Solara™ Quad CRT-P MRI SureScan™	W4TR03	Market released
	W4TR06 (available in Europe)	Market released
Viva™ Quad S CRT-D	DTBB1Q1	Market released
	DTBB2Q1 (available in Europe)	Market released
Viva™ Quad XT CRT-D	DTBA1Q1	Market released
	DTBA2Q1 (available in Europe)	Market released
Brava Quad XT CRT-D	DTBC1Q1	Market released
	DTBC2Q1 (available in Europe)	Market released
Claria MRI™ Quad CRT-D	DTMA1Q1	Market released
	DTMA2Q1 (available in Europe)	Market released
Amplia MRI™ Quad CRT-D	DTMB1Q1	Market released
	DTMB2Q1 (available in Europe)	Market released
Cobalt™ XT Quad CRT-D MRI SureScan™	DTPA2Q1	Market released

Cobalt™ HF Quad CRT-D MRI SureScan™	DTPB2Q1	Market released
Crome™ HF Quad CRT-D MRI SureScan™	DTPC2Q1	Market released

Table 5: CSPOT Research System Components

Model Number(s)	Component	Manufacturer	Investigational or Market-released
EA1B5S, EA1B5L (Belt) EA1A (amplifier) EA1T (tablet)	ECG Belt System	Medtronic	Investigational
825-0101	Millar Pressure Catheter	Millar	Market-Released
850-5148	Millar Connection Cable	Millar	US: Investigational OUS: Market-Released
00EPT01	Cardiotek EP-Tracer 38 System	Cardiotek	Market-Released
N/A	Threshold Cable	Any manufacturer	Market-Released
5392	Medtronic External Pacer	Medtronic	Market-Released
3830 SelectSecure	Medtronic Pacing Leads	Medtronic	Investigational when used in the study (due to implant location)
LV Quad polar leads: 4298, 4398, 4598 (Attain Performa) 4798 (Attain Stability)	Medtronic Pacing Leads	Medtronic	Market-Released
N/A	RA bipolar lead	Any manufacturer	Market-Released
RV defibrillation lead with IS1/DF1 connector: 6935 (Sprint Quattro single coil) 6947 (Sprint Quattro dual coil)	Medtronic Defibrillation Leads	Medtronic	Market-Released
CRT P Quad and CRT-D Quad w/DF-1 Connector Models (see Table 4)	Medtronic CRT devices	Medtronic	Market-Released

7.1.1 Medtronic Compatible CRT-D/CRT-P Devices

Any device compatible with the CSPOT Research System (outlined in Table 4 above) can be used in this study. CRT-D devices are indicated for providing cardiac resynchronization therapy in heart failure subjects and ventricular anti-tachycardia pacing and ventricular defibrillation for automated treatment of life-threatening ventricular arrhythmias. CRT-P devices are indicated for providing cardiac resynchronization therapy in heart failure subjects. In addition, these devices can be used in subjects

with atrial tachyarrhythmias, or those subjects who are at significant risk for developing atrial tachyarrhythmias. All devices should be implanted as per the current AHA/ACC/HRS Guideline [14]. The CRT-D/CRT-P devices used in the study are market released but are considered investigational during the course of the study.

7.1.2 ECG Belt System

[redacted]

7.1.3 Millar Pressure Catheter and Connection Cable

The Millar pressure catheter measures continuously the LV pressure and is market released. The connection cable for the catheter transmits the LV pressure data to the recording system and is considered investigational in the US only (i.e. CE-labeled for EMEA).

7.1.4 Cardiotek EP System and 12 Lead ECG system

The Cardiotek system will deliver either traditional CRT pacing, CSP-only pacing, or CSPOT pacing at different AV and VV intervals based on the trigger signal from the EPG. The Cardiotek EP system acquires and stores time-aligned ECG, EGM and LV pressure. It provides a configurable electrical connection for up to 4 leads and the pocket and provides synchronized pacing of selected lead configurations, including control of pacing amplitude, pulse width and relative timing.

The 12-Lead ECG is a standard configuration of 12 leads to understand the heart's electrical activity. A standard 12-lead ECG (supplied by Cardiotek) is connected to a Cardiotek EP recorder system will allow measurement of the necessary timing intervals.

7.1.5 Threshold Cables

Threshold cables are used during the CSPOT acute protocol. They are used for the connections between the Cardiotek device and the leads. Any market-released single model lead cables may be used that are compatible with the CSPOT Research system. Compatible models can be found in the CSPOT System User Manual. In addition, instead of a single cable, two connected cables (e.g. Oscor ATAR D-R and Oscor ATAR D-V2) that meet the above may be used.

7.1.6 Medtronic External Pacer

A Medtronic External Pulse Generator Model 5392 will be configured to provide atrial pacing and to trigger the Cardiotek system. The external pacer is a temporary pacer that allows atrial pacing, including control of the amplitude and rate.

7.1.7 Pacing Leads

Medtronic compatible (refer to Table 5 above) commercially available transvenous leads CSP, RV and LV are required to be used in the study. Any commercially available RA lead can be used in the study. Every subject's CRT system shall include the following leads:

- Right atrial pacing lead

- Left ventricular pacing lead
- Right ventricular defibrillation lead (CRT-D only)
- Conduction system pacing lead (Model 3830)

1. Right Atrial Leads

Any commercially available RA lead

2. Left Ventricular Leads

Medtronic commercially available LV transvenous pacing leads are required.

3. Right Ventricular Leads

Medtronic commercially available RV pacing or defibrillation (for CRT-D) leads are required.

4. Conduction System Pacing Leads

Medtronic commercially available CSP pacing leads are required.

7.2 Labeling

In all geographies, the CRT-D/CRT-P devices used in this study are market-released and will be labeled according to the approved CE-mark labeling. The devices will be considered investigational during the course of the study.

Market-released components will be provided with the approved CE-mark labeling.

In the US, investigational labeling requirements for the ECG Belt and Millar Connector Cable will include the following statements:

"CAUTION – Investigational device. Limited by Federal Law (USA) to Investigational use".

In EMEA, labeling for the ECG Belt will include the following statement (labeling will be in English unless otherwise required for local regulations):

"Exclusively for Clinical Investigations."

7.3 Product Use

The CSPOT system is comprised of the components identified in Table 5: CSPOT Research System Components. The system components have all been individually approved (with the exception of the ECG Belt and the Millar Connection Cable (US only)) for other human use applications. The unique aspects of the CSPOT system are introduced by the use of these existing elements in combination and coordination as described throughout this specification. Each of the existing elements have instructions for use related to their existing uses; as part of the CSPOT Research System, the 3830

lead will be implanted in a non-market approved location. The rationale for using the 3830 lead is that it is the only available lead with a published record of use in the intraseptal location.

Components intended for use in the sterile field, including the leads, pressure catheter and lead cables/pocket clip are provided in sterile packaging, except for the Millar connection cable. The Millar connection cable may be re-sterilized/sterilized per its instructions for use or a sterile sleeve may be used. Reusable components that may be exposed to body fluids, including the ECG Belt amplifier, the ECG cables and the lead cables, can be cleaned per their individual instructions for use. Disposable components of the system, including only the pressure sensor catheter and ECG electrode array have a shelf life of at least 2 years.

7.4 Product Storage

Any components of the CSPOT Research System that are received or kept at the study site must be stored in a secure location at the study site. It is the responsibility of the investigator to correctly handle, store, and track the investigational products maintained at the study site. Investigational products will be used only in the clinical study according to the CIP.

The market released components of the CSPOT Research System are the responsibility of the investigator to correctly handle and store.

7.5 Product Accountability

The CSPOT system is comprised of both commercially market-released and investigational products. The market-released devices used in this study will be considered investigational once they are used with the CSPOT Research System. Commercially available product supply will be managed in a manner consistent with other market-released products.

For investigational products used during the study, Product Distribution/Accountability logs will be used for tracking of products during and after the study. The tracking method might vary but could use either an electronic or paper accountability logs provided by Medtronic. The logs must be updated when the investigational product is received, opened, implanted, explanted, disposed of or returned to Medtronic. In addition to tracking the date of events, the log tracks product information including, but not limited to, date, model/serial number/lot number and expiration date for received product, subject ID of implanted subject, date implanted/used, date explanted (if applicable), date returned to Medtronic and reason for return (if applicable), reason for and method of destruction/disposal for explanted components not returned to Medtronic (if applicable), and name of person responsible for return or destruction/disposal (if applicable).

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

If there are additional local requirements related to the CSPOT Research System beyond what is collected by Medtronic on the eCRF, this is the Investigator's responsibility and should be recorded in the subject's medical records, but will not be collected by Medtronic (e.g., national registration card number, identification code linked to names and contact information, log of all subjects enrolled in the study, lot or batch number).

7.6 Product Training Materials

Investigator training on use and handling on the CSPOT system will be required prior to first enrollment at a particular site. Study training on the CSPOT system was based according to the risk assessment.

7.7 Product Return

All explanted, unused or malfunctioning devices (devices or leads or activators, etc.) should be returned to Medtronic for analysis when permissible by local laws and regulations. If the products are explanted but not returned, a justification will be reported on the appropriate case report forms or disposition logs. To receive a Returned Product Mailer Kit, please contact your local Medtronic field personnel.

8. Study Site Requirements

8.1 Investigator/Investigation Site Selection

All investigators managing the subject's health care 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-D/CRT-P devices.

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

The principal investigator shall:

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

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

8.2 Study Site Activation

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

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

- EC approval (and voting list, as required by local law) of the current version of the CIP and IC
- Regulatory Authority approval or notification (as required per local law)
- Fully executed CTA; Medtronic contracts with participating institutions/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
- Financial disclosure
- CV of investigators and key members of the investigation study site team (as required). The signature on the CV must be dated within 3 years prior to the date of activation of the study site
- Documentation of Delegated Tasks
- Documentation of Site Technical Support
- Documentation of study training
- Additional requirements imposed by local regulations, the EC and RA shall be followed, if appropriate

In addition, all participating study site staff must be trained on the current version of the CIP as well as on the applicable study requirements depending on their role and must be delegated by the principal investigator to perform study related activities.

Medtronic will provide each study site with documentation of study site/investigator readiness; this letter must be received prior to performing study related activities.

8.3 Role of the Sponsor Representatives

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

- Provide study training relevant and pertinent to the involvement of personnel conducting study activities and investigator responsibilities
- Technical support for acute study protocol and 6 months follow up visit under the supervision of a study investigator, but no data entry, shall be performed by Medtronic personnel or their representatives at study sites
- Support study investigators in performing the study implant procedure
- Monitoring and auditing activities

In addition, for this study, sponsor representatives will be authorized to perform the following significant trial related duties:

- Support data collection and performing the CSPOT protocol during the acute and during the 6-month chronic phase study follow up visit.
- Support data collection during the implant procedure

9. Selection of Subjects

9.1 Study Population

The target population for the CSPOT study will include subjects who are indicated to receive a Medtronic CRT-D or CRT-P based on market approved indications.

9.2 Subject Enrollment

Ethics Board/IRB and Medtronic approval of this Clinical Investigation Plan, the informed consent form and any other applicable documents must be obtained prior to enrolling subjects in the study. Medtronic will provide each study site with documentation of study site/investigator readiness; this letter must be received prior to subject enrollment.

When a patient and the Principal Investigator or authorized designee, as required, have personally signed and dated the informed consent form, the patient is considered a subject enrolled in the study. Subjects must provide informed consent before any study related procedures occur. The date the subject signed the informed consent form and data protection authorization as required by local law must be documented in the subject's medical records.

Subjects will be screened to ensure they meet all the inclusion and none of the exclusion criteria prior to study enrollment.

9.3 Inclusion Criteria

- Patient is willing and able to provide written informed consent
- Subject is at least 18 years of age
- Patient is willing and able to comply with the protocol, including follow-up visits
- The patient'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

9.4 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

10. Study Procedures

10.1 Schedule of Events and Data Collection

A patient will be considered enrolled in the study once they sign and date the Informed Consent. Subjects will complete an in-office visit at 6 months. The requirements for data collection and study procedures by visit are summarized in Table 6 below.

Table 6: Data collection and study procedure requirements

STUDY PROCEDURE	Baseline (occur within 30 days prior to enrollment)	Implant (occur within 30 days after enrollment)	6 month follow up and Study Exit
Patient Informed Consent	X		
Inclusion/Exclusion Assessment	X		
Demographics	X		
Medical History	X		
Physical Exam	X		X
Medication Assessment	X		X
Baseline 12-Lead ECG (within 60 days prior to enrollment/consent)	X		
Baseline Echocardiography including LVEF and LVESV (within 60 days prior to enrollment/consent)	X		
NYHA	X		X
ECG Belt		X	

Lead Placement		X	
CSPOT Research System Protocol		X	
Insertion procedure information		X	
Fluoroscopic Images of final LBBP lead placement		X	
Patient Global Assessment			X
6 Month Echocardiography including LVEF and LVESV (within 30 days prior to visit)			X
6 Month 12-Lead ECG (within 30 days prior to visit)			X
Final device programming		X	X
Initial and Final Device Interrogation (with either initial or final interrogate ALL) and collect a .pdd file		X	X
Adverse Events	As they occur		
Hospitalizations			
Death			
Device Deficiency			
System Modification			
Study Deviations			

10.2 Prior and Concomitant Medications/Therapies

There are no medication/therapy restrictions in the study unless they are investigational and may confound the study results, in which case, prior approval would be needed from Medtronic. Medications will be collected at baseline and at 6-month follow up.

10.3 Subject Consent

The ICF is defined as a legally effective documented confirmation of a subject's voluntary agreement to participate in a particular clinical study after information has been given to the subject on all aspects of the clinical study that are relevant to the subject's decision to participate. This process includes obtaining an ICF and an Authorization to Use and Disclose Personal Health Information/Research Authorization/other privacy language as required by law that has been approved by the study site's Institutional Review Board/Ethics Committee (IRB/EC) and signed and dated by the subject.

Investigators shall consider all subjects who meet eligibility requirements for study participation to avoid any bias in the subject population. Prior to enrolling subjects, approval of the CIP, ICF, and any other written study information to be provided to the subjects must have been obtained from each site's IRB/EC. The document(s) must be controlled (i.e. versioned and dated) to ensure it is clear which version(s) were approved by the IRB/EC. Any adaptation of the sample ICF must be reviewed and approved by Medtronic and the IRB/EC reviewing the application prior to enrolling the subject.

The investigator must notify the subject of any significant new findings about the study that become available during 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, informed consent must be obtained from the subject. Likewise, privacy or health information protection regulation may require subjects to sign additional forms to authorize sites to submit subject information to the study sponsor. The informed consent process must be conducted by the principal investigator or his/her authorized designee, and the ICF and Authorization to Use and Disclose Personal Health Information/Research Authorization/other privacy language as required by law must be given to the subject in a language he/she is able to read and understand. The process of obtaining 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 site personnel. The informed consent process shall not waive or appear to waive subject's legal rights. The language used shall be as non-technical as possible and the impartial witness, where applicable.

The subject must have ample time and opportunity to read and understand the ICF, to inquire about details of the study, and to decide whether to participate in the clinical study. All questions about the study should be answered to the satisfaction of the subject.

When the subject decides to participate in the clinical study, the ICF must be signed and personally dated by the subject acknowledging that their participation is voluntary and signed and personally dated by the 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, signed and dated as required by law, must be provided to the subject.

If informed consent is obtained the same day the subject begins participating in study-related procedures, it must be documented in the subject's case history that consent was obtained prior to participation in any study-related procedures.

In the event the subject cannot read and/or write, the IC process shall be obtained through a supervised oral process. In this situation, an independent witness must be present throughout the informed consent process. The written informed consent form and any other information shall be read aloud and explained to the prospective subject. The witness signs and personally dates the IC attesting that the information was accurately explained and that informed consent was freely given. Whenever possible, the subject shall sign and personally date the informed consent form.

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

Detailed documentation of the consent process must be recorded in the subject's case history. The ICF should document a supervised oral process was used for communication with the prospective subject and the specific means by which the prospective subject communicated agreement to participate in the study.

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

Consistent with the DoH, vulnerable adults (i.e. those subjects mentally incapable of giving consent) are excluded from this protocol. Any subjects with mental incompetence (e.g., Alzheimer's, dementia, psychiatric disorders, developmental disorders) should be assessed for vulnerable status. If the IC is signed by an individual other than the subject, the monitor may discuss whether the Investigator believes the subject meets the definition of a vulnerable adult. This protocol defines vulnerable adult as those subjects 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: "individuals who are unable to fully understand all aspects of the investigation that are relevant to the decision to participate, or who could be manipulated or unduly influenced as a result of a compromised position, expectation of benefits or fear of a retaliatory response. 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 IC. 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.

10.4 Enrollment

A subject is considered enrolled when the consent process has been finalized. The date the subject signed the IC and Data Protection Authorization, as required by law, must be documented in the subject's medical records. A log of all subjects enrolled in the study should be maintained. Enrollment can be a stand-alone visit or can occur on the same day as the baseline visit. Once consent is obtained, report adverse events/deaths, study deviations and subject exits as they occur.

10.5 Baseline

Following subject enrollment, a baseline visit will be performed within 30 days. The baseline visit can be a standalone visit or occur on the same day as enrollment. The following procedures/data collection will be conducted during the baseline visit:

- Inclusion/exclusion criteria assessment
- Demographics
- Medical History
- Physical Exam

- Medication Assessment
- Baseline 12-Lead ECG (within 60 days prior to enrollment)
- Baseline Echocardiography including LVEF and LVESV (within 60 days prior to enrollment)
- NYHA classification
- Adverse events (as applicable)
- Hospitalizations (as applicable)
- Death (as applicable)
- Study Deviations (as applicable)

10.6 CRT-D/CRT-P Implant

Following subject baseline, implant procedure of the CRT-D/CRT-P device will be performed within 30 days from subject enrollment. The implant procedure visit can be a standalone visit or occur on the same day as baseline. The following procedures/data collection will be conducted during the implant visit:

- Insertion procedure information
- ECG Belt application and data collection
- Lead Placement
- CSPOT Research System protocol
- CSPOT Chronic Final Device programming
- Initial and Final Device Interrogation (with either the initial or final being an interrogate ALL) and collection of .pdd file
- Fluoroscopic Images of final LBBP lead placement in RAO 30-45 degrees, LAO 30-45 degrees, and AP
- Adverse events (if applicable)
- Hospitalizations (if applicable)
- Death (if applicable)
- Device Deficiency (if applicable)
- System Modifications (if applicable)
- Study Deviations (if applicable)

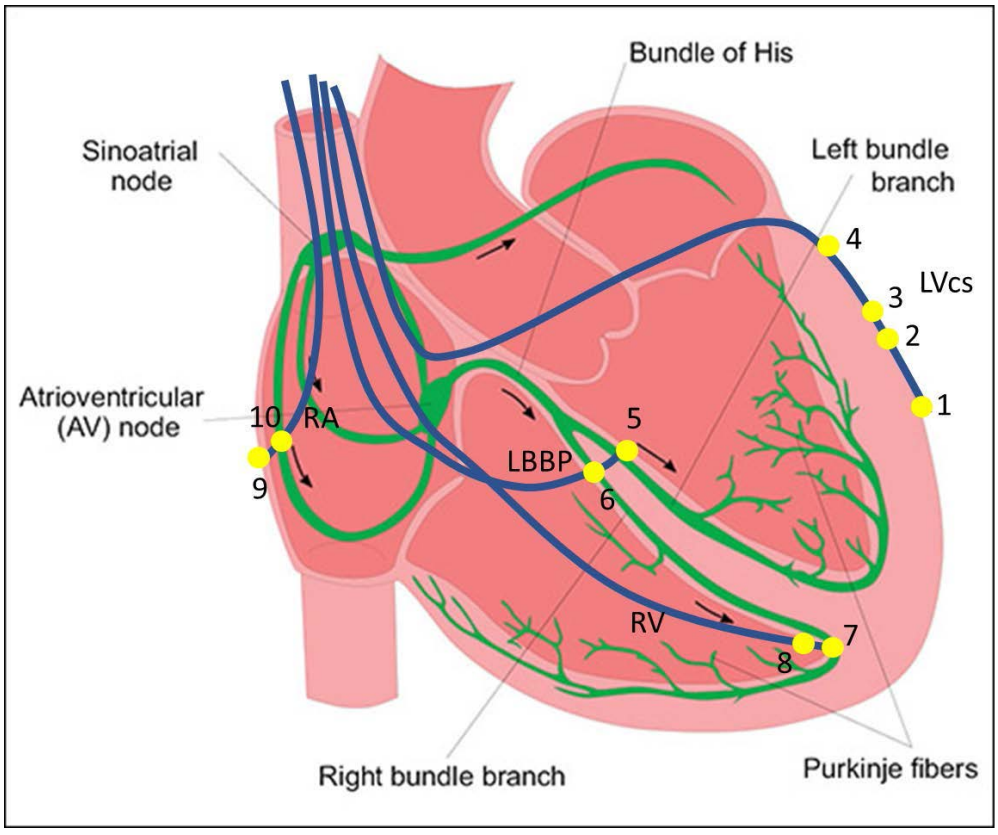
10.6.1 CSPOT Acute Pacing Protocol

The CSPOT Acute Pacing Protocol and Medtronic CRT-D/CRT-P implant procedure must occur within 30 days of enrollment and will be performed in accordance with the Medtronic respective CRT-D/CRT-P implant instructions. The CSPOT pacing protocol should take place prior to the implant of the Medtronic CRT-D/CRT-P. During the CSPOT pacing protocol, two different sets of electrodes will be placed on the patient's chest: 1) a 12-lead surface ECG and 2) a multi-electrode ECG-belt.

Pacing leads (and defibrillation lead for CRT-D) will then be positioned as described in the CSPOT User Manual. Finally, a Millar pressure catheter will be introduced via the femoral artery retrograde across the aortic valve into the LV for hemodynamic pressure monitoring.

The different pacing configurations are depicted below and include univentricular (LVcs) pacing (CRT-P implants only), LVcs and RV pacing (CRT-D implants only) , univentricular CSP (LBBP), and conduction system pacing optimized therapy (CSPOT) which is dual LV pacing of best LVcs and CSP. Different atrioventricular (AV) and intra-ventricular VV intervals will be evaluated. See figure 3 below for an overview.

Figure 3: Pacing Configurations



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10.6.2 CSPOT Chronic Final Device Programming

After the acute pacing protocol, the patient is implanted with a CRT-P or CRT-D device, connected to the leads that were positioned during the acute study. For CRT-D patients, the pin for RV tip and ring will be capped. After the CRT device is implanted and the pocket is closed per standard of care, the device will be programmed to the CSPOT configuration that indicated the best optimization according to ECG Belt and/or physician discretion. This includes the SAV, PAV, and VV delay. The best LVcs electrode that was used during the acute testing will also be used for chronic programming unless phrenic nerve stimulation, lead dislodgement or high capture threshold occur. If the patient is not programmed to the CSPOT configuration, the subject must be exited from the study.

The chronic device programming includes:

Table 7: Device programming during chronic follow up.

Feature	Programmed Value
AdaptivCRT	Nonadaptive CRT
V-V pace delay	According to best result from ECG Belt during acute study and/or physician discretion
Paced AV	According to best result from ECG Belt during acute study and/or physician discretion
Sensed AV	Programmed to a value between (Paced AV – 30ms) and (Paced AV – 100ms), according to physician discretion.
LV pacing vector	Select the best LV cathode according to ECG Belt and/or physician discretion. Select anode according to physician discretion.
Multiple Point Pacing (MPP)	Off
RV Pace Polarity	Bipolar

Rate Adaptive AV	On
Pace Amplitudes and Pulse Widths	Automatic capture management recommended
All other device parameters	According to physician discretion

10.7 Scheduled Follow-up Visits

A scheduled visit will occur at 6 months post implant. Should a subject miss the visit or the visit fall outside the pre-specified window, a study deviation must be reported. A late visit is preferred over a missed visit but must be accompanied by a deviation. The table below indicates the follow up visit windows.

Table 8: Windows for follow-up visits

Visit	**Window (days post enrollment)**		
	Open	Target	Close
Baseline	0	15	30
Visit	**Window (days post enrollment)**		
	Open	Target	Close
Implant	0	15	30
Visit	**Window (days post implant)**		
	Open	Target	Close
6-Month Follow Up	150	180	210

10.7.1 6-Month In-Office Follow Up Visit

An in-office follow-up visit will be completed at 6 months post device insertion to collect chronic data from the CSPOT system.

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

- Physical Exam
- Medications Assessment
- NYHA Classification
- Patient Global Assessment
- 6-Month 12 lead ECG (within 30 days prior to visit date)
- 6-Month Echocardiography including LVEF and LVESV (within 30 days prior to visit date)
- Final Device Programming
- Initial and Final Device Interrogation (with either the initial or final being an interrogate ALL) and collection of .pdd file
- Adverse events (if applicable)
- Hospitalizations (if applicable)
- Device Deficiencies (if applicable)
- Study Deviations (if applicable)
- System Modifications (if applicable)
- Death (if applicable)

10.7.1.1 Final Device Programming

After the 6-month follow up visit procedures are completed, the subject's device will be programmed per physician discretion. A final device interrogation and collection of .pdd file is required to capture final device settings.

10.7.2 Study Exit

At the completion of the 6-month follow-up visit, subjects will be exited from the study. The 6-month follow-up visit and exit visit should be combined and both a 6-month follow-up CRF and a Study Exit CRF need to be completed.

Prior to exiting a subject from the study, it is recommended to follow the subject until all ongoing 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. All data available through the time of the subject's exit will be used for analysis. Subjects who are exited from the study prior to the 6 months visit will not be replaced with another enrolled subject.

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:

- Study completion or termination

- Subject lost to follow-up
- CRT-D/CRT-P device explanted and not replaced
- Implant attempt, however, no CRT-D/CRT-P was implanted
- Subject has an invasive system modification that has intent to change the pacing behavior from the acute system configuration settings
- The following occurs during the lead positioning in the acute protocol testing:
  - Unable to place the LBBP lead
  - Unable to place the LV lead through the CS
  - Subject has a sustained sinus rate > 110 BPM
  - Subject has sustained AV block, AF, or SVT
- Subject death
- Subject did not meet inclusion/exclusion criteria
- Subject was not implanted with a Medtronic CRT-D/CRT-D device
- Subject did not provide consent or data use protection authorization
- 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/procedure is to be collected/performed at study exit:

- Date of Exit
- Reason for Exit
- Initial and Final Device Interrogation (with either the initial or final being an interrogate ALL) and collection of .pdd file
- Adverse Event Collection
- Device deficiencies
- Study deviations

If discontinuation is because of safety or lack of effectiveness, the subject may be asked to be followed for collecting safety data outside the clinical investigation.

10.7.3 Lost to Follow-up

A subject is considered to be lost to follow-up if at least two attempts to contact the subject are unsuccessful. The method of attempt (e.g., one letter and one phone record, or two letters) must be documented in the subject's medical record. In addition, regulation set forth by the governing EC must be followed If allowed per local regulations, a person identified by the subject is informed of the possibility to be contacted by the principal investigator regarding how to reach the subject and the

subject's health status and a civil register may be contacted by the principal investigator to inquire about the subject's whereabouts

10.7.4 Subject Chooses to Exit (i.e., Revokes Consent)

A subject can withdraw from the study at any time. If the subject wishes to exit from the study (i.e. the subject revokes consent), the study site is required to document the reason for exit on the Exit CRF. In addition, study sites shall follow the regulations set forth by the governing EC. Permission may be requested to follow up with the subject outside of the study due to withdrawal based on problems related to the investigational feature safety or performance. If possible, the following data should be collected prior to subject withdrawal:

- Reason for exit if patient is willing to share
- All ongoing AEs are resolved or unresolved with no further actions planned

If no physical visit is associated with the withdrawal or withdrawal occurs prior to baseline visit, none of the procedures listed are required.

10.7.5 Investigator Withdraws Subject

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

- Reason for investigator withdrawal from the study
- All ongoing AEs are resolved or unresolved with no further actions planned

In the event of subject relocation, it is recommended to contact the study team to attempt to transfer the subject to another investigational site and retain the subject in the study.

10.8 Device Interrogation

For any programming changes or device interrogations occurring at the study site, an initial and final device interrogation .pdd file (with either the initial or final being an "Interrogate ALL") must be obtained and saved in a digital format. Store the original file at the study site and send a copy to Medtronic. It is recommended that data are not cleared during any interrogation.

10.9 System Modification

A system modification will be reported via a System Modification CRF in the event the initially implanted device or leads require non-invasive modification (repositioning of leads, device battery change out) and the intent is to continue the same pacing behavior as the original system was configured.

If the implanted device or leads require an invasive modification (e.g., device or lead explant, device or lead replacement/repositioning with intent to change pacing behavior from original system) the System Modification CRF will be completed and the subject will be exited after all system and/or procedure related AEs have been resolved or remain unresolved with no further action planned.

In the event of a non-invasive system modification, the follow-up schedule for the subject will remain unchanged.

For any system modification the following activities are required:

- Complete the System Modification CRF regarding details of the system modification procedure
- Device interrogation on the system modification if at all possible:
  - if device is explanted: Interrogate ALL and collect .pdd file
  - if new device implanted: Interrogate ALL and collect .pdd file
  - if lead revision: Interrogate (with either initial or final being an interrogate ALL) and collect .pdd file
- Adverse Event Collection if applicable
- Device Deficiencies if applicable
- Study Deviations if applicable

All explanted product should be returned to Medtronic for analysis when permissible by local laws and regulations.

10.10 Medication Assessment

The name, dose, frequency and route of all medications will be collected at baseline and at the 6 month follow up visit. Changes to medications will be captured on the Medication Log eCRF.

There are no medications that are required for this study although some medications may be administered in treating specific conditions at the discretion of the physician. The only medications that are excluded from use during this study are investigational.

10.11 Assessment of Safety

AE information is collected in this study. See Section 12 for further information on the collection of AEs and safety information.

All AEs will be collected throughout the duration of a subject's participation in the study, beginning at the time of informed consent. Additionally, any device deficiencies related to the Medtronic CRT-D/CRT-P will be collected. Adverse events and device deficiencies will be reported to Medtronic via completion of eCRFs. See section 12 for additional details.

10.12 Recording Data

Subject data will be collected on electronic case report forms (eCRFs) via an electronic data capture (EDC) system. The investigator must ensure accuracy, completeness and timeliness of the data reported in the eCRFs. Only authorized persons can complete and sign e-CRFs, as specified on the Delegated Tasks List included in the Investigator Site File.

Procedures in the CIP require source documentation. Source documentation is defined as the first time data appear, and may include original documents, data, and records (e.g., hospital records, clinical and

office charts, procedure reports, laboratory notes, memoranda, subjects' diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate copies, microfiches, photographic negatives, microfilm or magnetic media, X-rays, subject files, device data and records kept at the pharmacy, at the laboratories and at medico-technical departments involved in the study).

In general, eCRFs (or paper copies) may not serve as source documents. Source documentation for data elements not routinely captured in medical records may vary from study site to study site; the study site may use source document worksheets if identified as source documents.

The investigator must ensure the availability of source documents from which the information on the eCRFs was derived. The type and location of source documents should be documented. Where printouts of electronic medical records, are provided as source documents, or where copies of source documents are retained as source documents, those should be certified. Certification must contain (1) the signature of the individual making the copy, (2) the date the copy was made and (3) a statement attesting to the accuracy and completeness of the copy.

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

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

- Enrollment Notification
  - Study site assigned subject reference
- Baseline
  - Administrative information
- AE eCRF
  - Date study site became aware of event
  - Relatedness of adverse event
- DD eCRF
  - Date study site became aware of event
- Subject Death
  - Date study site became aware of death
  - Relatedness of death
  - System explant information
- System Modification
  - Justification for explanted product not being returned to Medtronic
- Deviations
  - Reason for deviation

Device data from transmissions will be uploaded to secure servers. Media/USB data collected at office visits will be sent to Medtronic. Upon receipt, device data will be maintained with databases and retrieved for analysis and reporting.

Refer to section 16.2 for additional detail regarding data management for the study.

10.13 Deviation Handling

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 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.

11. Risks and Benefits

11.1 Potential Risks

Medtronic follows rigorous Quality Assurance and Control procedures throughout the life of a product, from the business analysis phase through development, market release, and post-market surveillance. The risk analysis process for the CSPOT Research System is being performed in accordance with ISO 14971:2019 and ensures that the level of risk is acceptable prior to starting the study. In Europe a summary of the risk analysis and risk assessment will be listed in the IB.

The potential risks to a subject participating in this study are believed to be somewhat higher than those encountered during standard CRT (CRT-P and/or CRT-D) implantation. This is due to 1) the prolonged duration of the complete procedure, 2) the insertion of the Millar catheter in the left ventricle, and 3) in CRT-D devices, the addition of the CSP lead for LBBP. The potential adverse events are outlined below:

- Allergic reaction
- AV fistula
- Bradyarrhythmia
- Cardiac arrest
- Cardiac inflammation
- Cardiac perforation
- Cardiac tamponade
- Cardiac valve damage
- Discomfort
- Dizziness
- Dyspnea
- Embolism
- Fever
- Groin site injury
- Hematoma
- Hemorrhage
- Hiccups
- Hospitalization
- Infection
- Lethargy
- Mental anguish
- Palpitations
- Pneumothorax
- Physical injury

- Return of cardiac symptoms
- Skeletal muscle sensation or twitching
- Skin disorders
- SVC tear
- Syncope
- Tachyarrhythmia
- Threshold elevation
- Tissue trauma
- Vessel perforation

Kidney dysfunction could be another risk because of increased use of contrast fluid used during the total study protocol.

Bleeding and bruising may be more likely to occur with the administration of blood-thinning medications (heparin) to minimize the risk of blood clot formation during the procedure.

Procedure prolongation will not only increase duration of the anesthesia but also the risk of infection. The protocol procedures may take up to 90 minutes longer than the standard CRT procedure time which includes up to 10 minutes of fluoroscopy exposure.

Placement of the 3830 lead to pace the left bundle branch could result in: temporary or permanent right bundle branch block, tricuspid valve damage, or perforation of the ventricular septum.

Additional potential risks associated with the CSPOT Research System to a subject participating in this study are:

- The CSPOT system is investigational and may be no more effective or less effective than a commercially available CRT system.
- The CSPOT system may recommend values that are different than anticipated due to unknown circumstances or medical conditions.
- There may be other discomforts and risks related to the CRT-D/CRT-P, Millar Catheter, ECG Belt and/or this study that are not foreseen at this time.
- The lead implant configurations for this study are considered investigational and have not been studied for MRI use. Therefore, the MRI conditional labeling will not apply for these patients.

11.2 Risk Minimization

The potential risks associated with the CSPOT Research System were identified and have been mitigated; see Table 9 below. Any potential risks associated with this study are further minimized by selecting qualified investigators and training study personnel on the CIP.

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

Risks will be minimized by careful assessment of each subject prior to, during, and after implant of the CRT-D/CRT-P device. Prior to implant, it is recommended subjects undergo a complete physical evaluation.

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

After implantation, subjects in the CSPOT study will be followed for 6 months to monitor the condition of the implanted system. At each protocol required follow-up, the investigator must interrogate the CRT-D/CRT-P to verify appropriate function and to evaluate pacing and sensing characteristics and to assess any adverse events.

Table 9: Potential risks and risk minimization

Potential risk	Risk Minimization
Precursor to infection Associated AEs: Infection, Cardiac inflammation, Discomfort, Fever	• CSPOT research system design verification ensuring intended use in the sterile field - including the leads, Millar LV pressure catheter, and lead cables/pocket clip are all provided in sterile packaging • CSPOT research system design verification ensuring reusable components can be re-sterilized – including IFU instructions on re-sterilization (if applicable) • Instruction provided in IFU for implant procedure; specifically, for the placement of leads, set-up of Millar LV pressure catheter, and appropriate pacing protocol/configuration
Precursor to acute tissue/vascular trauma Associated AEs: Cardiac perforation, Cardiac tamponade, Cardiac valve damage, Discomfort, SVC tear, Hematoma, Embolism, Hemorrhage, AV fistula, Cardiac inflammation, Tissue trauma, Vessel perforation	• CSPOT research system design verification ensuring compliance to EN 60601-1:2006/A1:2013 • Instruction provided in IFU for implant procedure; specifically, for the placement of leads and set-up of Millar LV pressure catheter

Potential risk	Risk Minimization
Missing/misleading information causing insufficient/inappropriate medical intervention Associated AEs: Cardiac arrest, Lethargy, Dizziness, Return of cardiac symptoms, Syncope, Threshold elevation, Skeletal muscle sensation or twitching, Discomfort, Dyspnea, Mental anguish, Hiccups, Infection, Hospitalization, Hematoma	• CSPOT research system design verification ensuring dependability (instantaneous reliability required for implant) and shelf life • Instruction provided in IFU to verify that components are not used beyond prescribed shelf life
Bio-incompatibility Associated AEs: Allergic reaction, Skin disorders	• CSPOT research system design verification ensuring no bioincompatible materials are used
Arrhythmia induction (pacing during vulnerable period, proarrhythmic pauses, electrical/mechanical stimulus) Associated AEs: Cardiac arrest, Lethargy, Dizziness, Palpitations, Syncope, Tachyarrhythmia, Bradyarrhythmia	• CSPOT research system design verification ensuring electrical immunity to interference within its environment of use • Instruction provided in IFU for implant procedure; specifically, for the placement of leads, set-up of Millar LV pressure catheter, and appropriate pacing protocol/configuration
Inadequate tachyarrhythmia therapy Associated AEs: Cardiac arrest, Lethargy, Dizziness, Palpitations, Return of cardiac symptoms, Syncope	• CSPOT research system design verification ensuring electrical immunity to interference within its environment of use
Extracardiac stimulation Associated AEs: Dyspnea, Hiccups, Skeletal muscle sensation or twitching, Discomfort, Mental anguish	• CSPOT research system design verification ensuring electrical immunity to interference within its environment of use • Instruction provided in IFU for implant procedure; specifically, for appropriate pacing protocol/configuration
User/patient exposure to physical injury Associated AEs: Cardiac arrest, Physical injury	• Instruction provided in IFU for implant procedure; specifically, for to include ways to secure components to minimize risk to the user, and disclosure of thermal risks and warnings for the isolation transformer

Potential risk	Risk Minimization
Product integrity/functionality failure from environment influences Associated AEs: Many harm outcomes are possible. Cardiac arrest is chosen as the worst-case outcome in terms of safety risk (severity*occurrence).	• CSPOT research system design verification ensuring electrical immunity to interference within its environment of use

11.3 Potential Benefits

The CSPOT Research System may offer no direct personal benefit to individual subjects. The potential benefits of using the CSPOT research system include receiving a patient specific configuration to optimize pacing. The information gained from this study could result in the improved management of other optimized pacing therapies. [redacted]

11.4 Risk-Benefit Rationale

The result of the analysis for risks, along with the mitigation of the risks as described above, led to consider that the potential benefits that may derive from an optimized and customized CRT therapy outweigh the amount of risk. Overall residual risk of participating in the CSPOT study is considered low and acceptable.

12. Adverse Events and Device Deficiencies

12.1 Adverse Events

AE definitions are provided in Table 10. To comply with ISO 14155:2020, all adverse events (AEs) will be collected throughout the duration of a subject's participation in the study and reported per the study protocol. In addition, AEs impacting users or other persons, Non-subject Adverse Events will be collected. In all geographies, Unavoidable AEs, listed in Table 10, need not be reported unless the adverse event worsens or is present outside the stated timeframe post-implant.

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

Any medication/treatment associated with the treatment of an AE must be reported.

Subject deaths are also required to be reported. Refer to Section 12.6 for Subject Death collection and reporting requirements.

12.2 Device Deficiency

The DD (Device Deficiency) definition is provided in Table 10. To comply with ISO 14155:2020, DD information will be collected throughout the study and reported to Medtronic. Note that a DD that results in an AE to the subject should be captured as an AE only.

A DD that did not lead to an AE but could have led to a SADE (i.e., if suitable action had not been taken, if intervention had not been made, or if the circumstances had been less fortunate) requires immediate reporting.

12.3 Processing Updates and Resolution

For any changes in status of a previously reported adverse event or DD (i.e., change in actions taken, change in outcome, change in relatedness), information needs to be updated on, or added to the original AE or DD form. All 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 completion, all efforts should be made to continue following the subject until all AEs are resolved or unresolved with no further actions planned. Additionally, if there are unresolved system or procedure related AEs at the time of study completion, all efforts should be made to collect additional information to have AEs resolved. Once the ongoing system or procedure AE(s) is/are resolved, the subject should be exited. If AEs are still ongoing at study completion after efforts have been made to resolve them, it should be noted on the AE CRF that the AE is unresolved at time of study exit.

At the time of study exit, all collected adverse events that are unresolved must be reviewed and an update to the original AE must be reported.

12.4 Definitions/Classifications

Adverse event (AE) and device deficiency (DD) ISO 14155:2020 definitions are provided in Table 10 below. Where the definition indicates "device", it refers to any device used in the study. This might be the device under investigation, or any market released component of the system. Where the US and ISO terminology differs, the US term is listed first, followed by the ISO term.

Table 10: Adverse Event and Device Deficiency Definitions

General	
Adverse Event (AE)	Untoward medical occurrence, unintended disease or injury, or untoward clinical signs (including abnormal laboratory findings) in subjects, users or other persons, whether or not related to the investigational medical device and whether anticipated or unanticipated. NOTE 1: This definition includes events related to the investigational medical device or the comparator. NOTE 2: This definition includes events related to the procedures involved. NOTE 3: For users or other persons, this definition is restricted to events related to investigational medical devices or comparators. (ISO 14155:2020, 3.2)

Adverse Device Effect (ADE)	Adverse event related to the use of an investigational medical device. 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. NOTE 2: This definition includes any event resulting from an error use or from intentional misuse of the investigational medical device. NOTE 3: this includes 'comparator' if the comparator is a medical device (ISO 14155:2020, 3.1)
Device Deficiency (DD)	Inadequacy of a medical device with respect to its identity, quality, durability, reliability, safety or performance. NOTE 1: Device deficiencies include malfunctions, use errors and inadequate in the information supplied by the manufacturer including labeling. NOTE 2: This definition includes device deficiencies related to the investigational medical device or the comparator. (ISO 14155:2020, 3.19)
Relatedness	
CRT-D/CRT-P Procedure Related	An adverse event that occurs that is directly related to the insertion or modification of the CRT-P/CRT-D system.
CRT-D/CRT-P System Related	An adverse event that occurs that is directly related to the CRT-P/CRT-D system (including components like the CRTP/CRTD incision/insertion tools)
CSPOT System Related	An adverse event that results from the presence or performance of any component of the CSPOT system (including the Cardiotek, ECG Belt, and other system components)
Cardiovascular Event	An adverse event related to the heart and blood vessels or the circulation.
Not Related	Relationship to the device or procedures can be excluded when: • The event is not a known side effect of the product category the device belongs to or of similar devices and procedures; • The event has no temporal relationship with the use of the device or the procedures;

	• 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; • 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; • The event involves a body-site, or an organ not expected to be affected by the device or procedure; • 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); • The event does not depend on a false result given by the device used for diagnosis (when applicable); • Harm to the subject are not clearly due to use error; 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.
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 be explained by another cause, but additional information may be obtained.
Causal Relationship	The event is associated with the device or study procedures beyond reasonable doubt when: ▪ The event is a known side effect of the product category the device belongs to or of similar devices and procedures; ▪ The event has a temporal relationship with device use/application or procedures; ▪ The event involves a body-site or organ that ○ the investigational device or procedures are applied to ○ the investigational device or procedures have an effect on; ▪ The serious event follows a known response pattern to the medical device (if the response pattern is previously known);

	▪ 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); ▪ 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; ▪ Harm to the subject is due to error in use; ▪ The event depends on a false result given by the device used for diagnosis (when applicable); To establish the relatedness, not all the criteria listed above might be met at the same time, depending on the type of device/procedures and the serious event.
Seriousness	
Serious Adverse Event (SAE)	Adverse event that led to any of the following: a) death, b) serious deterioration in the health of the subject, users or other persons as defined by one or more of the following: 1. a life-threatening illness or injury, or 2. a permanent impairment of a body structure or a body function, including chronic disease, or 3. in-patient or prolonged hospitalization, or 4. medical or surgical intervention to prevent life threatening illness or injury or permanent impairment to a body structure or a body function, c) foetal distress, foetal death or a congenital abnormality or birth defect including physical or mental impairment NOTE 1: Planned hospitalization for a pre-existing condition, or a procedure required by the CIP, without serious deterioration in health, is not considered a serious adverse event. (ISO 14155:2020, 3.45)
Serious Adverse Device Effect (SADE)	Adverse device effect that has resulted in any of the consequences characteristic of a serious adverse event. (ISO 14155:2020, 3.44)
Complication	An adverse event that includes the following is considered a complication: • Results in death, • Involves any termination of significant device function, or

	• Requires an invasive intervention Non-invasive (21 CFR 812): when applied to a diagnostic device or procedure, means one that does not by design or intention: • Penetrate or pierce the skin or mucous membranes of the body, the ocular cavity, or the urethra, or ○ Penetrate: to pass, extend, pierce, or diffuse into or through something; to enter by overcoming resistance; to gain entrance to ○ Pierce: to force a way into or through something • Enter the ear beyond the external auditory canal, the nose beyond the nares, the mouth beyond the pharynx, the anal canal beyond the rectum, or the vagina beyond the cervical os *Note* (FDA): Blood sampling that involves simple venipuncture is considered noninvasive, and the use of surplus samples of body fluids or tissues that are left over from samples taken for non- investigational purposes is also considered noninvasive.
Observation	Any Adverse Event that is not a complication. *Note 1:* Cardiovascular and Heart failure related AEs will be the only AEs requiring classification of either Complication or Observation by Sponsor and CEC.
Unanticipated Adverse Device Effect (UADE)	Any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death, was not previously identified in a nature, severity, or degree of incidence in the investigational plan or application (including a supplementary plan or application), or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects. (21 CFR 812.3(s))
Unanticipated Serious Adverse Device Effect (USADE):	Serious adverse device effect which by its nature, incidence, severity or outcome has not been identified in the current version of the risk assessment *NOTE 1:* Anticipated serious adverse device effect (ASADE) is an effect which by its nature, incidence,

<table>
<tr><td></td><td>severity or outcome has been identified in the risk assessment.

(ISO 14155:2020, 3.42)</td></tr>
<tr><td>Serious Health Threat</td><td>Signal from any adverse event or device deficiency that indicates an imminent risk of death or a serious deterioration in the health in subjects, users or other persons, and that requires prompt remedial action for other subjects, users or other persons

NOTE 1: This would include events that are of significant and unexpected nature such that they become alarming as a potential serious health hazard or possibility of multiple deaths occurring at short intervals.

(ISO 14155:2020, 3.46)</td></tr>
<tr><td colspan="2">Other</td></tr>
<tr><td>Non-Subject Adverse Event (users or other persons)</td><td>An Adverse Event or Serious Health Threat related to the investigational medical devices or comparators that impact users or other persons</td></tr>
<tr><td>Unavoidable Adverse Event</td><td>An Adverse Event inherent to a surgical procedure that is expected to occur in all subjects for a projected duration according to the Investigator's opinion, including, but not limited to:

<table>
<tr><th>Event Description</th><th>Timeframe (hours) from the Surgical Procedure</th></tr>
<tr><td>Anesthesia related nausea / vomiting</td><td>24</td></tr>
<tr><td>Low-grade fever (<100°F or 37.8°C)</td><td>48</td></tr>
<tr><td>Pocket site / Incisional pain</td><td>72</td></tr>
<tr><td>Mild to moderate bruising / ecchymosis</td><td>168</td></tr>
<tr><td>Sleep problems (insomnia)</td><td>72</td></tr>
<tr><td>Back pain related to laying on table</td><td>72</td></tr>
<tr><td>Shoulder pain/discomfort/stiffness related to shoulder immobilization during procedure</td><td>72</td></tr>
</table>
Unavoidable adverse events are not reportable unless the AE worsens or is present outside the stated timeframe.</td></tr>
</table>

12.5 Reporting of 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 will be conducted in accordance with these procedures and regulations.

Adverse Event and Device Deficiency data collection starts once the subject is consented and continues throughout the study, and updates are expected when there are changes in status of a previously reported adverse event including change in actions taken, change in outcome, or change in relatedness. If applicable, these AEs and DDs will be reported to other countries where studies are conducted with the same or a similar product.

12.5.1 Adverse Event and Device Deficiency Collection

12.5.1.1 Adverse Events

Reporting of AEs to Medtronic will occur on an Adverse Event eCRF, including a description of the event, the diagnosis, the date of event onset, the date the site became aware of the event, the relatedness and seriousness of the event, diagnostic tests and procedures performed, actions taken as a result of the event, and outcome of the event. Each AE must be recorded on a separate AE eCRF. Subject deaths are also required to be reported and should be collected on an AE CRF with a Fatal outcome. Refer to section 12.6.1 for subject death collection and reporting requirements. In addition, AEs impacting users or other persons will be collected on a Non-subject Adverse Event eCRF.

Documented pre-existing conditions are not considered AEs unless the nature or severity of the condition has worsened post implant. In all geographies, unavoidable adverse events, listed in Table 10, need not be reported unless the adverse event worsens or is present outside the stated timeframe.

For any changes in status of a previously reported AE (i.e., change in actions taken, change in outcome, change in relatedness), an update to the original AE must be provided. All reported adverse events must be followed until the adverse event has been resolved, the subject exits the study or until study closure, whichever occurs first. At the time of study exit, all collected AEs with an outcome of "not recovered/not resolved", "recovering/resolving" or "unknown" must be reviewed and updates provided as applicable.

12.5.1.2 Device Deficiencies

Device deficiency (DD) information will be collected throughout the study and reported to Medtronic. Reporting of DDs to Medtronic will occur on a device deficiency eCRF. Note that DDs that result in an adverse device effect (ADE) to the subject should be captured on an AE eCRF 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.

12.5.2 Adverse Event and Device Deficiency Classification

All reported AEs and DDs will be reviewed by a Medtronic representative. Adverse events will be classified according to the standard definitions as outlined in Table 11.

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

Regulatory reporting of AEs and DDs will be completed according to local regulatory requirements. Refer to Table 12 for a list of required investigator and Medtronic reporting requirements and timeframes. It is the responsibility of both to abide by any additional AE reporting requirements stipulated by the EC responsible for oversight of the study.

Section 18.7 contains the FAL, which is a list of AEs related to harms observed in previous studies and may be experienced by subjects. This list may help to assist if an AE is unanticipated in nature.

Anticipated adverse events and adverse device effects along with residual risk with the study product is identified in the risk analysis report, located in the IB.

For emergency contact regarding a U(S)ADE, SAE and/or SADE, contact a study representative immediately (refer to the study contact list provided in the study site's study documents binder/investigator site file or refer to the Sponsor contact information provided on the title page).

An independent Clinical Event Committee (CEC) will conduct a medical review and adjudicate at a minimum all CRT-D/CRT-P system and procedure-related adverse events, all CSPOT system and procedure-related adverse events, all cardiovascular related AEs (regardless of seriousness), all SAEs and all AEs with a fatal outcome. The CEC will consist of non-Medtronic employed physicians that are not participating investigators for the study.

Table 11: Adverse Event Classification Responsibilities

What is classified?	Who classifies?	Classification Parameters
Relatedness	Investigator	• CRT-D/CRT-P Procedure Related • CRT-D/CRT-P System Related • CSPOT System Related
	Sponsor	• CRT-D/CRT-P Procedure Related • CRT-D/CRT-P System Related • CSPOT System Related • Complication or Observation (for all system or procedure related AEs)
	CEC	• CRT-D/CRT-P Procedure Related • CRT-D/CRT-P System Related • CSPOT System Related • Not Related • Cardiovascular related • Complication or Observation (for all system or procedure related AEs)
Seriousness	Investigator	SAE, DD with SADE potential
	Sponsor	SAE, UADE/USADE, DD 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
	CEC	Sudden Cardiac, Non-sudden Cardiac, Non-Cardiac, Unknown

12.5.3 Adverse Event and Device Deficiency Reporting Requirements

Regulatory reporting of AEs and DDs will be recorded and reported according to local regulatory requirements. It is the responsibility of the Investigator and the sponsor to abide by the AE reporting requirements stipulated by local law and the study site's EC.

Table 12: Reporting Requirements

Unanticipated Adverse Device Effect (UADE), Unanticipated Serious Adverse Device Effects (USADE)	
Investigator submit to:	
Medtronic	Submit as soon as possible as per local reporting requirement, but not later than within 10 working days after the investigator first learns of the event.
IRB/Ethics Committee	Submit per local reporting requirement.

Regulatory Authorities	Submit per local reporting requirement.
Sponsor submit to:	
Regulatory Authorities	Submit per local reporting requirement.
IRB/Ethics Committee	Submit per local reporting requirement.
Serious Adverse Events (SAE) in EEA & UK	
Investigator submit to:	
Medtronic	Submit as soon as possible as per local reporting requirement, but not later than within 3 calendar days after the study personnel's awareness of the event.
IRB/Ethics Committee	Submit per local reporting requirement.
Regulatory Authorities	Submit per local reporting requirement.
Sponsor submit to:	
Regulatory Authorities	Submit per local reporting requirement.
IRB/Ethics Committee	Submit per local reporting requirement.
AEs, Serious Adverse Events in U.S. (SAE)/ Adverse Device Effects (ADE), SADE, Deaths	
Investigator submit to:	
Medtronic	Submit as soon as possible as per local reporting requirement, but not later than within 10 working days after the investigator first learns of the event.
Regulatory Authorities	Submit per local reporting requirement.
IRB/Ethics Committee	Submit per local reporting requirement.
Sponsor submit to:	
Regulatory Authorities	Submit per local reporting requirement.
IRB/Ethics Committee	Submit per local reporting requirement.
Device Deficiency (DD)/Device Deficiency with SADE potential	
Investigator submit to:	
Medtronic	Submit as soon as possible as per local reporting requirement, but not later than 3 days after the investigator first learns of the event or of new information in relation with an already reported event.
Regulatory Authorities	Submit per local reporting requirement.
IRB/Ethics Committee	Submit per local reporting requirement.

Sponsor submit to:	
Regulatory Authorities	Submit per local reporting requirement.
IRB/Ethics Committee	Submit per local reporting requirement.

12.6 Subject Death

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

In the event of a subject's death, it is recommended that the implanted system be explanted and returned to Medtronic for analysis whenever possible per local process. Local laws and procedures must be followed where applicable. If any system component is returned to Medtronic, internal return product reporting systems may be used to gather additional information about the returned device/component.

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, if available should be sent to the Medtronic clinical study team. If an autopsy is conducted, a copy of 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 study site, it is the investigative study site'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
- Relatedness to CRT-P/CRT-D system and/or procedure
- Relatedness to CSPOT system
- Device interrogation information/reports and .pdd file information/reports (if available)
- 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 allowed by state/local law)

12.6.1 Death Classification and Reporting

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

- Cardiac Death: A death directly related to the electrical or mechanical dysfunction of the heart.
- Sudden Cardiac Death: Natural death due to cardiac causes, indicated by abrupt loss of consciousness within one hour of the onset of acute symptoms; preexisting heart disease may have been known to be present, but the time and mode of death are unexpected. If time of

onset cannot be determined, Sudden Cardiac Death 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 Death Classification: Unknown death classification is intended for use only when there is insufficient or inadequate information to classify the death.

Table 13: Subject death classification responsibilities

What is classified?	Who classifies?	Classification Parameters
Relatedness	Investigator	• CRT-D/CRT-P Procedure related • CRT-D/CRT-P System related AEs • CSPOT System related • Not related • Possibly Related • Probably Related • Causal Related
Death Classification	Investigator	Sudden Cardiac, Non-sudden Cardiac, Non-cardiac, Unknown

The CEC will review all AEs with a fatal outcome and provide a final adjudication of both cardiovascular event and death classification. Regulatory reporting of subject deaths will be completed according to local regulatory requirements.

12.7 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. The reporting of product complaints by the clinical team must be done according to the local Standard Operating Procedures. Medtronic will notify the RAs (e.g., CA) as applicable for the following incidents immediately upon learning of them and is not limited to AEs and DDs only:

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

13. Data Review Committees

13.1 Clinical Events Committee

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.

The CEC will consist of a minimum of three (3) non-Medtronic employed physicians that are not participating investigators for the study, including a CEC chairperson. At least three CEC members must adjudicate, at a minimum, all adverse events that are related to CRT-D/CRT-P system and/or procedure, CSPOT system, and/or cardiovascular related events. All SAEs, adverse events with outcome of death, and cardiovascular events will be reviewed by one CEC Member. If the one physician CEC member deems an event to be related, it will then go to three CEC member adjudication. The CEC will operate under a charter that documents the process of adjudication of data for this study.

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

If the CEC disagrees with the investigator's classification of the event, the rationale will be provided to the investigator. If the investigator agrees with the CEC's adjudication, the CRF documenting the AE will be updated accordingly.

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

Source documents to support adjudication may be requested.

14. Statistical Design and Methods

The CSPOT study is a prospective, non-randomized, multi-center, global, feasibility clinical study designed to assess different approaches to resynchronization in CRT-indicated patients.

The study may enroll up to 60 subjects at up to 12 sites in the US and Europe, with no more than 15 subjects enrolled per site. The site maximum of 15 subjects will ensure that evidence generated by this study is not overly dependent on a single site. Study subjects will be followed for 6 months after the utilization of the CSPOT Research System and acute pacing protocol.

[redacted]

14.1 General Aspects of Analysis

Medtronic statisticians or designees will perform all statistical analyses.

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

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.

P-values for hypothesis testing will be evaluated based on a two-sided significance level of 0.05. No adjustments will be made for multiple testing because of the exploratory nature of this study.

No imputation of missing data 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 patients, additional analysis to characterize baseline factors associated with missing data may be considered.

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, do not violate any inclusion or exclusion criteria, and have all leads successfully placed during the CSPOT Acute Pacing 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, but will be reported in a subject disposition table, and may be included in some secondary analysis approaches.

14.2 Analysis Execution

Analysis for CSPOT will occur after the last subject has been exited or upon study closure determine by the sponsor. Analysis will include both primary and all secondary objectives. Ancillary objectives will be addressed based on available data. A final report will be prepared once all data collection has ended and all subjects have completed the 6-month follow-up visit or have been exited.

14.3 Interim Analysis

No interim analyses are planned for this study.

14.4 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. Each objective entails two statistical hypotheses between pacing configurations: CSPOT vs. CSP-only and CSPOT vs. Traditional CRT.

14.4.1 Primary Objective #1

Two statistical hypothesis tests will be used to evaluate this objective. The null and alternative hypotheses for the first test are:

H_0: Improvement in SDAT relative to baseline in the CSPOT pacing configuration = Improvement in SDAT relative to baseline in the CSP-only configuration

H_A: Improvement in SDAT relative to baseline in the CSPOT pacing configuration ≠ Improvement in SDAT relative to baseline in the CSP-only configuration

The bipolar CSP-only configuration will be used in this comparison.

The null and alternative hypotheses for the second test are:

H_0: Improvement in SDAT relative to baseline in the CSPOT pacing configuration = Improvement in SDAT relative to baseline in the traditional CRT configuration

H_A: Improvement in SDAT relative to baseline in the CSPOT pacing configuration ≠ Improvement in SDAT relative to baseline in the traditional CRT configuration

For both hypothesis tests, the best LV cathode, chosen for the CSPOT configuration, as described in Section 10.6.1, will be used.

Paired two-sided t-tests are planned to test the hypotheses, but a Wilcoxon signed-rank test will be considered as an additional analysis approach.

14.4.2 Primary Objective #2

Two statistical hypothesis tests will be used to evaluate this objective.

The null and alternative hypotheses for the first test are:

H_0: Improvement in positive LV dP/dt max relative to baseline in the CSPOT pacing configuration = Improvement in positive LV dP/dt max relative to baseline in the CSP-only configuration

H_A: Improvement in positive LV dP/dt max relative to baseline in the CSPOT pacing configuration ≠ Improvement in positive LV dP/dt max relative to baseline in the CSP-only configuration

The bipolar CSP-only configuration will be used in this comparison. A paired two-sided t-test is planned to test this hypothesis.

The null and alternative hypotheses for the second test are:

H_0: Improvement in positive LV dP/dt max relative to baseline in the CSPOT pacing configuration = Improvement in positive LV dP/dt max relative to baseline in the traditional CRT configuration

H_A: Improvement in positive LV dP/dt max relative to baseline in the CSPOT pacing configuration ≠ Improvement in positive LV dP/dt max relative to baseline in the traditional CRT configuration

For both hypothesis tests, the best LV cathode, chosen for the CSPOT configuration, as described in Section 10.6.1, will be used.

Paired two-sided t-test are planned to test the hypotheses, but a Wilcoxon signed-rank test will be considered as an additional analysis approach.

For each subject and each pacing configuration, multiple positive LV dP/dt max measurements will be taken because individual measurements are known to be highly variable. The primary analysis approach for this hypothesis test will summarize these measurements to one value for each subject-pacing configuration combination. However, a repeated measures analysis of the individual measurements may also be considered as additional analysis.

14.5 Secondary Objectives

The following secondary objectives will all be evaluated, regardless of their results or the results of the primary objectives, given the exploratory nature of this study.

14.5.1 Secondary Objective #1

Descriptive summary statistics of SDAT improvement relative to baseline (mean, 95% confidence interval, median, 25th and 75th percentile, and minimum and maximum) will be calculated for each combination of pacing configuration, measurement, and subpopulation.
Subjects missing the data required to assign them to a subgroup for this objective (i.e. QRS width, conduction disorder presence, cardiomyopathy etiology) will not be included in either subgroup.

14.5.2 Secondary Objective #2

Descriptive summary statistics of positive LV dP/dt max improvement relative to baseline (mean, 95% confidence interval, median, 25th and 75th percentile, and minimum and maximum) will be calculated for each combination of pacing configuration, measurement, and subpopulation.

Subjects missing the data required to assign them to a subgroup for this objective (i.e. QRS width, conduction disorder presence, cardiomyopathy etiology) will not be included in either subgroup.

14.5.3 Secondary Objective #3

For each subject with LVEF measured at implant and 6-month visit, LVEF change will be calculated as an absolute change from baseline:

$$(\text{EF measured at 6 months}) - (\text{EF measured at baseline})$$

LVEF change will then be summarized with mean, 95% confidence interval, median, 25th and 75th percentile, and minimum and maximum.

Subjects will be included in this analysis only if they are in the Analysis Cohort and successfully complete CRT implant and the 6-month follow-up visit.

14.5.4 Secondary Objective #4

For each subject with LVESV measured at implant and 6-month visit, LVESV change will be calculated as a relative change from baseline:

$$\frac{(\text{LVESV measured at 6 months}) - (\text{LVESV measured at baseline})}{\text{LVESVI measured at baseline}}$$

LVESV change will then be summarized with mean, 95% confidence interval, median, 25th and 75th percentile, and minimum and maximum.

Subjects will be included in this analysis only if they are in the Analysis Cohort and successfully complete CRT implant and the 6-month follow-up visit.

14.5.5 Secondary Objective #5

The Clinical Composite Score (CCS) is a 3-level categorical variable that can take the values – Improved, Unchanged, or Worsened – at each follow-up visit. It is based on mortality, HF events, termination of device function, NYHA score, and patient global assessment. The count and proportion of subjects with each of these CCS values based on the 6-month visit will be provided.

Subjects will be included in this analysis only if they are in the Analysis Cohort and have an observed CCS.

[redacted]

14.8 Sample Size Determination

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

15. Ethics

15.1 Statement(s) of Compliance

This study will be conducted in compliance with international ethical and scientific quality standards, known as GCP. GCP includes review and approval by an independent EC before initiating a study, continuing review of an ongoing study by an EC, and obtaining and documenting the freely given informed consent of a subject before initiating the study.

The CSPOT study was designed to reflect the GCP principles outlined in ISO 14155:2020 and other international clinical requirements outlined below. These include the protection of the rights, safety and well-being of human subjects, controls to ensure the scientific conduct and credibility of the clinical investigation and the definition of responsibilities of the sponsor and investigators. In accordance with ISO 14155:2020, the sponsor shall avoid improper influence on, or inducement of, the subject, monitor, any investigator(s) or other parties participating in, or contributing to, the clinical investigation. All investigators shall avoid improper influence on or inducement of the subject, sponsor, monitor, other investigator(s) or other parties participating in or contributing to the clinical investigation. AE and DD handling in the CSPOT study is ISO 14155:2020 compliant for all participating geographies.

The principles of the DoH have been implemented through the IC process, EC approval, study training, clinical trial registration, pre-clinical testing, risk-benefit assessment and publication policy.

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

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

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

- In the United States, the study will be conducted under an FDA IDE in compliance with 21 CFR Parts:
  - 50: Protection of Human Subjects
  - 54: Financial Disclosure by Clinical Investigators
  - 56: IRBs
  - 812: IDEs
- In Europe the study will be conducted in compliance with the local regulations

The study will be publicly registered prior to in accordance with the 2007 FDAAA and DoH on http://clinicaltrials.gov (PL 110-85, section 810(a)). In addition, the study may be registered in local regulatory databases where required by local law.

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

- Medtronic
- Principal Investigators (where required by local law/regulations)
- Geography-specific regulatory authorities (if regulatory approval is required)
- An independent medical EC or IRB.

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

16. Study Administration

16.1 Monitoring

It is the responsibility of Medtronic to ensure proper monitoring of this study. Trained Medtronic personnel or delegates appointed by Medtronic may perform study monitoring at the study site in order to ensure that the study is conducted in accordance with the CIP, the CTA, and the applicable regulatory and local requirements. Medtronic, or delegates, must therefore be allowed direct access to the subjects' case histories (clinic and hospital records, and other source data/documentation) upon request as per the IC, Research Authorization (where applicable) and CTA. The principal investigator should also be available during monitoring visits.

16.1.1 Monitoring Visits

Frequency of monitoring visits may be based upon subject enrollment, study compliance, number of adverse events, number of deviations, observations from previous monitoring visits and any suspected inconsistency in data that requires investigation. Regulatory documents may be reviewed at each

study site. Monitoring for the study, including, site initiation visits, interim monitoring visits, and closeout visits will be done in accordance to the study-specific monitoring plan.

Monitoring visits may be conducted periodically to assess study site progress, the investigator's adherence to the CIP, regulatory compliance including but not limited to EC approval and review of the study, maintenance of records and reports, and review of source documents against subject CRFs in accordance to the study-specific monitoring plan. Monitors review study site regulatory and study compliance by identifying observations of non-compliance and communicating those observations along with recommendations for preventative/corrective actions to study 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 study site.

The Investigator will permit study related monitoring, audits, IRB review and regulatory inspections by providing direct access to source data and source documents.

Medtronic will request that the study site upload identified subject case history files and regulatory documents to a secure, password-protected website prior to remote monitoring visits.

16.2 Data Management

Data will be collected using an electronic data management system for studies. eCRF data will be stored in a secure, password-protected database which will be backed up nightly. Data will be reviewed using programmed and manual data checks. Data queries will be made available to study sites for resolution. Study management reports may be generated to monitor data quality and study progress. At the end of the study, the data will be frozen and will be retained 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. If it's impossible to pseudonymize (where the subject's name cannot be removed, such as fluoroscopy images) from the data carrier, data will not be transferred electronically.

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

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

The data reported on the CRFs shall be derived from source documents and be consistent with these source documents, and any discrepancies shall be explained in writing. See Section 16.3 for CRFs and data collection elements that may be considered source.

Device data from transmissions and any save-to-disk data collected at office visits will be sent to Medtronic. Upon receipt, device data will be maintained with databases and retrieved for analysis and reporting.

Investigator will be required to sign off on all entered and completed data on the eCRF.

16.3 Direct Access to Source Data/Documents

Medtronic may conduct audits at participating study sites. The purpose of an audit is to verify the performance of the monitoring process and the study conduct, independently of the personnel directly involved in the study. RAs, such as the FDA, may also perform inspections at participating study sites. The investigator and/or institution shall permit Medtronic, ECs and RAs direct access to source data and documents during monitoring, audits and regulatory inspections.

16.4 Confidentiality

All information and data sent to parties involved in study conduct concerning subjects or their participation in this study will be considered confidential. Study sites will assign a unique SID to each subject. Records of the subject/SID relationship will be maintained by the study site. The SID number is to be recorded on all study documents to link them to the subject's medical records at the study site. Confidentiality of data will be observed by all parties involved at all times throughout the clinical investigation. All data shall be secured against unauthorized access. The privacy of each subject and confidentiality of his/her information shall be preserved in reports and when publishing any data. In the US, "Protected Health Information" (PHI) will be maintained in compliance with the HIPAA of 1996. To maintain confidentiality, the subject's name or any other PHI should not be recorded on any study document other than the IC. This scenario will be covered in the IC. In the event a subject's name/PHI is included for any reason, it will be blinded as applicable. In the event of inability to blind the identification (e.g., digital media, fluoroscopy images), it will be handled in a confidential manner by the authorized personnel. Data relating to the study might be made available to third parties (for example in case of an audit performed by RA), provided the data are treated as confidential and that the subject's privacy is guaranteed. No identifiable subject information will be published.

16.5 Liability/Warranty/Insurance Information

16.5.1 Warranty

Warranty information will be provided in the product packaging for the investigational or commercially released system and components and will be available upon request.

Medtronic maintains appropriate clinical study liability insurance coverage as required under applicable laws and regulations and will comply with applicable local law and custom concerning specific insurance coverage. If required, a clinical study insurance statement/certificate will be provided to the IRB/EC.

16.5.2 Insurance (Europe)

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

16.6 CIP Amendments

Any revisions or amendments to documents that are submitted to the competent authorities (including CIP and IC) along with a statement of justification for the changes, will be submitted to all affected RAs (FDA, CA) and governing ECs, according to applicable regulations. All amendments to the CIP shall be agreed upon between Medtronic and the principal investigator(s), or the coordinating investigator. Approval by regulatory agencies and ECs (where applicable) must be obtained prior to implementing a CIP revision at the study site.

16.7 Record Retention

All study-related documents must be retained for a period of at least 2 years after end of study in his/her region and after study closure (or longer if required by local law). Medtronic will inform the investigator/study site when these documents are no longer required to be retained.

No study document or image will be destroyed without prior written agreement between Medtronic and the investigator. The investigator should take measures to prevent accidental or premature destruction of documents. Should the investigator wish to assign the study records to another party or move them to another location, advance written notice must be given to Medtronic.

Medtronic will retain the study records according to Medtronic corporate policy and record retention schedule.

16.7.1 Investigator Records

The investigator is responsible for the preparation and retention of the records cited below. All of the below records, with the exception of case history records and case report forms, should be kept in the 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) or the date that the records are no longer required for purposes of supporting a pre-market approval application.

- All correspondence between the EC/IRB, sponsor, monitor, FDA, RA and the investigator that pertains to the investigation, including required reports.
- Subject's case history records, including:
  - Signed and dated IC:
    - U.S.: signed by subject.
    - Europe: signed by subject and investigator.
  - Observations of AEs/ADEs/DDs
  - Medical history
  - Baseline, Implant, CSPOT system protocol and follow up data (if applicable)
  - Documentation of the dates and rationale for any deviation from the protocol
- List of investigation study sites
- FD (if applicable)

- Subject screening log & ID log (if applicable)
- Normal value(s)/range(s) for clinical laboratory test (if applicable)
- Lab certificate (if applicable)
- Device Disposition Logs (if applicable).
- Non implantable device Disposition Logs (if applicable)
- All approved versions of the CIP, IC, IBs/Report of Prior Investigation Summary
- Fully executed CTA.
- CV (signed and dated in Europe only) of principal investigators and key members of investigation study site team (as required by applicable regulations).
- Documentation of delegated tasks.
- EC approval documentation. Written information that the investigator or other study staff, when member of the EC, did not participate in the approval process. Approval documentation must include the ECs composition, where required per local law.
- RA notification, correspondence and approval, where required per local law.
- Study training records for study site staff.
- Insurance certificates (Europe only).
- Any other records that FDA and local regulatory agencies require to be maintained.
- Final Study Report including the statistical analysis.

16.7.2 Sponsor Records

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

- All correspondence which pertains to the investigation
- Investigational device traceability record containing Model and serial numbers of devices, shipping date and name and address of person that received shipped device, location (if different than person shipped to), transfer and receipt by Medtronic dates (if applicable)
- Non implantable device traceability records containing Model and serial/lot numbers, shipping date and name and address of person that received shipped device, location (if different than person shipped to), transfer and receipt by Medtronic dates (if applicable)
- Sample of label attached to investigational device
- Signed Investigator Trial Agreements, FD (if applicable) and current signed and dated (Europe only) CV of principal investigator and key members of the investigation study site team (as required by local law)
- All approved IC templates, and other information provided to the subjects and advertisements, including translations
- Copies of all EC approval letters and relevant EC correspondence and EC voting list/roster/letter of assurance

- Names of the institutions in which the study will be conducted
- RA correspondence, notification and approval as required by national legislation
- Insurance certificates (Europe only)
- Names/contact addresses of monitors
- Monitoring visit reports
- Statistical analyses and underlying supporting data
- Final report of the study
- The CIP, IB/Report of Prior Investigations summary and study related reports, and revisions
- Study training records for study site personnel and Medtronic personnel involved in the study
- Any other records that local regulatory agencies require to be maintained.

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

After closure of the study Medtronic will archive records and reports indefinitely.

16.8 Reporting Requirements

16.8.1 Investigator Reports

The investigator is responsible for the preparation (review and signature) and submission to the sponsor of all case report forms, adverse events and adverse device effects (reported per the country-specific collection requirements), device deficiencies, deaths, and any deviations from the clinical investigation plan. If any action is taken by an EC with respect to this 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 Section 12.5.3. The investigator shall prepare and submit in a complete, accurate and timely manner the reports listed in this section.

Table 14: Investigator reports applicable for all geographies per Medtronic requirements

Report	Submit to	Description/Constraints
Withdrawal of IRB/EC approval	Sponsor and Relevant Authorities	The investigator must report a withdrawal of approval by the reviewing IRB/EC of the investigator's part of the investigation within 5 working days.
Study Deviations	Sponsor and IRB/EC	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/ECs and Relevant Authorities	This report must be submitted within 3 months of study completion or termination.

Table 15: Additional Investigator reports applicable to the United States per FDA regulations

Report	Submit to	Description/Constraints
Withdrawal of IRB/EC approval (either suspension or termination)	Sponsor	The investigator must report a withdrawal of approval by the reviewing IRB/EC of the investigator's part of the investigation within 5 working days. (21 CFR 812.150(a)(2))
Progress report	Sponsor and IRB/EC	The investigator must submit this report to the sponsor and IRB/EC at regular intervals, but in no event less than yearly intervals. (21 CFR 812.150 (a)(3)).
Study deviations	Sponsor and IRB/EC	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/EC, and the FDA/applicable RA. If the deviation does not affect these issues then only Medtronic must approve it. (21 CFR 812.150(a)(4))
Failure to obtain IC prior to investigational device use	Sponsor and IRBs/ECs	If an investigator uses a device without obtaining IC, the investigator shall report such use within 5 working days after device use. (21 CFR 812.150(a)(5))
Final report	Sponsor IRBs/ECs Relevant Authorities	This report must be submitted within 3 months of study completion or termination of the investigation or completion or termination of the investigator's part of the investigation. (21 CFR 812.150(a)(6))
Other	IRB/EC and FDA	An investigator shall, upon request by a reviewing IRB/EC, FDA or any other RA, provide accurate, complete, and current information about any aspect of the investigation. (21 CFR 812.150(a)(7))

Table 16: Investigator reports applicable to Europe per ISO 14155

Report	Submit to	Description/Constraints
Withdrawal of IRB/EC approval	Sponsor	Report if required by local law.
Progress Report	Sponsor and IRB/EC	Provide if required by local law or IRB/EC.
Study Deviations	Sponsor, Competent Authority and IRB/EC	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. Note: When relevant, ethics committees, CAs or the appropriate RAs should be informed. (ISO 14155:2020)
Failure to obtain IC	Sponsor and IRBs/ECs	IC shall be obtained in writing and documented before a subject is enrolled into the clinical investigation. (ISO 14155:2020)

16.8.2 Sponsor Reports

Medtronic shall prepare and submit the following complete, accurate, and timely reports listed in the tables below (by geography). In addition to the reports listed below, Medtronic shall, upon request of the reviewing EC, RA or FDA, provide accurate, complete and current information about any aspect of the investigation. Safety data Medtronic reporting requirements are listed in section 12.5.3.

Table 21: Sponsor reports for Europe

Report	Submit to	Description/Constraints
Premature termination or suspension of the clinical investigation	Investigators, IRB/EC, Relevant authorities and Head of the Institution	Provide prompt notification of termination or suspension and reason(s). (ISO 14155:2020)
Withdrawal of IRB/EC approval	Investigators, Head of Institution, IRB/EC and relevant authorities	Investigators, IRBs/ECs will be notified only if required by local laws or by the IRB/EC.

Report	Submit to	Description/Constraints
Withdrawal of CA approval	Investigators, Head of Institution, IRB/EC, and relevant authorities	Investigators, IRBs/ECs will be notified only if required by local laws or by the IRB/EC.
Progress Reports	IRB/EC and RAs	This will be submitted to the IRB/EC only if required by the IRB//EC).
Final report	Investigators, IRB/EC, and RAs if required	For studies with study sites complying to ISO 14155: • The investigator shall have the opportunity to review and comment on the final report. • If a clinical investigator does not agree with the final report, his/her comments shall be communicated to the other investigator(s). • The coordinating investigator shall sign the report. If no coordinating investigator is appointed, then the signature of the principal Investigator in each study site should be obtained. (ISO 14155:2020)
Study deviation	Investigators	Ensure that all deviations from the CIP are reviewed with the appropriate clinical investigator(s), are reported on the CRFs and the final report of the clinical investigation. (ISO 14155:2020) Study site specific study deviations will be submitted to investigators periodically.

16.9 Publication and Use of Information

Publications from the CSPOT study will be handled according to Standard Operating Procedures and as indicated in the CTA.

16.9.1 Publication Committee

Medtronic may form the CSPOT Publication Committee from 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, 5) review and prioritize publication proposals, 6) provide input on publication content, and 7) determine

authorship. In addition, the committee will apply and reinforce the authorship guidelines set forth in the Publication Plan.

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

16.9.2 Management of Primary, Secondary, and Ancillary Publications

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

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

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

16.9.3 Criteria for Determining Authorship

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

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

- Substantial contributions to conception and design of the work, or the acquisition, analysis, or interpretation of data for the work; AND
- Drafting the work or revising it critically for important intellectual content; AND
- Final approval of the version to be published; AND
- Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Decisions regarding authorship and contributor-ship will be made by the committee. The selected authors will be responsible for drafting the publication. All selected authors must fulfill the authorship conditions stated above to be listed as authors, and all contributors who fulfill the conditions must be listed as authors.

All investigators not listed as co-authors will be acknowledged as the "Medtronic CSPOT 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.

16.9.4 Transparency

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

- A final report, describing the results of all objectives and analysis, will be distributed to all investigators, ECs and CAs of participating countries when required by local law
- Registering and posting the study results on a <publicly accessible database, e.g., ClinicalTrials.gov> based on the posting rules stipulated
- Submitting for publication the primary study results after the study ends
- Disclosing conflicts of interest (e.g., financial) of the co-authors of publications according to the policies set forth by the corresponding journals and conferences
- Making an individual study sites study data accessible to the corresponding investigator after the completion of the study, if requested

16.10 Suspension or Early Termination

16.10.1 Planned Study Closure

Study Closure is a process initiated by distribution of a study closure letter. Study closure is defined as closure of a study that occurs when Medtronic and/or regulatory requirements have been satisfied per the CIP and/or by a decision by Medtronic or RA), whichever occurs first. The study closure process is complete upon distribution of the Final Report or after final payments, whichever occurs last. Ongoing EC/IRB oversight is required until the overall study closure process is complete. Upon study closure, subjects should be managed and followed per physician discretion.

16.10.2 Early Termination or Suspension

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

16.10.2.1 Study-wide termination or suspension

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

- AEs associated with the system or product under investigation which might endanger the safety or welfare of the subject
- Observed/suspected performance different from the product's design intent
- Decision by Medtronic or RA (where the study is operating under RA)
- Technical issues during the manufacturing process

16.10.2.2 Investigator/study site termination or suspension

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

- Failure to obtain initial EC 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 CTA (e.g. failure to submit data in a timely manner, failure to follow-up on data queries and monitoring observations in a timely manner, etc.)
- EC suspension of the study site
- Fraud or fraudulent misconduct is discovered (as defined by local law and regulations)
- Investigator request (e.g. no longer able to support the study)

16.10.3 Procedures for Termination or Suspension

16.10.3.1 Medtronic-initiated and regulatory authority-initiated

- Medtronic will promptly inform the clinical investigators of the termination or suspension and the reasons and inform the RAs where required
- In the case of study termination or suspension for reasons other than a temporary EC approval lapse, the investigator will promptly inform the EC
- 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

16.10.3.2 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 EC
- The investigator will promptly inform the regulatory authorities
- 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

16.10.3.3 Ethics Committee-initiated

- The investigator will inform Medtronic and provide a detailed written explanation of the termination or suspension within 5 business days
- Subject enrollment must stop until the suspension is lifted
- Subjects already enrolled should continue to be followed in accordance with EC 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

17. References

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3. Lustgarten, D.L., et al., *His-bundle pacing versus biventricular pacing in cardiac resynchronization therapy patients: A crossover design comparison.* Heart Rhythm, 2015. **12**(7): p. 1548-57.
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7. Vijayaraman, P., et al., *His-Optimized Cardiac Resynchronization Therapy to Maximize Electrical Resynchronization: A Feasibility Study.* Circ Arrhythm Electrophysiol, 2019. **12**(2): p. e006934.
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10. Huang, W., et al., *A Novel Pacing Strategy With Low and Stable Output: Pacing the Left Bundle Branch Immediately Beyond the Conduction Block.* Can J Cardiol, 2017. **33**(12): p. 1736 e1-1736 e3.
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12. Li, X., et al., *Left bundle branch area pacing delivery of cardiac resynchronization therapy and comparison with biventricular pacing.* ESC Heart Fail, 2020. **7**(4): p. 1711-1722.
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.

14. Epstein, A.E., et al., *ACC/AHA/HRS 2008 Guidelines for device-based therapy of cardiac rhythm abnormalities.* Heart Rhythm, 2008. **5**(6): p. e1-62.
15. Sterlinski, M., et al., *In Heart Failure Patients with Left Bundle Branch Block Single Lead MultiSpot Left Ventricular Pacing Does Not Improve Acute Hemodynamic Response To Conventional Biventricular Pacing. A Multicenter Prospective, Interventional, Non-Randomized Study.* PLoS One, 2016. **11**(4): p. e0154024.

18. Appendices

18.1 Informed Consent Template

Patient informed consent form templates will be provided under separate cover.

18.2 Data Collection Elements (Electronic Case Report Forms)

Electronic Case Report Forms for the CSPOT study will be provided under separate cover. Final eCRFs will be provided to sites via the electronic data management system after the site has fulfilled all requirements for database access.

18.3 Participating Investigators and Institutions

A complete list of participating investigators and institutions (including names, titles/professional positions, address(es), and telephone numbers) where study activities will be conducted will be distributed under a separate cover when available. Approval of the CSPOT Study CIP will be documented by signing the Clinical Trial Agreement or a separate investigator agreement.

18.4 IRB Committee List

A complete list of participating IRBs and the Chairperson(s) will be provided under separate cover. This information will be updated throughout the course of the study. The updated list will be maintained at Medtronic and will be available upon request.

18.5 Committees

The CSPOT study will utilize an Event Adjudication Committee (CEC) for the assessment of all procedure and system related AEs, All SAEs, Cardiovascular related AEs and AEs with a fatal outcome.

The CSPOT study may utilize a Publication Committee aiming to manage study publications.

A Data Monitoring Committee (DMC) is not needed for this study. This decision was made based on the following criteria: it is felt there are no additional benefits of a DMC reviewing the data in addition to the Event Adjudication Committee (CEC)

The updated member lists will be maintained at Medtronic and will be made available upon request.

18.6 Labeling

Labeling for the CSPOT investigational components will be provided under separate cover. Labeling for all system components used in this study can be found with each package insert and/or will be available on http://manuals.medtronic.com.

18.7 Foreseeable Adverse Events List (FAL)

The information provided in this section pertains to foreseeable adverse events that may be observed in the CSPOT Feasibility Study and may collectively assist in identifying those events for a given device or therapy that are unexpected in nature. The foreseeable adverse events information consists of three parts: 1) observed adverse system effect(s) in comparable Medtronic studies, 2) adverse events reported in published literature, and3) additional foreseeable adverse events. An evaluation of potentially anticipated events observed in previous clinical studies and reported events in literature may be used in combination with device labeling, manuals, current event reporting information, and other published data to assess for an unexpected occurrence.

The implementation of the CSPOT Research System involves surgery, therefore, standard adverse events associated with a surgical procedure may be experienced (e.g., anesthesia complications, injury, infections, bleeding, exacerbation of pre-existing conditions, healing complications, etc.). However, the focus of this section is to address in more detail, those events that are foreseeable due to the implementation, use, performance, and/or presence of the system under investigation.

Potential risks associated with the implementation of the CSPOT Research System as well as risk minimization are discussed within Section 11.1 and 11.2. Treatment required for procedure and/or system related adverse events may include medication, system reprogramming, system modification (e.g., repositioning, surgical abandonment, surgical removal), or other surgical and medical remedies.

18.7.1 Observed Adverse System Effects in Previous Clinical Studies and Adverse Events Reported in Literature

The CSPOT Research System has not been used previously in a clinical study. Preclinical testing has been performed using the CSPOT Research System, including design verification testing, design validation testing and a hazard analysis. Review/analysis activities included confirmation of appropriate content in the labelling and specifications of individual components. Benchtop testing activities included checking the connections, use and performance of the individual components into a functional system. No adverse effects or malfunctioning were discovered.

The CSPOT Research System facilitates the interconnection between pacing devices and permanently implanted leads targeting selected pacing locations in the patient's right and/or left ventricle. It increases the safety of the patient while undergoing the procedure and determines the CSPOT timing-intervals used for the chronic study. A comparable setup has been used in previous MDT studies without any pacing delivery complications (iSPOT study: Clinical Trial Registration:

NTC01883141 and SYNSEQ study: Clinical Trial Registration: NTC 02914457). In total 62 patients were included with successful protocol execution and data collection. [15]

Foreseeable or potential adverse events and patient complications associated with the acute use of the implanted system the implementation or use of the CSPOT Research System have been identified through the hazard analysis. The hazard analysis is composed of a review of previous MDT studies and literature to compile the estimation of harm for the foreseeable adverse events. The CSPOT Research System Hazard Analysis Log – D00329642_C. provides an overview of additional foreseeable events, mitigations, conservative estimates of incidence rates, hazardous situations, derived from adverse event data from previous Medtronic clinical studies and literature around the components/use of the CSPOT system.

19. Version History

Version	Summary of changes	Justification of changes	Potential impact of the change on performance, effectiveness, or safety or other endpoints	Identification of the affected study documents	Author(s)/Title
1.0	N/A - First Version release	N/A	N/A	N/A	Rachael Rose, Pr Clinical Research Specialist Richard Cornelussen, Pr. Scientist Robert Stadler, Sr. Distinguished Scientist

Version	Summary of changes	Justification of changes	Potential impact of the change on performance, effectiveness, or safety or other endpoints	Identification of the affected study documents	Author(s)/Title
2.0	Updated language to section 11.1: • The protocol procedures may take up to 90 minutes longer than the standard CRT procedure time which includes up to 10 minutes of additional fluoroscopy exposure. • The lead implant configurations for this study are considered investigational and have not been studied for MRI use. Therefore, the MRI conditional labeling will not apply for these patients. Updates in Section 4.1: • His Pacing updated to His Bundle Pacing • CV+LV updated to CSP +LV Deletion in 10.4 of the language: (or the subject's authorized/designated representative or guardian) Table 5: updated Component column to reflect Medtronic Defibrillation Leads in respect to the RV defib leads Table 6 (also reflective in section 3 Synopsis): Implant (occur within 30 days prior to enrollment) update to Implant (occur within 30 days after to enrollment)	• Clarification to describe in more detail protocol procedure time and additional risk for lead implant configurations • Grammatical and language updates needed for consistency.	N/A	Master Informed Consent Template V1 dated 8-Mar-2021	Rachael Rose, Pr CRS Richard Cornelussen, Pr. Scientist Robert Stadler, Sr. Distinguished Scientist

Version	Summary of changes	Justification of changes	Potential impact of the change on performance, effectiveness, or safety or other endpoints	Identification of the affected study documents	Author(s)/Title
3.0	• Increase number of sites from 8 to 12 • Updated language in Exclusion criteria to: Subject has complex or repaired congenital heart disease	Allow for the study to include more sites if needed to meet total number of patients within the study timeframe Updating exclusion criteria for better clarification	N/A	N/A	Rachael Rose, Pr Clinical Research Specialist Richard Cornelussen, Pr. Scientist Robert Stadler, Sr. Distinguished Scientist

4.0	• Updated Secondary Objectives to measure improvement relative to baseline • Update to language in Section 10.6.2 and Table 7 for final device programming of the CSPOT configuration. Updates allow for physician discretion in final device programming and allow for the best LVcs electrode that was used during the acute testing to also be used for chronic programming unless phrenic nerve stimulation, lead dislodgement or high capture threshold occur • Updates to methods for statistical analysis in Section 14.4 and 14.5 to Primary objectives 1 & 2 as well as secondary objectives 1, 2, & 5	• Aligns with method for statistical analysis • Adjustment created for flexibility to ensure continued patient safety • Aligns more with the study statistical analysis plan	N/A	N/A	Rachael Rose, Pr Clinical Research Specialist Richard Cornelussen, Pr. Scientist Robert Stadler, Sr. Distinguished Scientist Patrick Zimmerman, Pr. Statistician