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Alleviating Pain · Restoring Health · Extending Life

SYNSEQ study

Left Ventricular Synchronous versus Sequential MultiSpot Pacing for CRT

Clinical Investigation Plan

Version 1.0

22 Oct 2015

Sponsor
Bakken Research Center BV, Medtronic Endepolsdomein 5 6229 GW Maastricht, The Netherlands

Change History record

CIP Change History		
Version	**Summary of Changes**	**Author**
1.0	Initial version	Laurence Hogge

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A SYNOPSIS

Left Ventricular Synchronous versus Sequential MultiSpot Pacing for CRT SYNSEQ study	
Purpose	The SYNSEQ study intends to assess the positive left ventricular dP/dt max achieved by multipoint LV pacing (either simultaneously or sequentially) in comparison to the response achieved by the current (standard) BiV pacing configuration in patients indicated/recommended for cardiac resynchronization therapy.
Design	This study is a prospective, interventional, non-randomized, multi-center research study.
Medical device	• Pacing system Analyzer 2290 • CareLink Programmer 2090 • Hand-held pacers 5388D or 5392 • Endocardial or transvenous leads (atrial, right ventricular and left ventricular leads) • Guiding catheters ATTAIN or ATTAIN SELECT II • LV pressure wire Millar (825-0101) • Invasive Blood pressure Codan PVB transducer (17.8059) and contact board (75.1068.00) • Electrophysiological catheters and pacing wires: Soloist, TORQR-CS, Map-iT or VisionWire • Surgical connection cables 5114, 5832S, 5833S or 5487 • Adaptor 5103 • Reference lead F7830S or F7832S • Catheter connecting cable 05518SP or 901957 • Motion sensing input device: Kinect camera or similar • Connection box and connectors 09083 The connection box (and its connectors) is investigational. All other products used in the present study (leads and pacing devices) are commercially released (and CE-marked) and used within their intended purpose.
Primary objectives	• Compare the hemodynamic response of a MultiSpot-SYN Left Ventricular pacing configuration (simultaneous LV pacing) to a single spot LV pacing configuration in patients undergoing a research study, an EP exploratory procedure or CRT implant using the contractility parameter positive LV dP/dt max. • Compare the hemodynamic response of a MultiSpot-SEQ Left Ventricular pacing configuration (sequential LV pacing) to a single spot LV pacing configuration in patients undergoing a research study, an EP exploratory procedure or CRT implant using the contractility parameter positive LV dP/dt max.
Secondary objectives	• Compare the positive LV dP/dt max from a MultiSpot-SEQ LV pacing configuration is non-inferior to a MultiSpot-SYN LV pacing configuration. • Correlate the (non)invasive measures (blood pressure, electrocardiographic mapping and RV/LV EGM timings) obtained during the different pacing configurations to the positive LV dP/dt max measures obtained. • Evaluate the (non)invasive measures ability to identify the pacing configuration with the highest positive LV dP/dt max.

Primary endpoint	The contractile ability of LV is characterized by the positive LV dP/dt max. It is a measure of the initial velocity of myocardial contraction and is a derivative of the LV-pressure. LV pressure is measured invasively using a high-fidelity micromanometer catheter inside the LV.
Secondary endpoint	Besides the contractility index, other hemodynamic/electrical parameters will also be used as endpoints. Blood pressure (systolic and diastolic) is measured by invasive arterial blood line connected to a sensitive membrane displacement sensor. Non-invasive blood pressure (systolic/diastolic) is acquired through finger volume clamp. The electrical signals (Q-LV timings, QRS width) are derived from intra-cardiac leads (invasive) and surface electrodes (non-invasive) respectively.
Subject population	Only “difficult” CRT patients are selected in order to adequately address the potential benefit of MultiSpot Pacing in this patient population. The term “difficult” represent those patients with an increased likelihood of non-response to conventional cardiac resynchronization therapy (e.g. ischemic patients or non-LBBB left ventricular dyssynchrony patients). The study will enroll up to 40 subjects who fulfill the eligibility criteria and who have completed the EP study procedure.
Number of sites	The study is expected to be conducted in approximately 10 centers in Europe.
Study duration	It is anticipated that this study will require approximately 12 to 18 months for subject enrollment. Patients’ participation in this study is expected to last approximately between 1 day and 3 months, depending on the time between enrollment and the EP study and the duration of hospital stay after the research study, or EP related procedure, or the CRT-implant. Subjects will be exited from the study just before the moment of hospital discharge. There will be no further follow-up required for subjects that are exited from the study.
Inclusion criteria	• Subject is indicated or recommended for CRT-P or CRT-D device according to current applicable ESC/AHA guidelines • Subject is in sinus rhythm • Subject receives optimal heart failure oral medical therapy • Subject is willing to sign the informed consent form • Subject is 18 years or older
Exclusion criteria	• Subject has permanent atrial fibrillation/flutter or tachycardia • Subject has pure right bundle branch block (= no additional left ventricular conduction delays) • Subject has left bundle branch block **and** QRS-duration of > 150 ms **and** no sign of myocardial scar indicated by late gadolinium enhancement MRI • Subject experienced recent myocardial infarction, 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 left ventricular assist device • Subject has severe renal disease (up to physicians discretion) • Subject is on continuous or uninterrupted infusion (inotropic) therapy for heart failure (≥ 2 stable infusions per week)

	• Subject has severe aortic stenosis (with a valve area of <1.0 cm^2 or significant valve disease expected to be operated within study period) • Subject has complex and uncorrected congenital heart disease • Subject has a mechanical heart valve • Pregnant or breastfeeding women, or women of child bearing potential and who are not on a reliable form of birth control • Subject is enrolled in another study that could confound the results of this study, without documented pre-approval from Medtronic study manager
Clinical Procedures	**Enrollment:** A subject is enrolled in the study when he/she signs and dates the Patient Informed Consent. **Baseline:** • Verification of all inclusion and all exclusion criteria • Enrollment • Demographics (age, gender) • Physical examination (height, weight, heart rate, blood pressure) • Left ventricular ejection fraction (within last 3 months, otherwise a new measurement should be performed) • Multi-lead ECG (within last 3 months, otherwise a new ECG should be performed) • Echocardiographic evaluation (if available within last 3 months, otherwise not collected) • NYHA classification • Medical history (cardiovascular or related) • Cardiovascular medications • Pregnancy test for women with child-bearing potential • Magnetic Resonance Imaging (MRI) to identify the location and transmurality of any myocardial scar. If the patient has a LBBB conduction pattern and QRS-width above 150ms, the MRI images should be analyzed to quantify the presence of scar. If no scar is present (as indicated by gadolinium enhancement), the patient should not be included in the study. **EP visit:** The EP study visit should take place within 3 months after the MRI has been obtained. The following LV pacing configurations will be evaluated: **Biventricular pacing (BiV)** Pacing will be performed on one LV electrode pair, (at 3 different longitudinal locations), and on the tip of the RV-lead. In total, three different pacing BiV settings will be evaluated. Configuration 1: RV + LV lateral Apex Configuration 2: RV + LV lateral Mid Configuration 3: RV + LV lateral Base **(Reference: Standard CRT)** **MultiSpot simultaneous LV-ventricular pacing (MultiSpot-SYN)** Pacing will be performed on 3 electrodes on the LV wall, placed at different longitudinal locations, and on the tip of the RV-lead simultaneously.

Configuration 4: RV + LV lateral Apex + LV lateral Mid + LV lateral Base

MultiSpot sequential LV-ventricular pacing (MultiSpot-SEQ)

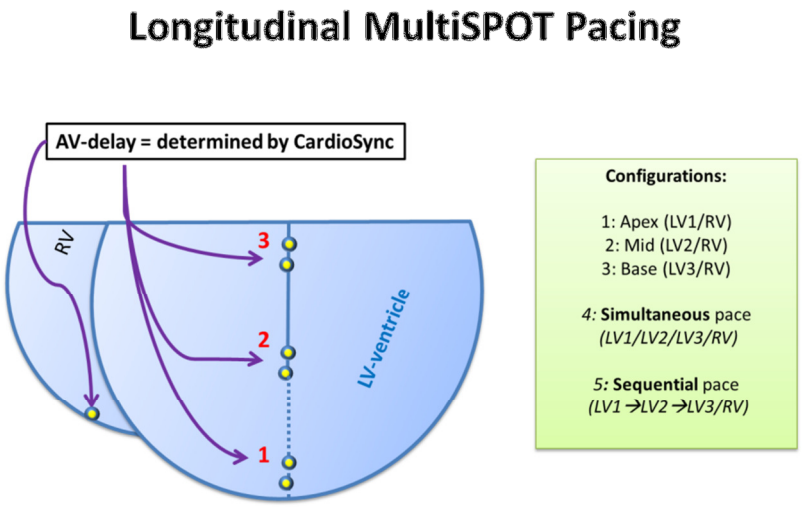
3 electrodes on the LV wall will be paced sequentially. The RV-electrode will be paced simultaneously with last paced LV-electrode. The timing-sequence and the amount of spots will depend on the electrical delays measured during the experiments.

Configuration 5: LV lateral Apex → LV lateral Mid → LV lateral Base + RV

The protocol procedures will result in an additional 30 to 45 minutes to the standard procedure time, and up to an additional 10 minutes to the fluoroscopy exposure. Once the configurations have been evaluated the investigational procedures will end and the EP/CRT-implant-procedure will continue as per standard practice.

Non-invasive sensor data include the measurements of arterial pressure performed from the finger volume clamp and the surface ECG.

Invasive sensor data will be derived from the electrocardiogram timing, i.e. the electrical delay between the RV and different LV sites from the implanted leads/catheters. Invasive blood pressure will also be collected.



B GENERAL INFORMATION

B.1 Introduction

Cardiac Resynchronization Therapy (CRT) has been one of the most important advancements in the past decade for patients with systolic heart failure (HF) and a wide QRS. Several clinical trials have shown improvements in mortality, exercise capacity, clinical symptoms, and quality of life [1, 2]. However, a considerable amount of CRT patients show only limited benefit from the therapy [3]. Multiple reasons for a low responder rate have been proposed, such as underlying HF severity and etiology, suboptimal device

programming, inadequate viable myocardium, lack of baseline dyssynchrony, and non-optimal Left Ventricular (LV) lead position [4].

Recent efforts to increase the responder rate is to pace from multiple sites on the left ventricle (LV). Multi-site pacing can be achieved either by stimulating on a second LV lead or right ventricular (RV) lead or by stimulating additional electrodes on one lead (e.g. Quadripolar system). The use of one-lead with multiple electrodes stimulated has recently been investigated in more detail with regard to improving (hemodynamic) response in CRT patients. The results are inconclusive. Several studies have shown acute hemodynamic benefit from multipoint pacing [5-7] while others have failed or only showed marginal benefit (own data (iSPOT-study) and [8-10]). It might be that the current inter-electrode distance or the sequence of RV and LV activation is suboptimal.

It is shown that besides synchrony the sequence of electrical/mechanical activation is a major determinant of cardiac function. Activating the LV lateral wall first (before septum and RV lateral wall) prevents paradoxical movement of the septum initiated by RV-pacing. In addition, a physiological apex-to-base sequence of activation is induced by LV apical pacing in children, which results in synchronous electrical activation and contraction at the circumferential level of the LV [11]. Moreover, LV apical pacing preserved septal to lateral LV synchrony and systolic function, as well as maintaining cardiac function at a normal level [12, 13].

More studies have shown the possible mechanisms involved in proper sequence of cardiac stimulation [15, 16]. The relative contribution of these different cardiac properties (like torsion, vortex and different strains) in hemodynamic function in the heart failure patient is unknown although it seems intuitive to mimic the physiological propagation of electrical conduction.

LV sequential pace has now become more easily achievable with the new Quadripolar LV lead systems. The use of one-lead with multiple paced electrodes (i.e. MultiSpot or MultiPoint) to improve CRT-response has recently been investigated in more detail. The overall outcome of these studies is difficult to interpret scientifically. Some studies have failed to prove additional benefit [8, 17] while others show acute benefit but are difficult to interpret because of their methodology, like using non-optimal atrioventricular (AV)-delays [6, 7, 9, 18]. Other studies show only borderline but significant better hemodynamic response to multipoint pacing than to standard biventricular (BiV) pacing [10].

The inconclusiveness might be attributed to the patient population. In a recent study of multisite pacing in humans it was shown that MultiSpot pacing had no incremental hemodynamic effect in responders to CRT with strict criteria for left bundle branch block (LBBB) [19]. However, in hemodynamic non-responders who did not have strict LBBB there was a significant hemodynamic benefit with multisite pacing. These findings are in keeping with the iSPOT study in that all the patients studied had LBBB. It is possible that multisite pacing may have a role but for patients with non-strict LBBB.

The SYNSEQ study intends to assess the positive LV dP/dt max achieved by multiple LV pacing either simultaneously or sequentially in comparison to the response achieved by the current (standard) BiV pacing configuration. The protocol includes rigorous methodology to decrease measurement variability and to be patient-tailored (e.g. AV-delay) in order to provide a justified conclusion to the acute hemodynamic benefit of MultiSpot Pacing (MSP) [20]. In addition, only “difficult” CRT patients are selected in order to adequately address the potential benefit of MSP in this patient population. The term “difficult” represent those patients with an increased likelihood of non-response to conventional CRT (e.g. ischemic patients or non-LBBB LV dyssynchrony patients). In addition to the hemodynamic evaluation, electrical parameters such as Q-LV/RV timing and QRS-width will be measured.

The study will also evaluate the feasibility of non-invasive sensors to assist with optimal lead placement and pacing sequence. Additionally, it is anticipated that this study will provide data that can be used to design future studies.

For further literature review, pre-clinical testing and previous clinical experience please refer to the Investigator's Brochure.

B.2 Device information

B.2.1 Pacing devices

In order to deliver pacing on 4 different regions on the heart a system was developed which consists of a "master" pacer and four "slaves" pacers (Figure 1 and Table 1).

The master pacer is the 2290 analyzer (in the 2090 Programmer) which will be used to pace the right atrium (RA). The other pacing output (i.e. the ventricular) of the 2290 analyzer will be used as an atrial input for the up to four "slaves". The "slaves" are used to pace the right ventricle (RV) and the three LV electrodes. The master pacer can be used to adjust AV-delay for all "slaves". The "slaves" are hand-held pacers (Medtronic model number: 5388 DDD or 5392) and can be programmed independently. In this study the "slaves" will be programmed to specific settings before start of the experimental protocol. During the entire protocol the "slaves" will be either turned "on" or "off". No additional intra-protocol settings will be changed. Benchmark testing performed has found that upon pacing, i.e using all four "slaves" the delay between them was ~1 ms (range 0-2 ms).

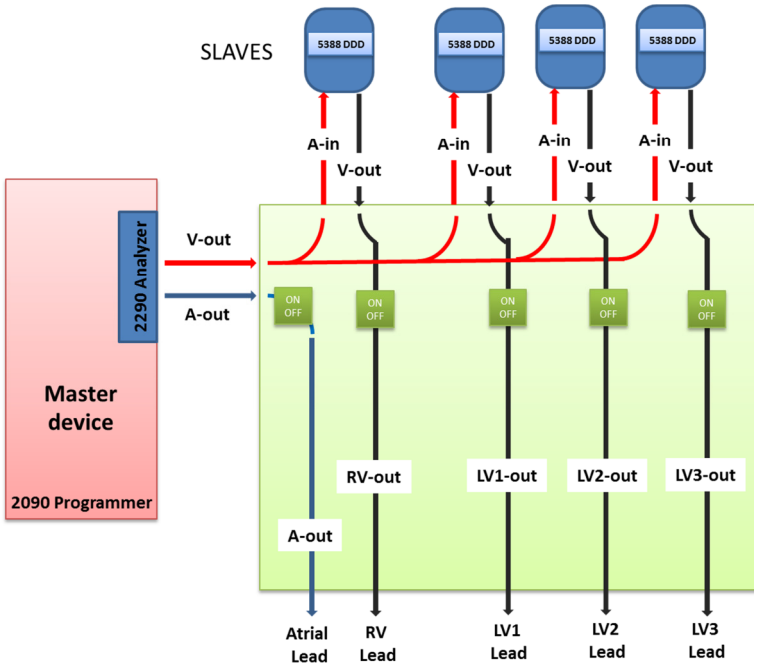


***Figure 1: SYNSEQ equipment set-up**. Green depicts the connection box.*

B.2.2 Leads and electrophysiological catheters

Only commercial market released leads and EP catheters will be used within their intended use to test the feasibility of MSP simultaneous or sequential pacing for increased acute hemodynamic response to CRT.

In this study we will use Medtronic or other commercially available intra-cardiac electrode catheters for the delivery of MSP pacing (see Table 1). These catheters are designed for recording intracardiac electrograms and temporary pacing associated with EP studies (Figure 2). For adequate delivery of these EP-catheters into the coronary veins specially designed Medtronic tools can be used (ATTAIN SELECT II and ATTAIN). For the part of

the study which requires two separate leads/catheters, standard Medtronic over-the-wire passive leads will be used (e.g. 4196) in addition to the possible replacement from a lateral position to a more anterior or posterior position of the EP-catheters.

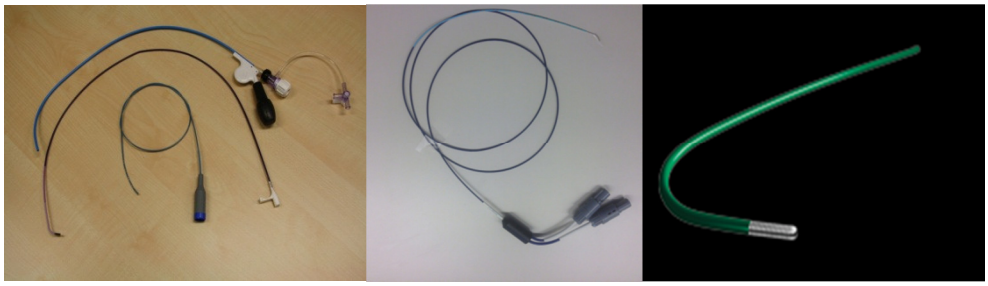


Figure 2: MultiSpot electrophysiological catheters. *Left to right: TORQR-CS, MAP-iT Duo-Decapolar and VisionWire.*

B.2.3 Acquisition system

All data–acquisition will be done using a multi-channel ambulatory system for (electro)-physiological research (porti-system by TMSI or CardioTek EP-tracer system). It will be possible to time-aligned acquire all parameters measured in the study. This includes up to 7 bipolar or unipolar electrograms (EGMs), a 12-lead electrocardiograms (ECG) and up to 3 pressure signals. After a recording is ended the PC reads out the memory card, making the measurement data available for further analysis. During the entire experimental protocol, the following will be measured continuously:

- Unipolar/bipolar EGMs for all the different leads in the heart (if not paced)
- Ventricular pressure (using a left ventricular Millar pressure catheter)
- Multi-lead ECG
- (Optional) Non-invasive blood pressure (using finger volume clamp)
- Invasive blood pressure (through an arterial access line available because of LV pressure measurement)

The devices that will be involved in the conduct of this study are listed in Table 1. Medtronic may incorporate additional Medtronic devices, programmers, software and accessories into this clinical study as they receive appropriate license or regulatory approval or/and are commercially released by Medtronic, providing the scientific soundness of the study is not adversely affected.

Table 1: Devices and accessories		
Component	**Model Number (or latest Medtronic or other company release)**	**Investigational or commercially released**
Pacing system Analyzer (Medtronic)	2290	Commercially Released
CareLink® Programmer (Medtronic)	2090	Commercially Released
Hand-held pacers (Medtronic)	5388 DDD or 5392	Commercially Released
Leads Endocardial or transvenous leads (Medtronic or other company)	Atrial lead RV lead LV lead	Commercially Released
Guiding catheters (Medtronic)	ATTAIN (all available) ATTAIN SELECT II (all available)	Commercially Released
LV pressure wire (Millar Instruments)	Millar (825-0101) or similar	Commercially Released
Invasive Blood pressure (Codan)	Codan PVB transducer (17.8059) and contact board (75.1068.00) or similar	Commercially Released
EP catheters and pacing wires (Medtronic) (AP technologies)	Soloist (all available) TORQR-CS (all available) Map-iT (903256)	Commercially Released

Table 1: Devices and accessories		
(Biotronik)	VisionWire or similar	
Surgical connection cables (Medtronic)	5114, 5832S 5833S, 5487	Commercially Released
Adaptor (Medtronic)	5103	Commercially Released
Reference lead (Fiab)	Recommended: F7830S F7832S	Commercially Released
Catheter connecting cable (Medtronic) (AP Technologies) (Millar)	 05518SP 901957 TEC-10D	Commercially Released
Motion sensing input device	Kinect camera or similar	Commercially Released
External computerized electrophysiology measurement system TMSi porti (Twente Medical Systems Enschede NL) or Cardiotek EPTracer38 (Schwarzer Germany Cardiotek)	TMSi porti: porti7-16e12b4at Cardiotek: 00SYS01	Commercially Released
Connection Box and connectors (Medtronic)	09083	Investigational

The connection box and its connectors are investigational. All other products used in the present study (leads and pacing devices) are commercially released (and CE-marked) and used within their intended purpose.

More detail on the basic components of the system:

The **Medtronic Analyzer 2290** is intended for use by a clinician to analyze the pacing and sensing performance of the cardiac lead system during the implant of a cardiac arrhythmia management device, or during invasive troubleshooting of a cardiac lead system.

The **Medtronic or competitor catheters** are intended for use in diagnostic EP procedures. The catheter is designed for recording intracardiac EGMs and temporary pacing associated with EP studies.

The **Medtronic Model 5388 DDD or 5392** hand-held pacemaker is a dual chamber temporary pacemaker. A dual pacemaker has the ability to sense and pace in both chambers of the heart.

Reference lead (recommended F7830S and F7832S): Extension cable for threshold analysis for permanent or temporary cardiac pacing

Catheter connecting cable (05518SP and 901957) is used during EP studies to connect electrode catheter to ECG recording/stimulation equipment.

LV Pressure wire (825-0101): The Mikro-Cath is a single-use cardiovascular catheter intended to be used for medical research and diagnostic purposes. The catheter is used to measure hemodynamic cardiac pressures in the human body to allow physicians to better understand cardiac performance.

Invasive blood pressure monitoring (DPT9003): The sample line of the sheath used to guide the LV pressure wire is connected to the xtrans pressure transducer.

The motion sensing camera is used to visualize the 3-dimension location of the 12-lead ECG on the thorax. The 3-dimensional information of the ECG electrodes is needed to obtain reliable estimates of the ventricular activation (e.g. ventricular activation isochrones) by solving the inverse ECG problem. The total image recording time of the chest area approximates 30 seconds.

The Cardiotek EPTracer38 system is a computerized electrophysiology measurement system with CE Mark and designed for both regular and experimental electrophysiology (EP) studies. An EPTracer system consists of an EPTracer unit and a Personal Computer. The EPTracer unit is connected to the computer by an USB cable. The EPTracer unit contains a two-channel stimulator and a multi-channel amplifier which can replace and is similar in function as the Medtronic analyzer. The system is used to display the electrocardiogram (ECG) traces and to inspect, command and control the EPTracer unit. EPTracer38 provides the acquisition of the 12 lead Surface ECG, 20 intracardiac channels and 6 auxiliary channels. Cardiotek EPTracer38 will be used in the SYNSEQ study as the master-pacer and acquisition system.

The Model 09083 Connection Box:

The Medtronic Model 09083 Connection Box connects pacing electrodes or temporary stimulation electrodes to external pacemakers during the pre-implant EP testing procedure. The connection box allows easy, flexible and safe connection of pacing electrodes to external stimulators, while simultaneously offering the possibility to feed ECG signals obtained from the pacing electrodes into an EP monitoring and recording system. The connection box contains six channels. Each channel can be individually switched on or off,

connecting the stimulator to the connected pacing electrode, as needed. Each of the six channels can be switched to unipolar of bipolar cardiac stimulation independently.

The connection box has been designed to facilitate connection during the EP pre-implant testing procedure, when multiple electrodes are used. The connection box improves the management of the intervention and helps thereby to minimize the prolongation of the procedure and improve safety. Additionally the connection box helps to minimize the likelihood of arrhythmias as a result of setups.

The connection box is designed such that the setup is intuitive. Connections to the monitoring system are located on one side, all connections to external pacemakers are located at another side of the box, and all connections towards the stimulation electrodes are located at a third site of the device. All switches are placed on the top of the device. Switches are consistently physically linked to the switched stimulation channel, connecting an external stimulator and a stimulation electrode.

All the recommended devices connecting to the connection box have CE-mark with clear defined functionality and electrical standards. Inserting the connection box into the electrical pathway does not significantly change the electrical characteristics (impedance, capacitance) of the pacing system.

The connection box will be accompanied with cabling to connect to recommended Medtronic equipment. The box nor its pacing connection cables are in direct contact with the patient, or will be in the sterile patient field, and do not need to be sterilized.

The intended use of the connection box is to facilitate, the CRT pre-implant physiological testing procedure, involving multiple cardiac stimulation sites in the right and/or LV. The box facilitates the interconnection between pacing devices and selected pacing locations in the patient's right and/or LV. It increases the safety of the patient while undergoing the procedure and will only indirectly (through a specific clinical protocol) aid in the diagnosis. The device is reusable, non-invasive, non-sterile box with no direct contact to the patient. The box will not be used in a magnetic resonance imaging (MRI) environment.

The connection box has been used in a previous study without any complications (iSPOT-study: **Clinical Trial Registration: NTC01883141**). In total 31 patients were included with successful therapy delivery and data collection. A similar protocol as was done in the iSPOT-study will be investigated in this study.

The non-CE marked devices will be labeled 'exclusively for clinical investigations' and labelling will be in English (unless otherwise required for local regulations).

For all other CE marked products the manual can be used for review and labeling is available in local languages.

B.3 Comparator information

This study does not involve any comparators.

C STUDY PLAN

C.1 Study objectives

The SYNSEQ study intends to assess the positive LV dP/dt max achieved by multipoint LV pacing (either simultaneously or sequentially) in comparison to the response achieved by the current (standard) BiV pacing configuration in patients indicated/recommended for CRT. The protocol includes rigorous methodology to decrease measurement variability and to be patient-tailored (e.g. AV-delay) in order to provide a justified conclusion to the acute hemodynamic benefit of MSP [20]. In addition, only "difficult" CRT patients are selected in order to adequately address the potential benefit of MSP in this patient population. The term "difficult" represent those patients with an increased likelihood of non-response to conventional CRT (e.g. ischemic patients or non-LBBB LV dyssynchrony patients). In addition to the hemodynamic evaluation, electrical parameters such as Q-LV/RV timing and QRS-width will be measured.

The study will also evaluate the feasibility of non-invasive sensors to assist with optimal lead placement and pacing sequence. Additionally, it is anticipated that this study will provide data that can be used to design future studies.

C.1.1 Primary objectives

C.1.1.1 Primary objective 1

Compare the hemodynamic response of a MultiSpot-SYN Left Ventricular pacing configuration (simultaneous LV pacing) to a single spot LV pacing configuration in patients undergoing a research study, an EP exploratory procedure or CRT implant using the contractility parameter positive LV dP/dt max.

C.1.1.2 Primary objective 2

Compare the hemodynamic response of a MultiSpot-SEQ Left Ventricular pacing configuration (sequential LV pacing) to a single spot LV pacing configuration in patients undergoing a research study, an EP exploratory procedure or CRT implant using the contractility parameter positive LV dP/dt max.

C.1.2 Secondary objectives

C.1.2.1 Secondary objective 1

Compare the positive LV dP/dt max from a MultiSpot-SEQ LV pacing configuration to a MultiSpot-SYN LV pacing configuration in patients undergoing a research study, an EP exploratory procedure or CRT-implant using the contractility parameter positive LV dP/dt max.

C.1.2.2 Secondary objective 2

Correlate the (non)invasive measures (blood pressure, electrocardiographic mapping and RV/LV EGM timings and QRS width) obtained during the different pacing configurations to the positive LV dP/dt max measures obtained.

C.1.2.3 Secondary objective 3

Evaluate the (non)invasive measures ability to identify the pacing configuration with the highest positive LV dP/dt max

C.2 Clinical endpoints

C.2.1 Primary endpoints

The contractile ability of LV is characterized by +dP/dt max of LV. It is a measure of the initial velocity of myocardial contraction and is a derivative of the LV-pressure. Left ventricular pressure is measured invasively using a high-fidelity micromanometer catheter inside the LV. The primary endpoint for primary objectives 1 and 2 and secondary objective 1 will be the % change LV dP/dt max from baseline (AAI setting).

C.2.2 Secondary endpoints

Besides the contractility index, other hemodynamic/electrical parameters will also be used as endpoints. Blood pressure (systolic and diastolic) is measured by invasive arterial blood line connected to a sensitive membrane displacement sensor. Non-invasive blood pressure (systolic and diastolic) is acquired through finger volume clamp. The electrical signals (Q-LV timings, QRS width) are derived from intra-cardiac leads (invasive) and surface electrodes (non-invasive) respectively.

In summary, the following secondary endpoints might be determined:

- Invasively measured systolic blood pressure
- Invasively measured diastolic blood pressure
- Non-invasively measured systolic blood pressure
- Non-invasively measured diastolic blood pressure
- Q-LV timings
- QRS width
- RV/LV timings

All the mentioned secondary endpoints will be used to calculate the pairwise correlation with the contractility endpoint (+LV dP/dt max) acquired during the different configurations.

C.3 Study hypothesis

- It is hypothesized that MultiSpot pacing simultaneously is superior to BiV pacing
- It is hypothesized that MultiSpot pacing sequentially (from apex to mid and then to base) is superior to BiV pacing
- It is hypothesized that MultiSpot pacing sequentially (from apex to mid and then to base) is non-inferior to MultiSpot pacing simultaneously.

Hypothesis testing will be performed at significance level of 0.05 expect for non-inferiority testing which will be performed at a significance level of 0.025. Statistical hypotheses are further described in section H.1

C.4 Study population

Subjects indicated or recommended for a CRT-P or CRT-D device (according to the current applicable ESC/AHA guidelines) are potential subjects for this study. Only “difficult” CRT patients are selected in order to adequately address the potential benefit of MSP in this patient population. The term “difficult” represent those patients with an increased likelihood of non-response to conventional CRT. They should be 18 or older, they should receive optimal heart failure oral medical therapy and they should be in stable sinus rhythm at the time of the EP visit. Subjects must meet all of the inclusion criteria and none of the exclusion criteria to be included in the study. There is no control group in this study. Since all configurations are planned to be measured longitudinally within each subject, subjects will serve as their own control.

C.5 Study design

This clinical trial is a prospective, interventional, non-randomized, multi-center research study designed to assess augmentation of contractility as measured by positive LV dP/dt max across LV pacing site(s) in patients indicated/recommended for CRT.

Therefore, the force of contraction during MultiSpot simultaneous or MultiSpot sequential pacing is compared to standard BiV pacing. Standard BiV pacing is defined as pacing from a (postero-) laterally placed lead with the electrode between the base and mid position of the LV with individually optimized AV delay and a VV-delay of zero or 20 or 40 ms.

In addition, the feasibility of (non)invasive sensors to identify site(s) of maximal positive dP/dt max values is assessed. Rationale for the study design is to aim for maximizing the acute hemodynamic response on a per patient basis in a patient population which is known to be more at risk for less response to conventional CRT.

The sample size calculation is based on the primary objective 1 and the primary endpoint, i.e.% change LV dP/dt max from baseline (AAI setting). More details can be found in Section C.7.

C.5.1 Minimization of bias

Potential sources of bias in this study may result from selection of subjects, treatment of subjects, and evaluation of study data. Methods incorporated in the study design to minimize potential bias include but are not limited to:

- Subjects will be their own control, and study measurements have been designed to minimize the impact of within-subject temporal variation.
- Subjects will be screened to confirm eligibility for enrollment with defined inclusion/exclusion criteria prior to enrollment
- Subject demographics will be collected at the enrollment visit on possible differences that may affect primary endpoints.
- Data collection requirements and study procedures (such as AV-optimization) will be standardized across all study centers, including identical and calibrated equipment.
- All implanters in the study will be experienced in the placement of LV leads, performing EP procedures, performing LV pressure measurements.
- To ensure a widespread distribution of data between centers, the maximum number of enrolled subjects per center is 15 subjects.
- A Statistical Analysis Plan will be developed prior to analyzing data which will document all pre-specified analyses and analysis methods.
- All study center personnel and Medtronic personnel will be trained on their respective aspects of the study using standardized training materials. All study clinicians will be trained on and required to follow the Clinical Investigational Plan.

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

C.6 Randomization and blinding

No randomization and no blinding are used in this study.

C.7 Sample size

The sample size calculation is based on the primary objective 1. This study is powered to show superiority of MultiSpot SYN pacing to BiV pacing (standard CRT) for the primary endpoint % change + LV dP/dt max from baseline (AAI pacing). Assuming an expected difference in % change between MultiSpot and BiV pacing of 3.5% and standard deviation

of 7%, 34 patients would have 80% power to demonstrate superiority. The total sample size is increased to 40 patients to accommodate for data collection problems during the EP procedure. The following null-hypothesis H_0 and alternative hypothesis H_1 will be evaluated at a significance level of 0.05:

H_0: $\Delta_{MultiSpot}$ SYN - $\Delta_{BiV} \equiv 0\%$
H_1: $\Delta_{MultiSpot}$ SYN - $\Delta_{BiV} \not\equiv 0$ %,

where Δ indicates percentage change from baseline for the corresponding configuration. Previous literature and results from the iSPOT study suggests that the average difference in percentage change between MultiSpot SYN and BiV pacing is 2.5% in a normal HF population (iSPOT-study, [9, 19]). For the standard deviation of the difference in % change between MultiSpot and BiV pacing we assume 7% based on previous literature and the iSPOT study.

Not much literature is available for the difference in % change between MultiSpot and BiV pacing for the study population targeted in this study. This study selects "difficult" CRT patients in order to adequately address the potential benefit of MultiSpot Pacing in this patient population. The term "difficult" represent those patients with an increased likelihood of non-response to conventional cardiac resynchronization therapy (e.g. ischemic patients or non-LBBB left ventricular dyssynchrony patients). Based on few small subgroup analyses (iSPOT study, [19]), we expect that the difference in % change between MultiSpot SYN and BiV pacing will be slightly higher in the targeted study population, namely 3.5%. The sample size calculation is based on this difference of 3.5% and a standard deviation of 7%.

For the second primary objective, previous literature suggests that the average difference in % change LV dP/dt max between MultiSpot SEQ and BiV pacing is 3% ([6, 17]) in a normal HF population. Assuming an increased difference between MultiSpot SEQ pacing and BiV pacing within the targeted study population similar to the increase for the difference between MultiSpot SYN pacing, i.e., 1 %, the expected difference between MultiSpot SEQ pacing and BiV pacing is 4%. Assuming this difference and a standard deviation of 7%, a sample size of 34 patients has 90 % power to demonstrate superiority.

For the secondary objective 1, a power of 80% is achieved with 34 patients. Based on previous research (iSPOT study, [19]), we assume that the lower-border of the 95 % confidence interval for % change MultiSpot SYN to baseline (AAI mode) in the targeted patient population is 12.6. In this study we consider MultiSpot SEQ non-inferior to MultiSpot SYN if the difference in their means is less than a quarter of the difference between MultiSpot SYN pacing and baseline. The non-inferiority margin is thus chosen to be – 3%. Assuming the expected difference in percentage change dP/dt max between MultiSpot SEQ and MultiSpot SYN pacing is 0.5% and a standard deviation in differences of 7%, 34 patients would have 80% power to demonstrate non-inferiority of MultiSpot SEQ to MultiSpot SYN.

C.8 Number of investigation sites and study duration

The study is expected to be conducted in approximately 10 centers in Europe. At the time this Clinical Investigation Plan was finalized, not all participating investigation sites were identified. A list of participating investigation sites and investigators will be available under a separate cover. The study will enroll up to 40 subjects who fulfill the eligibility criteria and who have completed the EP study procedure. It is anticipated that this study will require approximately 12 to 18 months for subject enrollment. Patients' participation in this study is expected to last approximately between 1 day and 3 months, depending on the time between enrollment and the EP study and the duration of hospital stay after this research study, or EP related procedure, or the CRT-implant. Subjects must meet all of the inclusion criteria and none of the exclusion criteria to be included in the study.

There will be no minimum limit that each investigator must enroll. To ensure a widespread distribution of data between centers, the maximum number of enrolled subjects per center is 15 subjects.

D SUBJECT SELECTION

D.1 Inclusion criteria

- Subject is indicated or recommended for CRT-P or CRT-D device according to the current ESC/AHA guidelines
- Subject is in sinus rhythm
- Subject receives optimal heart failure oral medical therapy
- Subject is willing to sign the informed consent form
- Subject is 18 years or older

D.2 Exclusion criteria

- Subject has permanent atrial fibrillation/flutter or tachycardia
- Subject has pure right bundle branch block (= no additional left ventricular conduction delays)
- Subject has left bundle branch block **and** QRS-duration of > 150 ms **and** no sign of myocardial scar indicated by late gadolinium enhancement MRI
- Subject experienced recent myocardial infarction, 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 left ventricular assist device
- Subject has severe renal disease (up to physicians discretion)
- Subject is on continuous or uninterrupted infusion (inotropic) therapy for heart failure (≥ 2 stable infusions per week)
- Subject has severe aortic stenosis (with a valve area of <1.0 cm^2 or significant valve disease expected to be operated within study period)
- Subject has complex and uncorrected congenital heart disease
- Subject has a mechanical heart valve
- Pregnant or breastfeeding women, or women of child bearing potential and who are not on a reliable form of birth control
- Subject is enrolled in another study that could confound the results of this study, without documented pre-approval from Medtronic study manager

E STUDY PREPARATION PROCEDURES

E.1 Investigator/Investigation site selection

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

An investigator/investigation site may be included in the investigation, if the investigator/investigation site complies with the following requirements:

- Investigator is qualified by training, education, and relevant experience appropriate to the use of the product and associated procedures (EP procedures and CRT- pacing)
- The center has adequate resources, facilities and equipment to conduct this trial
- The investigator/center has adequate volume of patients fulfilling the eligibility criteria to meet a monthly enrollment rate of 0.4 patient per month which can be maintained over a period of 12 to 18 months

- Investigator has experience in conducting clinical research trials
- Site has dedicated/qualified trial site team and/or Medtronic personnel available to support, activation, protocol compliance, data collection and record retention requirements
- Site has computer with high speed internet access and Microsoft Internet Explorer available for data entry
- Market released Medtronic programmer (Model 2090), Pacing System Analyzer (Model 2290) and MRI scanner (that has the ability to quantify scar amount) are available at the site for the study
- CRT implant reimbursement for the study patient population is secured

E.1.1 Clinical Investigation Agreement

A Clinical Investigation Agreement shall be in place, signed by the participating investigation site and/or principal investigator of each investigation site, as per the local legal requirements, and returned to Medtronic prior to the commencement of any clinical study activities. The investigator is indicating approval of the Clinical Investigation Plan and subsequent amendments, by a fully executed agreement. Amendments to this Clinical Investigation Plan shall be agreed upon between Medtronic and investigator(s) and be recorded with a justification for the amendments.

E.1.2 Curriculum Vitae

An up to date signed and dated curriculum vitae from each investigator participating in this clinical study, evidencing the required qualifications, including the year and where obtained, and shall include their current position at the investigation site. The signature on the CV must be dated within 3 years prior to the date of activation of the site.

E.2 Ethics

E.2.1 EC approval

Prior to enrolling subjects in this clinical study, each investigation site's EC will be required to approve the current Clinical Investigation Plan, the Patient Information and Informed Consent form, including any other written information to be provided to the subjects and, if applicable, the Investigator's Brochure and materials used to recruit subjects. EC approval of the clinical study must be received in the form of a letter and provided to Medtronic before commencement of the clinical study at an investigation site. The approval letter must contain enough information to identify the version or date of the documents approved. If this information is not contained in the approval letter, it must be retrievable from the corresponding submission letter. In addition, the approval letter needs to be accompanied by an EC roster or letter of compliance, to allow verification that the investigator, other investigation site personnel, and/or Medtronic personnel are not members of the EC. If they are members of the EC, written documentation is required stating that he/she did not participate in the approval process. If the EC imposes any additional requirements (e.g. safety reports, progress reports etc.), Medtronic will prepare the required documents and send them to the investigator for reporting to the EC. Investigators must inform Medtronic of any change in status of EC approval once the investigation site has started enrolment. If any action is taken by an EC with respect to the investigation, that information will be forwarded to Medtronic by the respective investigator.

E.2.2 Informed consent process

The investigator or authorized designee must obtain written informed consent before any clinical study related activity takes place.

Well in advance of the consent discussion, the subject should receive the EC approved Patient Information and Informed Consent Form. During the consent discussion, the investigator or his/her authorized designee must fully inform the patient of all aspects of the clinical study that are relevant to the patient's decision to participate in the clinical study. If a patient is illiterate, an impartial witness must be present during the entire informed

consent discussion. All items addressed in the Patient Information and the Informed Consent Form must be explained. The language used shall be as non-technical as possible and must be understandable to the patient and the impartial witness, where applicable.

The patient must have ample time and opportunity to read and understand the Patient Information and the Informed Consent Form, to inquire about details of the clinical study, and to decide whether or not to participate in the clinical study. All questions about the clinical study should be answered to the satisfaction of the patient.

Neither the investigator, nor the investigation site staff shall coerce or unduly influence a patient to participate or to continue to participate in the clinical study. The informed consent process shall not waive or appear to waive the patient's rights.

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

After all persons have signed and dated the Informed Consent Form, the investigator must provide the subject with a copy of the Patient Information and the signed and dated Informed Consent Form.

E.2.3 Revisions in Patient Information and Informed Consent Form

Medtronic will inform the investigators whenever information becomes available that may be relevant to the subject's confirmed participation in the clinical study. The investigator or his/her authorized designee should inform the subject in a timely manner.

Medtronic will revise the written Patient Information and Informed Consent Form whenever new information becomes available that may be relevant to the subject's confirmed participation in the clinical study. The revised information will be sent to the investigator for approval by the EC. After approval by the EC, a copy of this information must be provided to the participating subjects, and the informed consent process as described above needs to be repeated.

E.2.4 Regulatory notification / approval

In countries where submission to the regulatory authority is required per local law, no patients will be enrolled in the clinical study until the particular regulatory authority has approved the current Clinical Investigation Plan of the clinical study and other documents as required according to the local requirements.

E.3 Regulatory compliance

The SYNSEQ clinical study is a prospective, interventional, non-randomized, multi-center research study.

This clinical study will be conducted in compliance with the latest version of the Declaration of Helsinki, Good Clinical Practices (GCP), laws and regulations of the country/ies in which the clinical study is conducted, including data protection laws, the Clinical Investigation Agreement and the Clinical Investigation Plan.

All principles of the Declaration of Helsinki have been implemented in this clinical study by means of the patient informed consent process, EC approval, clinical study training, clinical trial registration, preclinical testing, risk benefit assessment, publication policy, etc.

The study was designed to reflect the good clinical practice principles outlined in ISO 14155:2011 (so the study is not fully ISO 14155:2011 compliant). 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.

Prior approval of the CIP and any subsequent amendments is required from the following groups prior to any study procedures at a study center: Medtronic, geography-specific

regulatory authorities (if regulatory approval or notification is required) and an independent medical ethics committee or institutional review board.

The legally incompetent persons are not going to be included in the study.

If the regulatory authority imposes any additional requirements (e.g. safety reports, progress reports etc.), Medtronic will prepare the required documents and send them to the respective authority.

E.4 Training requirements

Prior to investigation site activation or subsequent involvement in clinical study activities, Medtronic will provide clinical study training relevant and pertinent to the involvement of personnel conducting clinical study activities and investigator responsibilities.

Training will be given as a minimum on the CIP, the PIC process, the use of data collection tools, applicable local regulations, as well as device training are required. Study-specific training will be documented prior to investigation site activation.

Investigator and/or study coordinator meeting(s) or conference call(s) may be held to discuss the CIP, provide training, discuss study results, etc. Continued training may occur through interim meetings or conference calls to discuss relevant study issues.

Trained clinical site personnel can provide training to other site study personnel on study documents and procedures.

E.5 Study materials and study-specific equipment

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

- Computer with high speed internet access and Microsoft Internet Explorer available for data entry
- Market released Medtronic programmer (Model 2090)
- Pacing System Analyzer (Model 2290)
- MRI scanner (that has the ability to quantify scar amount)

It is preferable that the following study equipment is available at a center to support study activities:

- Non-invasive beat-to-beat blood pressure monitor (such as Finapres, Finapres Medical Systems, Amsterdam, the Netherlands; Nexfin, Bmeye, Amsterdam, the Netherlands, or similar).

All study equipment must be properly maintained and calibrated if required. Programmer calibration and maintenance will be performed at the Medtronic office in Heerlen, the Netherlands. Only calibrated programmers may be used. Centers are responsible for maintaining and calibrating other equipment not provided by Medtronic and used in the course of this study in accordance with established center practice.

Each investigational site will be provided with study materials (e.g. Investigator Site File and electronic Case Report Forms access).

E.6 Study device/product traceability

The connection box and its connectors are investigational.

All other products used in the present study (leads and pacing devices) are commercially released (and CE-marked) and used within their intended purpose. Therefore, no accountability is needed for these products.

E.6.1 Supply of investigational devices

Medtronic will only allow shipment of investigational devices/products to the investigation site or investigator, after the Clinical Study Manager has declared the investigation site ready to start the clinical study.

The connection box can only be sent/brought to a center by Medtronic personnel for use during the EP study visit. Medtronic personnel will take the connection box back to Medtronic after completion of the EP study visit.

E.6.2 Storage and handling of investigational devices

Investigational devices/products must be stored in a secured area. The method of storage shall prevent the use of investigational devices/products for other applications than mentioned in this Clinical Investigation Plan. The connection box will be used only in the study according to the CIP.

E.6.3 Device explant and return procedures

Medtronic personnel will take the connection box back to Medtronic after completion of the EP study visit. The connection box will remain in the possession of Medtronic personnel and will not be stored at the site between EP study visits.

The connection box will be traced during the clinical study. The investigator is responsible for maintenance of a Device Tracking Log in the Investigator Site File. The distribution logs are provided to the center and will be used for tracking the presence of a connection box at the site by assignment of serial numbers. The logs will contain the date of receipt, the name of person who receives it, the date of use, the subject ID of the subjects paced with the connection box, the date of return and the name of the person who complete the log. The logs must be maintained at each investigational center and updated when a connection box is brought to the site for an EP study visit and taken back to Medtronic after the EP study visit. The log should be sent to Medtronic each time they are updated.

At the end of the clinical study the principal investigator must sign and date the original Device Tracking Log.

F STUDY METHODS

F.1 Point of enrollment

A subject is enrolled in the study when he/she signs and dates the PIC. At this point, the patient will be assigned a subject number and is considered a subject in the investigation.

The investigator will maintain a log of all subjects enrolled in the clinical investigation, assigning an identification code linked to their names, alternative subject identification or contact information.

F.2 Implant or procedure aspects

F.2.1 Baseline visit

The baseline visit can be a standalone visit or occur on the same day as the EP study.

The following procedures/data collection will be conducted during the baseline visit:

- Verification of all inclusion and all exclusion criteria
- Enrollment
- Demographics (age, gender)
- Physical examination (height, weight, heart rate, blood pressure)
- Left ventricular ejection fraction (within last 3 months, otherwise a new measurement should be performed)
- Multi-lead ECG (within last 3 months, otherwise a new ECG should be performed)
- Echocardiographic evaluation (if available within last 3 months, otherwise not collected)
- NYHA classification
- Medical history (cardiovascular or related)
- Cardiovascular medications

- Pregnancy test for women with child-bearing potential
- MRI as explained in paragraph below

F.2.1.1 Magnetic Resonance Imaging (MRI)

Patients will undergo a baseline MRI before scheduled CRT-related surgery (i.e. dedicated research study or EP procedure or actual CRT implant) to identify the location and transmurality of any myocardial scar using late gadolinium enhancement-magnetic resonance imaging according to standard hospital practice. During the MRI a thorax scan is required to be able to reconstruct the thorax and lungs, i.e. a transverse scan with neck and liver visible. An appropriate marker should be placed on the xyphoid and 10 cm above the xyphoid during this scan. In addition, left ventricular end systolic volume (LVESV), left ventricular end diastolic volume (LVEDV) and left ventricular ejection fraction (LVEF) will be determined. MRI can be performed as standard of care or solely for the study. If the patient has a LBBB conduction pattern and QRS-width above 150ms, the MRI images should be analyzed before the EP study to detect the presence of scar. If no scar is present on late gadolinium enhancement MRI, the LBBB patient with QRS > 150ms should not be included in the study (if MRI done as standard of care) or should be exited from the study (if MRI done solely for the study).

F.2.2 Electrophysiological (EP) study visit

The EP study visit can be a standalone visit or can occur on the same day as the baseline visit. The EP study visit should take place within 3 months after the MRI has been obtained. Patients will undergo standard implant of a biventricular pacing system (CRT-P or CRT-D) or will undergo the EP study (data for this research study will be collected) before possible CRT-implant or will participate in this dedicated research study as a standalone visit (without any concomitant procedure).

If available in the center, a finger volume clamp system (e.g. model Nexfin, BMEYE B.V.) will be connected to one of the subject's fingers to measure the blood pressure non-invasively. In addition, a multi-lead surface ECG is collected during the whole procedure.

Pacing electrodes (cardiac leads or EP catheters) will be placed in the right atrium (RA) and right ventricle (RV). The coronary sinus will be cannulated, a venogram will be obtained and target vessels for LV stimulation will be identified. An EP-catheter ("Multi-electrode lead") or LV lead will be used for LV pacing. The temporary LV pacing electrodes (e.g. EP catheter or LV lead) will be inserted into the coronary sinus and then sequentially into the suitable target vein. Targeted myocardial regions for LV lead/catheter placement are: lateral or posterolateral vein (standard vein), and the vein displaying the most promise to reach the true LV apical position (to be anticipated the anterior vein). To reach the most LV apical position small EP-catheters or pacing guide wire will be used.

Pacing will be performed at up to three electrodes simultaneously or sequentially within the (standard) vein(s) (MultiSpot-SYN and MultiSpot-SEQ), covering the LV basal to apical locations when feasible (see figures 4, 5 and 6). A lateral LAO, RAO and/or AP fluoro-screen shot will be taken to document the different (temporary) electrode positions. A marker is placed on the xyphoid to register the fluoroscopy images.

A Millar pressure catheter or similar will be introduced via the femoral artery retrograde across the aortic valve into the LV for hemodynamic pressure monitoring. Heparin will be administered to ensure that the activated clotting time is monitored per standard hospital practice.

The following LV pacing configurations will be evaluated:

Biventricular pacing (BiV)
Pacing will be performed on one LV electrode pair, (at 3 different longitudinal locations), and on the tip of the RV-lead. In total, three different pacing BiV settings will be evaluated.

Configuration 1: RV + LV lateral Apex

Configuration 2: RV + LV lateral Mid

Configuration 3: RV + LV lateral Base **(Reference: Standard CRT)**

MultiSpot simultaneous LV-ventricular pacing (MultiSpot-SYN)
Pacing will be performed on 3 electrodes on the LV wall, placed at different longitudinal locations, and on the tip of the RV-lead simultaneously.

Configuration 4: RV + LV lateral Apex + LV lateral Mid + LV lateral Base

MultiSpot sequential LV-ventricular pacing (MultiSpot-SEQ)

3 electrodes on the LV wall will be paced sequentially. The RV-electrode will be paced simultaneously with last paced LV-electrode. The timing-sequence and the amount of spots will depend on the electrical delays measured during the experiments.

Configuration 5: LV lateral Apex → LV lateral Mid → LV lateral Base + RV

The different pacing settings include simultaneous and sequential RV and LV pacing and are in bipolar or unipolar mode. At each pacing site, the evaluation of the effect of CRT will be performed approximately 4 times (repetition) in order to increase signal to noise ratio. Each setting lasts about 20 beats (10-15 sec) interspersed with baseline (AAI; also 20 beats, 10-15 sec) pacing. The heart rate will be elevated by atrial pacing to a base rate about 10 beats above intrinsic or maximally tolerable rate, to ensure a constant heart rate. The RV-LV and the LV-LV (= VV-timing) intervals will be zero (MultiSpot-SYN) or will be sequential with VV-delay depending on the per patient measured electrical timing between the different electrode positions (MultiSpot-SEQ). For the latter, the VV-delay between Apical and Mid electrode position will be similar to the VV-delay between Mid and Basal electrode position. Optimal AV-delay will be calculated using CardioSync™ formulas (PAV_{ECG}=min (Ap-Pend + 30 ms, Ap-RVs – 50 ms)) derived from a correlation study between electrocardiographic measures such as the intrinsic AV interval and P-wave duration. The method aims at absence of truncation of the E/A waves. Up to five different AV-delays will be evaluated in this study (i.e. the optimal AV-delay and optimal AV-delay +/- 30 and +/- 60 ms). Hemodynamic measurements of positive LV dP/dt max, LV end diastolic pressure and arterial pressures will be measured during baseline and CRT. Additionally, at each pacing setting, the electrical delay from RV-pace to the different LV activations will be measured.

The signals from the LV pressure catheter, finger volume clamp system, internal electrograms, and surface ECG will be collected in real time and stored for later analysis as explained earlier. The CRT implant or EP procedure will be completed as per standard practice.

The protocol procedures will result in an additional 30 to 45 minutes to the standard procedure time. Pacing will be achieved by using a Medtronic 2290 analyzer and temporary pacemaker (5388DDD or 5392) stimulators or equipment present in the operating room of the participating physicians.

All patients should be followed up according to standard of care after the end of the protocol procedures.

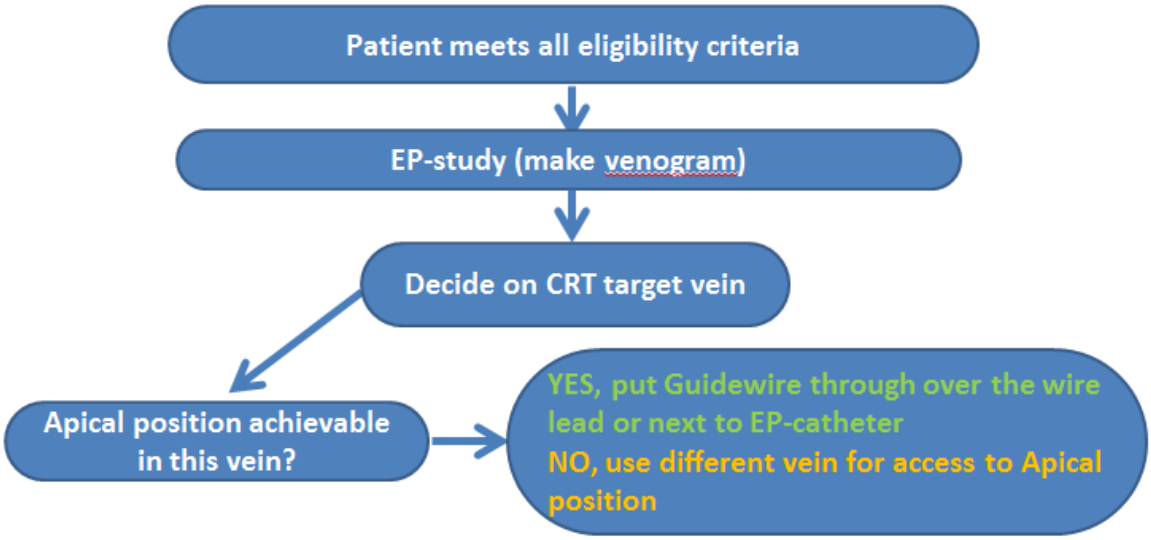


Figure 3: Start of protocol description.

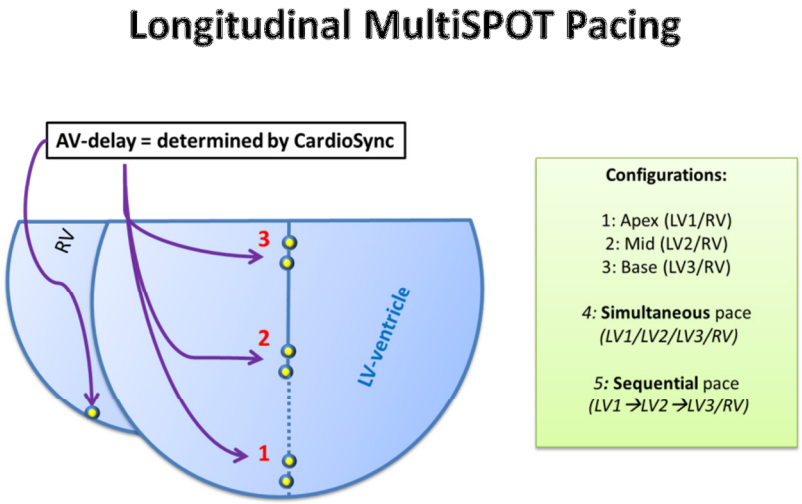
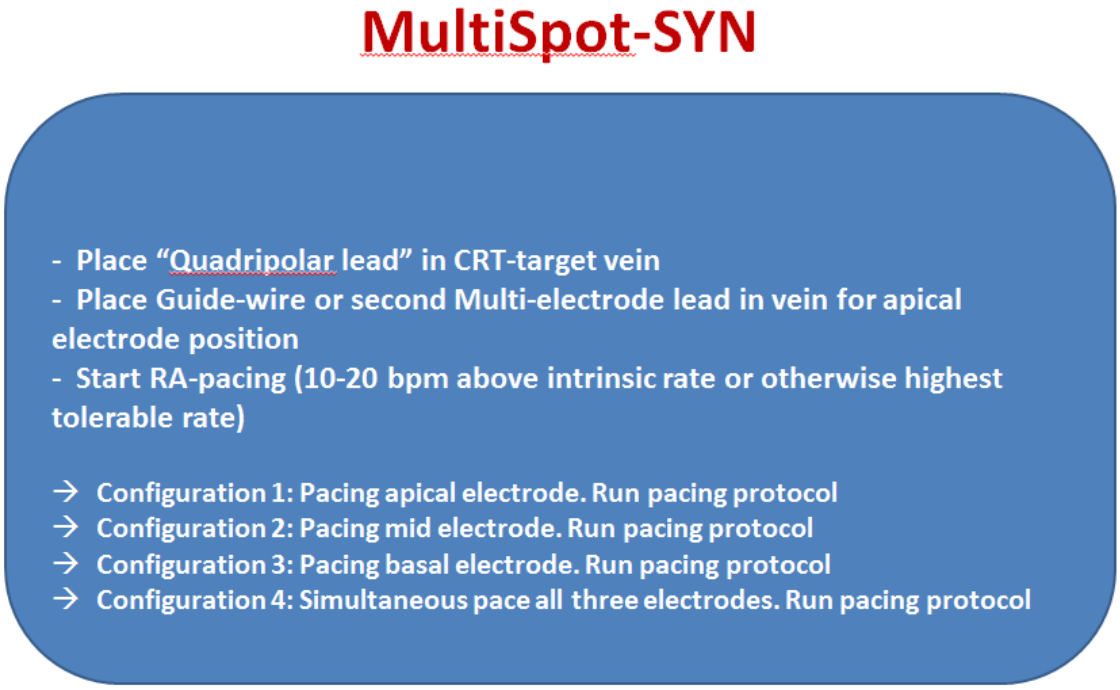
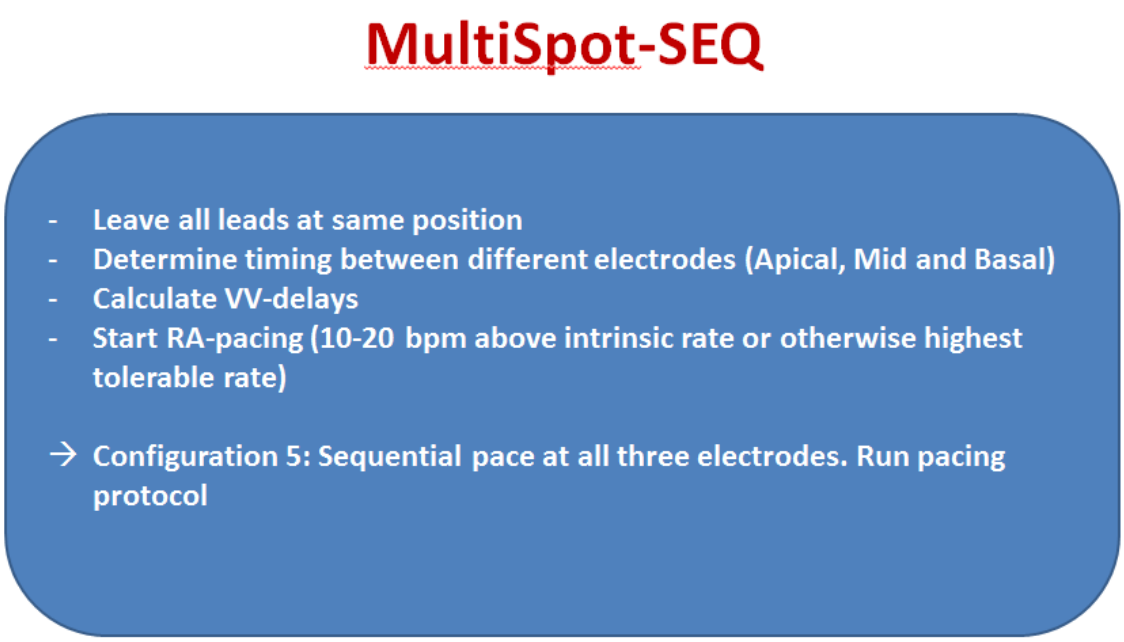


Figure 4: Different ventricular lead positions. *MultiSpot pacing at 3 electrodes at targeted LV locations synchronously or sequentially and RV. The mid and basal LV electrodes are placed in lateral or posterolateral vein. To reach the LV apex an alternative than the lateral vein can be used (to be anticipated the anterior vein). The delay between the different LV-electrodes will be determined during the experiment as it will be patient-dependent. AV-delay will be calculated using Cardiosync™*

Part A:


MultiSpot-SYN
- Place "Quadripolar lead" in CRT-target vein
- Place Guide-wire or second Multi-electrode lead in vein for apical electrode position
- Start RA-pacing (10-20 bpm above intrinsic rate or otherwise highest tolerable rate)
→ Configuration 1: Pacing apical electrode. Run pacing protocol
→ Configuration 2: Pacing mid electrode. Run pacing protocol
→ Configuration 3: Pacing basal electrode. Run pacing protocol
→ Configuration 4: Simultaneous pace all three electrodes. Run pacing protocol

Part B:


MultiSpot-SEQ
- Leave all leads at same position
- Determine timing between different electrodes (Apical, Mid and Basal)
- Calculate VV-delays
- Start RA-pacing (10-20 bpm above intrinsic rate or otherwise highest tolerable rate)
→ Configuration 5: Sequential pace at all three electrodes. Run pacing protocol

Part C:

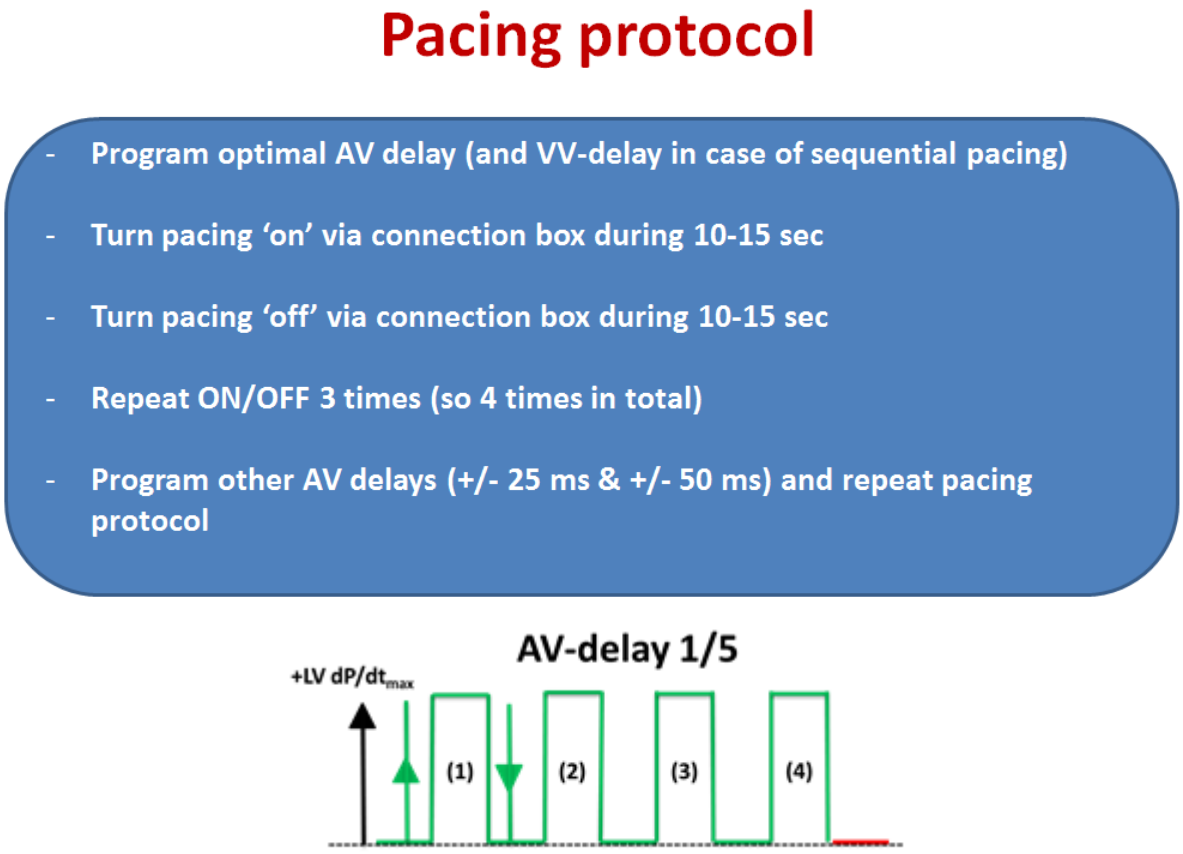


Figure 5: Description of the pacing protocol. *Part A is depicting the MultiSpot-SYN protocol while Part B is depicting the MultiSpot-SEQ protocol. Both protocols require the determination of the patient-specific AV-delay while Part B also requires the determination of patient-specific VV-delays. Part C is displaying the pacing procedure for 1 out of 5 total AV delays during which the positive dP/dt max will be measured. Each pacing ON and OFF setting will last 10-15 sec. The repetition of steps is used to increase sensitivity of the positive dP/dt max measurements. Five AV delays will be assessed: optimal AV, optimal AV delay +/- 30 and +/-60 ms.*

F.3 Data collection requirements

Clinical data will be collected at enrollment, baseline and during the study procedure. Table 2 summarizes the data requirements. Patients' participation in this study is expected to last approximately between 1 day and 3 months, depending on the time between enrollment/baseline and the EP study and the duration of hospital stay after the research study, or EP related procedure or the CRT-implant. The EP study visit should take place within 3 months after the MRI has been obtained. In case the EP study visit is not done within 3 months after the MRI, the patient should be exited from the study.

Subjects, who complete all study procedures, will be exited from the study just before the moment of hospital discharge. This will be documented on the Study Exit eCRF. There will be no further follow-up required for subjects that are exited from the study since no investigational products will be implanted or used in the study.

Table 2: Data Collection Requirements

Data	Baseline	EP Visit
Inclusion/Exclusion Criteria	x	
Subject Informed Consent	x	
Demographics	x	
Physical examination	x	
LVEF Within 3 months prior to enrollment, otherwise a new measurement should be performed	x	
Surface ECG Within 3 months prior to enrollment, otherwise a new ECG should be performed	x	x
Echocardiogram If available within last 3 months, otherwise not collected	x	
NYHA Class	x	
Medical history	x	
Cardiovascular medications	x	
MRI (structural and functional)	x	
Non-invasive blood pressure	x	x
Venogram		x
Invasive blood pressure		x
LV pressure		x
LV lead implant location (Chest X-ray)		x
Unipolar and Bipolar electrograms		x
Adverse events	x	x
Device deficiency		x
Deviation	x	x
Exit	x[1]	x

[1] In case the MRI is done solely for the study: If the patient has ischemic etiology and a LBBB conduction pattern and QRS-width above 150ms, the MRI images should be analyzed immediately to detect scar. If scar is not present on late gadolinium enhanced MRI, the patient should be exited from the study prior to EP visit

F.4 Role of the sponsor's representatives

Sponsor's representatives (e.g. Field Clinical Engineer, Field CRS, Technical Consultant) may provide support as required for the clinical study, including technical support during implant/procedure including completion of a technical support sheet and/or technical support. Documentation of study training and qualification of sponsor representatives will be maintained by Medtronic. The sponsor's representatives providing technical support may be listed on the sponsor technical support list.

F.5 Source documents

Source documents may be the PIC, hospital/clinic files, Electronic Media (MRI images, Echo images), programmer or ECG printouts, worksheets, MRI images and eCRFs.

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

Data that could be recorded directly on the eCRF and considered as source data are listed in section G.1.2.

F.6 Adverse events and Device Deficiencies

F.6.1 Definition/classification

Timely, accurate, and complete reporting and analysis of safety information for clinical studies are crucial for the protection of subjects, investigators, and the sponsor. Reporting and analysis of safety data are mandated by regulatory authorities worldwide. All events and deaths for the SYNSEQ study will be collected, classified, reviewed and reported from enrollment up till study exit. Documented pre-existing conditions are not considered AEs unless the nature or severity of the condition has worsened.

For the purposes of the clinical report, Medtronic will classify each Adverse Event according to ISO 14155:2011.

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.

Adverse Event (AE): *(ISO14155:2011 3.2)*

Any untoward medical occurrence, unintended disease or injury, or untoward clinical signs (including abnormal laboratory findings) in subjects, users or other persons, whether or not related to the investigational medical device

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.

Adverse Device Effect (ADE): *(ISO14155:2011 3.1)*

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 use error or from intentional misuse of the investigational medical device

Serious Adverse Event (SAE): *(ISO 14155:2011 3.37)*

Adverse event that
a) led to death,
b) led to serious deterioration in the health of the subject, that either resulted in
   1) a life-threatening illness or injury, or
   2) a permanent impairment of a body structure or a body function, 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) led to foetal distress, foetal death or a congenital abnormality or birth defect.

NOTE: Planned hospitalization for a pre-existing condition, or a procedure required by the CIP, without serious deterioration in health, is not considered a serious adverse event.

Serious Adverse Device Effect (SADE): *(ISO 14155:2011 3.36)*

Adverse device effect that has resulted in any of the consequences characteristic of a Serious Adverse Event

Unanticipated Serious Adverse Device Effect (USADE): *(ISO 14155:2011 3.42)*

Serious adverse device effect which by its nature, incidence, severity or outcome has not been identified in the current version of the risk analysis report

NOTE: Anticipated serious adverse device effect (ASADE) is an effect which by its nature, incidence, severity or outcome has been identified in the risk analysis report.

Device deficiency: *(ISO 14155:2011 3.15)*

Inadequacy of a medical device with respect to its identity, quality, durability, reliability, safety or performance

NOTE: Device deficiencies include malfunctions, use errors, and inadequate labelling.

Unavoidable Adverse Event:

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:

Event Description	Time Frame (Hours) from the Surgical Procedure
Anesthesia related nausea / vomiting	24
Low-grade fever (<100°F or 37.8°C)	48
Pocket site / Incisional pain	72
Mild to moderate bruising / ecchymosis	168
Sleep problems (insomnia)	72
Back pain related to laying on table	72
Shoulder pain/discomfort/stiffness related to shoulder immobilization during procedure	72

Further adverse event definitions:

Relatedness	
Procedure Related	An adverse event that occurs due to any procedure related to the investigational study procedure/protocol
System Related	• **Pacing system Related**: An adverse event that results from the presence or performance (intended or otherwise) of the Pacing system (Connection Box, hand-held pacers and connection cables) • **Lead Related**: An adverse event that results from the presence or performance (intended or otherwise) of the right atrial, right ventricular or left ventricular lead • **Implant or Introduction Tool Related**: An adverse event that results from the presence or performance (intended or otherwise) of the implant or introduction tool • **LV Catheter Related**: An adverse event that results from the presence or performance (intended or otherwise) of the LV Catheter
Timing	

Pre-study procedure testing AE	An adverse event that occurs after the patient informed consent form has been signed but before the skin incision related to the investigational study procedure/protocol
During study procedure testing AE	An adverse event that occurs during investigational study procedure testing/protocol
Post study procedure testing AE	An adverse event that occurs between the completion of skin closure for the investigational study procedure testing/protocol and before hospital discharge of the patient
Other	
Hospitalization	A therapeutic inpatient hospitalization (excludes outpatient and emergency room visits) lasting greater than or equal to 24 hours.

F.6.2 Recording and reporting of Adverse Events

Adverse Event (AE) information will be collected throughout the study and reported to Medtronic on an Adverse Event Form, one for each Adverse Event. This Adverse Event form must be entered in the database.

In the event the database is unavailable an alternative data collection system may be implemented such as an email notification to the sponsor. Upon database (re)-instatement, the data contained in the email notification to the sponsor will be entered in to the database by the investigator or authorized designee. The email notification must be sent to the study contact person as listed in Table 4.

All Adverse Events, regardless of relatedness or outcome, must be reported.

See the Adverse Event eCRF for the information to be reported for each Adverse Event.

For Adverse Events that require immediate reporting (see table 3), initial reporting may be done on the eCRF completing as much information as is available. The completed AE eCRF must be sent to Medtronic as soon as possible.

In case the investigator requires information from the sponsor in an emergency situation, the investigator can contact the study contact person as listed in Table 4.

In case the Adverse Event is related to a market released device used during the study, post market surveillance is also applicable and the investigator is responsible for immediate reporting of the product complaint via the regular channels for market released products. The reporting of product complaints, abuse, and misuse of these CE-labeled devices is not part of the clinical study and should be done in addition to the AE reporting requirements.

F.6.3 Recording and reporting of Device Deficiencies

Device Deficiency information will be collected throughout the study and reported to Medtronic. Device Deficiencies that did not lead to an Adverse Event should be reported on a Device Deficiency Form, one for each Device Deficiency. This Device Deficiency form must be entered in the database.

In the event the database is unavailable an alternative data collection system may be implemented such as an email notification to the sponsor. Upon database (re)-instatement,

the data contained in the email notification to the sponsor will be entered in to the database by the investigator or authorized designee. The email notification must be sent to the study contact person as listed in Table 4.

See the Device Deficiency eCRF for the information to be reported for each Device Deficiency that did not lead to an Adverse Event.

Device deficiencies that did not lead to an Adverse Event but could have led to an SADE
a) if either suitable action had not been taken,
b) if intervention had not been made, or
c) if circumstances had been less fortunate,

require immediate reporting (see table 3). Initial reporting may be done by on the eCRF by completing as much information as is available. The original completed Device Deficiency eCRF must be sent to Medtronic as soon as possible.

F.6.4 Adverse Event and Device Deficiency review process

All Adverse Events and Device Deficiencies will be reviewed by a Medtronic responsible person. This review will include the determination whether the Adverse Event/Device Deficiency meets regulatory reporting requirements (see table 3). The sponsor will ensure timely Adverse Event/Device Deficiency reporting to meet global regulatory requirements.

A list of anticipated adverse events that are expected in nature is included in Appendix L.2 of this CIP.

In case the Adverse Event/Device Deficiency is related to a market released device used during the study, the Medtronic responsible person will immediately report this device related Adverse Event/Device Deficiency to the Medtronic internal Complaint Handling Unit. The Medtronic internal Complaint Handling Unit will ensure prompt review, and appropriate reporting.

Table 3*:* Adverse Event reporting requirements	
Serious Adverse Device Effects (SADE), including Unanticipated Serious Adverse Device Effect (USADE):	
Investigator submit to:	
Medtronic	Immediately after the investigator first learns of the event or of new information in relation with an already reported event.
Regulatory Authority	As per local reporting requirement
EC	Reporting timeframe as per local EC/IRB requirement.
Sponsor submit to:	
Regulatory Authorities	Reporting timeframe as per local requirement.
EC	Submit to EC/IRB per local reporting requirement.
Serious Adverse Events (SAE)	
Investigator submit to:	
Medtronic	Immediately after the investigator first learns of the event or of new information in relation with an already reported event.
Regulatory Authority	As per local reporting requirement
EC	Submit to EC/IRB per local reporting requirement.
Sponsor submit to:	

Regulatory Authorities	Reporting timeframe as per local requirement.
EC	Submit to EC/IRB per local reporting requirement.
Adverse Device Effects (ADE)	
Investigator submit to:	
Medtronic	Immediately after the investigator first learns of the event.
Regulatory Authority	As per local reporting requirement
EC	Submit to EC/IRB per local reporting requirement.
Sponsor submit to:	
Regulatory Authorities	Reporting timeframe as per local requirement
EC	Submit to EC/IRB per local reporting requirement.
All other AEs	
Investigator submit to:	
Medtronic	Submit in a timely manner after the investigator first learns of the event.
Regulatory Authority	As per local reporting requirement
EC	Submit to EC/IRB per local reporting requirement.
Device Deficiency with SADE potential	
Investigator submit to:	
Medtronic	Immediately after the investigator first learns of the deficiency or of new information in relation with an already reported deficiency.
Regulatory Authority	As per local reporting requirement
EC	Submit to EC/IRB per local reporting requirement.
Sponsor submit to:	
Regulatory Authorities	Reporting timeframe as per local requirement
EC	Submit to EC/IRB per local reporting requirement.
All other Device Deficiencies	
Investigator submit to:	
Medtronic	Submit in a timely manner after the investigator first learns of the deficiency.
Regulatory Authority	As per local reporting requirement
EC	Submit to EC/IRB per local reporting requirement.

F.6.5 Adverse Event Advisory Committee

An independent Adverse Event Advisory Committee (AEAC) will review all Adverse Events, all deaths and all Device Deficiencies with SADE potential.

The AEAC will consist of a minimum of three non-Medtronic physicians. This committee will determine the relatedness of all adverse events and deaths to the device, system, and testing procedure.

All Adverse Events, all deaths and Device Deficiencies with SADE potential will be reviewed by a minimum of three members of the committee.

The responsibilities of an AEAC committee are:

- to review all reported all Adverse Events, all deaths and all Device Deficiencies with SADE potential and its classification on a periodic basis
- upon request advise Medtronic about the potential clinical impact of an observed unintended device performance
- advise Medtronic in cases of SADE's, Device Deficiencies with SADE potential

F.6.6 Emergency contact details in case of serious AEs

In case of an immediately reportable Adverse Event the investigators can contact the study contact person as listed in table 4.

F.6.7 Subject Death

All subject deaths must be reported by the investigator to Medtronic on a Subject Death form as soon as possible after the investigator first learns of the death.

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

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

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

- Cardiac Death: A death directly related to the electrical or mechanical dysfunction of the heart.
- Sudden Cardiac Death (SCD): Natural death due to cardiac causes, indicated by abrupt loss of consciousness within one hour of the onset of acute symptoms; preexisting heart disease may have been known to be present, but the time and mode of death are unexpected. If time of onset cannot be determined, SCD will alternatively be defined as any unexpected cardiac death occurring out of the hospital or in the emergency room as dead on arrival.
- Non-sudden Cardiac Death: All cardiac deaths that are not classified as sudden deaths, including all cardiac deaths of hospitalized subjects on inotropic support.
- Non-cardiac Death: A death not classified as a cardiac death.
- Unknown Cardiac Classification: Unknown death classification is intended for use only when there is insufficient or inadequate information to classify the death.

The AEAC will review deaths and provide a final adjudication of the primary cause of death, relatedness, and cardiac classification.

F.7 Subject accountability

A subject will be exited from the study in the event that he or she is unable to participate, expresses a desire to withdraw, or is unwilling to continue participation in the study. The reason for withdrawal needs to be documented in the subject's hospital record and in the eCRF. The subject should be informed that their future care or treatment will not be affected in any way as a result of choosing to not participate in this study. Furthermore,

alternative treatments and medical consequences of exiting the study should be discussed with the subject. Any significant new findings related to the study that may develop, which may relate to the subject's willingness to continue participation, should be communicated to the subject. Unless the patient explicitly revokes informed consent, available data will be reported.

A subject may be exited from the study if an investigator feels it is necessary to withdraw the subject from the study due to a medical condition or other reason. In such cases, the subject will be notified and provided an explanation regarding the reasons for the study exit. Unless the patient explicitly revokes informed consent, available data will be reported.

Upon withdrawal from the study, no further study data will be collected for the subject.

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

The subjects who withdraw or who are withdrawn are not replaced.

If the subject is determined to be lost to follow-up, the details regarding a minimum of two attempts and the method of attempt (e.g., one letter and one phone record or two letters) to contact the subject must be documented in the patient medical record. Any additional regulations set forth by the governing MEC must be followed.

F.8 Study deviations and CIP changes

A study deviation is an event where the investigator or site personnel did not conduct the clinical study according to the Clinical Investigational Plan or Clinical Investigation Agreement. The investigator is not allowed to deviate from the above mentioned documents except with prior approval and under emergency circumstances. All deviations shall be documented and explained, regardless the reason for the deviation.

Medtronic will assess the significance of all deviations and evaluate the need to amend the Clinical Investigation Plan or to early terminate the investigation, in accordance with Medtronic SOPs.

F.8.1 Request for approval of study deviations

The investigator shall obtain documented approval from Medtronic and, if required, from EC and regulatory authority, before implementation of any change in- or deviation from the Clinical Investigation Plan. The investigator shall timely contact the Clinical Study Manager for review of the proposed change/deviation.

In any emergency situation the investigator shall exercise his/her judgment to safeguard the subject's interest. Such deviations from the Clinical Investigation Plan do not require the prior approval of Medtronic. The investigator shall report the deviation as soon as possible to Medtronic and the reviewing EC, if applicable. Medtronic will inform the regulatory authorities, if required.

F.8.2 Reporting requirements for study deviations

Study deviations directly related to a subject, including informed consent violations, will be documented in the subject's case history record and recorded on the Deviation eCRF.

The investigator shall adhere to EC requirements and procedures, local laws and regulatory agency for reporting study deviations.

Medtronic is responsible for analyzing deviations, assessing their significance, and identifying any additional corrective and/or preventive actions (e.g. amend the CIP, additional training, terminate the study, etc.). Repetitive or serious investigator compliance issues may result in the need to initiate a corrective action plan, and in some cases freeze enrolment or ultimately terminate the investigator's participation in the clinical study. Medtronic will provide investigation site-specific reports to the investigators on a periodic basis summarizing information on deviations that occurred at the investigational site.

F.8.3 Amendments to the Clinical Investigation Plan

The investigator may propose any appropriate modification(s) of the Clinical Investigation Plan or investigational device or investigational device use. Medtronic will review this proposal and decide whether the modification(s) will be implemented.

Medtronic will submit any significant amendment to the Clinical Investigation Plan, including a justification for this amendment, to the appropriate regulatory authorities and to the investigators to obtain approval from their EC, if applicable. Administrative amendments to the Clinical Investigation Plan will be submitted to the EC and appropriate regulatory authorities for notification, if applicable.

G QUALITY CONTROL PROCEDURES

G.1 Procedures for database management

G.1.1 Data collection

The investigator must ensure accuracy, completeness and timeliness of the data reported in the eCRFs and in all other required reports. Data reported on the eCRFs which are derived from source documents must be consistent with the source documents and discrepancies need to be justified in a documented rationale, signed and dated by the (principal) investigator and filed in the patient medical file.

Only authorized persons can complete eCRFs. eCRFs shall be signed by investigators (physicians only) as specified on the Delegated Tasks List included in the Investigator Site File.

The Electronic Data Capture system is used for study visit data, adverse event data, device deficiency data, study deviations and exits collection. This system maintains an audit trail on entries, changes or corrections in eCRFs. If a person is only authorized to complete eCRFs or make changes to an already signed eCRF, the investigator shall re-sign this eCRF.

The data collected during the EP study visit coming from the heart, chest or finger (i.e. surface ECG, (non-)invasive blood pressure, LV pressure, unipolar and bipolar electrograms) will be collected simultaneously on the universal data acquisition system (i.e. PORTI-system is a multi-channel ambulatory and stationary system for physiological research). The raw data from the PORTI-system will not be processed during the experiment, and no data will be used to guide patient care. The data from the PORTI-system, MRI images, echo images (if available) and venogram will be brought to the Medtronic office by attending Medtronic personnel. A copy of the data will remain at the site. Offline analyses include standard calculations of first time derivative of left ventricular pressure (filter settings), and timing between the different electrodes on the heart or on the chest.

All data will be stored in a secure, password-protected database which will be backed up nightly. 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 retained indefinitely by Medtronic.

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.

G.1.2 Source data to be directly recorded on the Case Report Forms

The following data will be recorded directly on the eCRF and is considered as source data:

- Baseline form: the subject number
- Baseline form: exclusion criteria “Pregnant of breast feeding women, or women of child bearing potential and who are not on a reliable form of birth control” and ”Subject is enrolled in one or more concurrent studies that would confound the results of this study”

- AE form and death form: the date the study center became aware of the AE/Death
- AE form: check box “Device interrogation” and “Device reprogramming”
- Death form: “Location of subject at time of death”

Even when the eCRF may be considered as source, an alternate method of source documentation is always strongly encouraged.

G.1.3 Data review and processing

Data management will be done according to Medtronic SOPs and the Data Management Plan for this clinical study. These documents will be made available on request.

All collected data will be reviewed for completeness, correctness and consistency. In case of issues, queries will be sent to the investigator to complete, correct or comment the data.

G.2 Monitoring procedures

Monitoring visits will be conducted before site activation, during the study and at the closure of the clinical study in accordance with Medtronic SOPs and the Monitoring Plan.

Frequency of monitoring visits may be based on subject enrollment, duration of the study and study compliance.

During the monitoring visit, it will be verified whether signed and dated Informed Consent Forms have been obtained from each subject before any clinical-study-related procedures are undertaken.

Regulatory documents (e.g., EC approval letters, Competent Authorities approval letters and CTAs) will be reviewed at each study center. Subject data will be monitored against source documentation (e.g., clinic and hospital charts). Center study progress, investigator’s adherence to the CIP and maintenance of records and reports will also be checked.

G.2.1 Accessibility of investigation site staff and study materials

The principal investigator(s), his/her delegate(s) and the study coordinator(s) shall be accessible to Medtronic field personnel and the Clinical Study Manager. This accessibility is of particular importance for reviewing data in the eCRF. Direct access to patient medical files for source data verification (if applicable) will need to be granted and prepared prior to any monitoring visits.

G.2.2 Audits and investigation site inspections

In addition to regular monitoring visits, Medtronic may conduct audits at participating investigation sites. The purpose of an audit is to verify the adequate performance of the clinical study related activities. Independent of the employees involved in the clinical study. Regulatory authorities may also perform inspections at participating investigation sites. Any regulatory authority inspection announcements shall be forwarded immediately to the sponsor contact person (e.g. Clinical Study Manager).

The investigator and/or institution shall permit Medtronic and regulatory bodies direct access to source data and documents, taking into account any restrictions due to local law, to perform clinical study-related monitoring, audits, EC review, and regulatory inspections.

G.3 Study suspension or early termination

G.3.1 Early study suspension or termination

Medtronic or Regulatory Authority may decide to suspend or prematurely terminate the clinical study (e.g. adverse event and device deficiencies associated with the EP study procedure under investigation which might endanger the safety or welfare of subjects). If the clinical study is terminated prematurely or suspended, Medtronic shall promptly inform the regulatory authorities and the clinical investigators of the termination or suspension and the reason(s) for this. The investigator shall then promptly inform the reviewing EC, if required, and the study subjects or their legal representative.

G.3.2 Early investigation site suspension or termination

Medtronic, EC or Regulatory Authority may decide to suspend or prematurely terminate an investigation site. Possible reasons include but are not limited to:

- Failure to obtain initial Ethics Board approval or annual renewal of the study
- Consistent non-compliance to the CIP (e.g. failure to adhere to inclusion/exclusion criteria, failure to schedule subjects for study visit, etc.)
- Lack of enrollment
- Noncompliance to regulations and the terms of the Clinical Trial Agreement (e.g. failure to submit data in a timely manner, failure to follow-up on data queries and monitoring findings in a timely manner, etc.)
- Ethics Board suspension of the center
- Fraud or fraudulent misconduct (as defined by local law and regulations)
- Investigator request (e.g. no longer able to support the study).

If an investigation site is suspended or prematurely terminated, Medtronic shall promptly inform the investigator(s) of the termination or suspension and the reason(s) for this. The investigator shall then promptly inform the reviewing EC, if required, the study subjects or their legal representative.

When the risks are found to outweigh the potential benefits or when there is conclusive proof of definite outcomes, investigators must assess whether to continue, modify or immediately stop the clinical study in the respective investigation site and immediately inform the sponsor and EC, if applicable.

G.3.3 Subject follow-up in case of termination

In the case of a study suspension, enrolled subjects should continue to be followed out of consideration of their safety, rights and welfare.

G.4 Study close out

Study closure is defined as closure of a clinical study that occurs when Medtronic and/or regulatory requirements have been satisfied per the Clinical Investigational Plan and/or by a decision by Medtronic or regulatory authority, whichever occurs first. Continued MEC oversight is required until the overall study closure process is complete.

Study closure is a process initiated by distribution of an initial study closure letter to all investigators. In all geographies, the study closure process is complete upon distribution of the Final Report or after final payments, whichever occurs last. Study closure will also be notified to Regulatory Authority, if required.

With regard to individual subjects, no dedicated closure visit will occur in association with overall study closure, and no medical care as defined by the study will be provided to the subject following overall study closure.

H DATA ANALYSIS AND REPORTING

A detailed description of the statistical methods will be contained in the Statistical Analysis Plan. Any changes to the data analysis methods will be described and justified in the Final Report or publication.

H.1 Analysis of clinical data

Descriptive statistics will be used to summarize the patient demographic and clinical characteristics at baseline. Data for qualitative variables will be presented as incidence rates (total number of patients, 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 except for the secondary objective 1 which is evaluated using a one-sided significance

level of 0.025. No adjustments will be made for multiple testing because of the exploratory nature of this study. No imputation of missing data is planned. No interim reports are planned for this study.

Any change to the data analysis methods described in the Clinical Investigational Plan will require an amendment only if it changes an objective of the Clinical Investigational Plan. Any other change to the data analysis methods described in the Clinical Investigational Plan, and the justification for making the change, will be described in the clinical study report. Additional exploratory analyses of the data will be conducted as deemed appropriate.

All patients who signed the informed consent document will be defined as the enrolled population. The Analysis Population is defined as patients who are enrolled, have no inclusion or exclusion criteria violation regarding the most important criteria, i.e., inclusion criteria 1 and 2 and exclusion criterion 3, and for whom the EP procedure could be completed successfully. Patients, who are not part of the Analysis Population, will not be included in the primary analysis of the primary objectives, but will be reported in the patient disposition table. A secondary analysis might be performed including patients who have eligibility violations. Safety will be reported on the All Enrolled Population and the primary objectives will be reported on the Analysis Population.

Endpoint for the primary objective 1, primary objective 2 and secondary objective 1 will be % change LV dP/dt max from baseline. This percentage change is calculated as ([median dP/dt max during pacing On] –
[median baseline dP/dt max during pacing Off])/[median dP/dt max during pacing Off]. This endpoint will be used primarily to evaluate the hypothesis of objective 1, primary objective 2 and secondary objective 1. Other endpoints, e.g., blood pressures, might be included in an exploratory secondary analysis for these objectives.

H.1.1 Primary objective 1

Compare the hemodynamic response of a MultiSpot-SYN Left Ventricular pacing configuration (simultaneous LV pacing) to a single spot LV pacing configuration in patients undergoing a research study, an EP exploratory procedure or CRT implant using the contractility parameter positive LV dP/dt max.

It is hypothesized that MultiSpot SYN (pacing on all 3 LV electrodes simultaneously) is superior to conventional BiV pacing (i.e. using only the basal LV electrode).

The null and alternative hypotheses are:

H_0: $\Delta_{\text{MultiSpot SYN}} - \Delta_{\text{BiV}} = 0\%$

H_1: $\Delta_{\text{MultiSpot SYN}} - \Delta_{\text{BiV}} \neq 0\%$,

where Δ indicates percentage change from baseline for the respective pacing configuration.

For each patient, a regression analysis will be performed to model % change LV dP/dt max dependent on configuration and AV delay. Based on the fitted model for each patient, the best AV delay for each configuration will be determined together with the predicted % change at this best AV delay. This best AV delay may differ from the optimal AV delay determined by the CardioSync formula. Paired two-sided t–tests will be used to evaluate whether there is a statistical significantly difference between MultiSpot-SYN and standard BiV pacing. Instead of paired t-tests, a Wilcoxon signed rank test might be performed if normality is violated.

H.1.2 Primary objective 2

Compare the hemodynamic response of a MultiSpot-SEQ Left Ventricular pacing configuration (sequential LV pacing) to a single spot LV pacing configuration in patients undergoing a research study, an EP exploratory procedure or CRT implant using the contractility parameter positive LV dP/dt max.

It is hypothesized that MultiSpot SEQ (pacing on 3 LV electrodes activated sequentially from apex to mid and then to base) is superior to conventional BiV pacing (i.e. using only the basal LV electrode).

The null and alternative hypotheses are thus:

H_0: $\Delta_{\text{MultiSpot SEQ}} - \Delta_{\text{BiV}} \equiv 0\%$

H_1: $\Delta_{\text{MultiSpot SEQ}} - \Delta_{\text{BiV}} \neq 0\%$,

where Δ indicates percentage change from baseline for the respective pacing configuration. Statistical analysis will use the methods described for the primary objective 1, with MultiSpot-SYN LV pacing replaced by MultiSpot-SEQ LV pacing configuration.

H.1.3 Secondary objective 1

Compare the positive LV dP/dt max from a MultiSpot-SEQ LV pacing configuration to a MultiSpot-SYN LV pacing configuration in patients undergoing a research study, an EP exploratory procedure or CRT-implant using the contractility parameter positive LV dP/dt max.

It is hypothesized that that MultiSpot SEQ (pacing using 3 LV electrodes activated sequentially from apex to mid and then to base) is non-inferior to MultiSpot SYN (pacing on all 3 LV electrodes simultaneously).

The null and alternative hypotheses are thus:

H_0: $\Delta_{\text{MultiSpot SEQ}} - \Delta_{\text{MultiSpot SYN}} \leq -3\%$ (inferiority)

H_1: $\Delta_{\text{MultiSpot SEQ}} - \Delta_{\text{MultiSpot SYN}} > -3\%$ (non-inferiority)

Statistical analysis will use the methods described for the primary objective 1, with single spot LV pacing configuration (standard BiV) replaced by MultiSpot-SEQ LV pacing.

Based on previous research (iSPOT study,[19]), we assume that the lower-border of the 95 % confidence interval for % change MultiSpot SYN to baseline (AAI mode) in the targeted patient population is 12.6. In this study we consider MultiSpot SEQ non-inferior to MultiSpot SYN if the difference in their means is less than a quarter of the difference between MultiSpot SYN pacing and baseline.

H.1.4 Secondary objective 2

Correlate the (non)invasive measures (blood pressure, electrocardiographic mapping and RV/LV EGM timings) obtained during the up to 6 different pacing configuration's to the positive LV dP/dt max measures obtained.

Regression analysis will be used to determine pairwise Pearson's correlation between the (non)invasive measures and LV dP/dt max. There are no hypotheses specified.

H.1.5 Secondary objective 3

Evaluate the (non)invasive measures ability to identify the pacing configuration with the highest positive LV dP/dt max.

A categorical variable of the best pacing configuration per patient will be calculated (the configuration that achieves the largest dP/dt value) and the agreement with each (non)invasive evaluation of best pacing configuration (also derived into a categorical variable) will be evaluated and tested with an unweighted Kappa statistic. There are no hypotheses specified.

H.2 Publication Policy

There are no plans to form a publication committee. Publication activities will be assessed during the study or after the study is completed and any collaboration with the investigators will be determined at that time. In case a Publication committee will be installed, all the roles and responsibilities will be defined in the Publication Plan.

Publications and presentations referring to this clinical study will be coordinated by Medtronic to allow the use of all available data. The following publication policy will have to be adhered to by all participating investigation sites:

Medtronic intends to publish the results of the clinical study in a scientific journal.

Authorship on any publication(s) resulting from this clinical study might be assigned according to:

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

This is in accordance with the Vancouver principles (The Uniform Requirements for Manuscripts Submitted to Biomedical Journals: Writing and Editing for Biomedical Publication, ICMJE), as agreed upon by the editors of all major medical journals.

The number of authors will be dependent on the regulations of the concerning journal.

Based on the principle that Medtronic owns the data of this clinical study, a single investigation site may access and use the data provided by itself for scientific publications following prior approval by Medtronic.

Pooling data from several investigation sites for publication purposes, national projects and international projects all require prior approval from Medtronic.

Medtronic as the owner of the data can use the data and/or any results derived from the data or publications based on that data for marketing purposes, further research and development of devices or educational use.

The study sponsor will collect data in such way that no subject can be identified, and monitor study records.

Participating subjects will not be identified by name in any published reports about the clinical study.

Each investigator must agree that no publications will be submitted that will jeopardize a multi-center publication.

The study results will also be published on http:/clinicaltrials.gov.

I STUDY MANAGEMENT

I.1 Study staff

The sponsor of this study is Medtronic Bakken Research Center BV, Endepolsdomein 5, 6229 GW, Maastricht, the Netherlands. Table 4 lists the sponsor contact information. This information is subject to change during the course of the clinical study and a list will be kept separate from the CIP. Periodic updates to study contact information will be sent to the centers. The Lead Monitor contact details are not yet known. As soon as the Lead Monitor is assigned to the study, an update will be sent to the sites.

Table 4: Sponsor Contact Information

Role / Name	[redacted]	Email
Scientist/ Richard Cornelussen	[redacted]	richard.cornelussen@medtronic.com
Scientist/ Berthold Stegemann	[redacted]	berthold.stegemann@medtronic.com
Clinical Research Specialist/ Laurence Hogge	[redacted]	laurence.hogge@medtronic.com

I.2 Advisory committees

I.2.1 Data Monitoring Committee

No Data Monitoring Committee will be installed for this clinical study considering:

- As a result of risk analysis and mitigation efforts as outlined in Section J, any residual risk associated with this study is considered low and acceptable.
- All products used in the study (leads and pacing devices) are commercially released (and CE-marked) and used within their intended purpose, except for the Connection Box which is investigational.

I.2.2 Publication Committee

There are no plans to form a publication committee. Publication activities will be assessed during the study or after the study is completed and any collaboration with the investigators will be determined at that time. In case a Publication committee will be installed, all the roles and responsibilities will be defined in the Publication Plan.

I.3 Records and reports

I.3.1 Investigator records

At a minimum, the following records must be kept by the investigator:

- Clinical Investigation Plan and, if applicable, any amendments
- Investigator's Brochure and Instructions for Use
- Medtronic and EC approved Patient Informed Consent

- Competent authority approval or notification, if required
- EC approval documents and documentation that the investigator did not participate in the approval process
- Fully signed clinical investigation agreement and confidentiality agreement (if not included in the clinical investigation agreement)
- Financial disclosures, if local requirements
- Insurance certificates
- Completed Delegated Task List and Curriculum Vitae of all investigation site personnel
- Training documentation of all investigation site personnel
- Relevant communications
- Subject screening log and/or subject identification log
- Signed, dated and fully executed informed consent forms
- Fully executed eCRFs and corrections
- Reports of Adverse Events and Device Deficiencies
- Connection box disposition log containing serial numbers of connection boxes brought to the site by Medtronic personnel for the EP study visit, received dates of the connection boxes, subject IDs of the subjects paced with the connection box and dates the connection boxes are taken back to Medtronic after the EP study visit.
- Final report
- Any other records that local regulatory agencies require to be maintained

I.3.2 Investigator reporting responsibilities

Each investigator must submit the final report to their EC (each investigator for their own EC). The final report contains a summary of the clinical study's findings and conclusions.

The investigator is responsible for the preparation (review and signature) and submission to Medtronic of all case report forms. If any action is taken by an EC with respect to the investigation, the information must be forwarded to Medtronic. The investigator shall prepare and submit in a complete, accurate and timely manner the reports listed in Table Table 5.

Table 5: Investigator Reports

Report	Submit To	Description / Constraints
Withdrawal of EC approval	Medtronic	report required by local law
Study Deviations	Medtronic, EC or competent authorities or other regulatory bodies	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 Boards, competent authorities or the appropriate regulatory bodies should be informed.
Failure to obtain informed consent	Medtronic, EC	Notification within five working days.
Progress Reports (if required)	Medtronic, EC	Provide if required by local law or Ethics Board

I.3.3 Sponsor records

At a minimum, the sponsor will keep the following records:

- All essential study documents and correspondence that pertains to the clinical study
- CIP and, if applicable, any amendments
- Investigator Brochure and Instructions for Use
- Sample of labeling attached to the investigational device
- Curriculum vitae of investigators and site staff
- Delegated Task Lists and training records of investigators and site staff
- Study training records of Medtronic personnel involved in the study
- EC approvals/notifications and regulatory approvals/notifications
- Signed Clinical Investigation Agreements and signed agreements with third parties
- Insurance certificates,
- Medtronic and EC approved Patient Informed Consents/Data Release Forms
- Monitoring visit reports
- Adverse event and Device Deficiency reports
- Financial disclosure information, if local requirements
- Fully executed eCRFs and corrections
- Connection box traceability record containing serial numbers of connection boxes, shipping date and name and address of person that received shipped connection box, location (if different than person shipped to), transfer and receipt by Medtronic dates
- Names of the institutions in which the clinical investigation will be conducted
- Correspondence with authorities as required by national legislation

- Final report of the clinical investigation
- Any other records that local regulatory agencies require to be maintained

I.3.4 Sponsor reporting responsibilities

Medtronic shall prepare and submit the following complete, accurate, and timely reports listed in the Table 6 below. In addition to the reports listed below, Medtronic shall, upon request of reviewing MEC or regulatory agency, provide accurate, complete and current information about any aspect of the investigation.

Table 6: Sponsor Reports

Report	Submit To	Description/Constraints
Premature termination or suspension of the clinical investigation	Investigators, EC, Relevant Authority	Provide prompt notification of termination or suspension and reason(s). *(ISO 14155:2011)*
Withdrawal of EC approval	Investigators, EC, Relevant Authority	All applicable investigators will be notified only if required by local laws or by the EC.
Withdrawal of CA approval	Investigators, EC, Relevant Authority	All applicable investigators and ECs will be notified only if required by local laws or by the EC.
Progress Reports	EC and/or CA	This will be submitted to the EC/CA only if required by the EC/CA.
Final Report	Investigators, EC, and Regulatory Authority	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 principal clinical investigator in each center shall sign the report. *(ISO 14155:2011)*
Study deviation	Investigators	Ensure that all deviations from the Clinical Investigation Plan are reviewed with the appropriate clinical investigator(s), are reported on the case report forms and the final report of the clinical investigation. Site specific study deviations will be submitted to investigators quarterly. *(ISO 14155:2011)*
Vigilance Reporting	Competent Authorities	Report incidents and near-incidents within 10 (incidents) or 30 (near-incidents) days. (Meddev.2.12-1 rev.5)
Significant New Evidence	EC, Regulatory Authorities	Ensure that EC and Regulatory Authorities are informed of significant new information about the clinical investigation. *(ISO 14155:-2011)*
Incident	Regulatory Authorities	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. *(Meddev.2.12-1 rev.5, AIMD 90/385/EEC)*

Electronic versions of Medtronic records and reports will be kept on a password-protected document management system during the course of the study. After closure of the study, all records and reports will be archived indefinitely.

I.3.5 Record retention

The investigator must retain the Investigator Site File, patient medical files and CRFs in accordance with local law and regulations for a minimum period of 2 year (or longer if local laws require).

The investigator should take measures to prevent accidental or early destruction of the clinical study related materials.

I.4 Miscellaneous

I.4.1 Insurance and warranty

The Medtronic Bakken Research Center B.V. is a wholly owned subsidiary of Medtronic Inc., 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 law and custom concerning specific insurance coverage. If required, a Clinical Trial Insurance statement/certificate will be provided to the EC.

Warranty information is provided in the product packaging for the connection box and additional copies are available upon request.

I.4.2 Subject confidentiality

All records and other information about subjects participating in this study will be treated as confidential. Participating subjects will not be identified by name in any published reports/publication about the study.

I.4.3 Subject compensation

The subject will not receive any compensation for the participation in this clinical investigation. Only the travel expenses related to the participation in the study (for visits which are not part of standard care) may be reimbursed depending on country regulations (all information are available in the Patient Informed Consent). A copy of the Patient Informed Consent is provided under separate cover.

J RISKS AND BENEFITS

J.1 Anticipated Clinical Benefits

There are no immediate direct patient benefits to participating in this study.

One potential benefit is that the response to CRT therapy in a given patient may be predicted on basis of the knowledge obtained in the experimental study. In addition, patients which are non-responders to conventional CRT, but displaying an improved acute hemodynamic response (i.e., LV dP/dt max) with the alternative CRT strategy are being recognized for potential future benefit. An indirect benefit is the knowledge that the subject may be helping doctors and scientists understand the best method for determining LV lead placement so that outcomes to CRT are optimized.

J.2 Risks

The potential risks to a subject participating in this study are believed to be somewhat higher to those encountered during standard CRT (CRT-P and/or CRT-D) implantation. This is due to the prolonged duration of the complete procedure, the addition of the temporary second LV-lead and the pacing from more than one position on the LV. The risks include, but are not limited to the following: increased arrhythmogenity, valve damage; puncture of the heart muscle, vein, artery or lung; infection; a blood or air embolism in the heart, lung, brain, arteries or veins; bleeding; hematoma; seroma; hemothorax; pneumothorax; swelling/bruising; stimulating muscles or nerves outside the heart; damage to a central vein including dissection and perforation; arteriovenous fistula; pseudo-aneurysm; or localized pain where the incision is made to insert the catheters and CRT device.

There may be additional risks related to study participation that are unknown at this time.

The risks associated with the use of the pressure catheter include, but are not limited to the following: infection, bleeding, hematoma, lack of blood flow to the tissue supplied by the artery, injury to blood vessel, valve or heart and localized pain where the incision is made to insert the catheter. The introducer used to insert the left ventricular pressure wire will also be used to measure invasively the blood pressure, adding no risk to the patient.

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 will result in an additional 30 to 45 minutes to the standard procedure time and an addition of about 10 minutes of fluoroscopy exposure. In case of the research study, all times are of course experimental time and no additional time on top of another procedure.

There is a very low risk of box malfunction, due to either failure of one of the components of the box (connectors, switches, cabling), potentially withholding pacing stimuli, causing unintended cardiac pacing, or leading to asynchronous pacing of the hand-held pacers, potentially causing arrhythmia.

Improper use of the connection box may lead to the false connection of cardiac leads and/or false delivery of stimulation to the heart, potentially causing cardiac arrhythmia.

For all the other CE marked devices used in this study:

Medtronic is not aware of any significant problems with the products. In the clinical study, the products will be used in accordance with their labeling, therefore no risks other than the risks typically associated with a routine device use are anticipated.

Standard risks associated with the medical device used in this clinical study, an analysis of Adverse Device Effects and a history of modification or recall of device under investigation or equivalent devices/products are listed in the Investigator's Brochure.

J.3 Risk-to-benefit rationale

Medtronic has minimized the occurrence of applicable risks by: providing guidelines for patient selection and evaluation, selecting an investigator who has demonstrated previous experience with CRT implantation and left heart catheterization, and clinical research (i.e. trained electrophysiologists). Investigators will be thoroughly trained on the study procedures and during the study Medtronic personnel will be present to provide technical support.

Investigators are also required to monitor continuously the study risks. They should assess what the risks are and document them.

Risks will be minimized through the use of strict aseptic technique and by close monitoring of the patient's physiologic status during the implant and follow-up procedures. The availability of the connection box in this study mitigates the risks of improper study conduction and/or data collection.

Data collection will be minimized to the essential data. Women who are pregnant should not participate in this study due to the radiation exposure. If a patient becomes pregnant during the duration of this study, they should notify the study physician immediately, as there may be potential risks to the patient and/or the embryo or fetus.

Subjects will be closely observed throughout the duration of the study to identify any adverse events.

The risks involved with the investigational device (i.e. connection box) are considered minor. It is a passive device designed to mitigate the risks of using alligator clips or other loose connections. Personnel using the connection box will be restricted. All personnel intended to use the connection box will be trained on how to use the box and how to mitigate human errors. Mitigation of connection box malfunction damage entails electrical pre-testing of the electrical connections before every study (100% inspection). The possible pro-arrhythmic effect will be mitigated by the proper instructions for use of the box and by the study protocol design.

The results of risk analysis, balancing benefits against risks associated with both the device system itself and procedures involved in its use, is included in the Investigator's Brochure.

K REFERENCES

1. Bristow, MR, Saxon, LA, Boehmer, J, et al. Cardiac-resynchronization therapy with or without an implantable defibrillator in advanced chronic heart failure. N Engl J Med, 2004;350:2140-50.
2. Cleland, JG, Daubert, JC, Erdmann, E, Freemantle, N, Gras, D, Kappenberger, L, Tavazzi, L, and Cardiac Resynchronization-Heart Failure Study, I. The effect of cardiac resynchronization on morbidity and mortality in heart failure. N Engl J Med, 2005;352:1539-49.
3. European Heart Rhythm, A, European Society of, C, Heart Rhythm, S, et al. 2012 EHRA/HRS expert consensus statement on cardiac resynchronization therapy in heart failure: implant and follow-up recommendations and management. Europace, 2012;14:1236-86.
4. Daubert, C, Cazeau, S, Ritter, P, and Leclercq, C. Past, present and future of cardiac resynchronization. Arch Cardiovasc Dis, 2012;105:291-9.
5. Pappone, C, Calovic, Z, Vicedomini, G, et al. Multipoint left ventricular pacing in a single coronary sinus branch improves mid-term echocardiographic and clinical response to cardiac resynchronization therapy. J Cardiovasc Electrophysiol, 2015;26:58-63.
6. Pappone, C, Calovic, Z, Vicedomini, G, et al. Multipoint left ventricular pacing improves acute hemodynamic response assessed with pressure-volume loops in cardiac resynchronization therapy patients. Heart Rhythm, 2014;11:394-401.
7. Rinaldi, CA, Leclercq, C, Kranig, W, et al. Improvement in acute contractility and hemodynamics with multipoint pacing via a left ventricular quadripolar pacing lead. J Interv Card Electrophysiol, 2014;40:75-80.
8. van Gelder, BM and Bracke, FA. Acute hemodynamic effects of single- and dual-site left ventricular pacing employing a dual cathodal coronary sinus lead. Pacing Clin Electrophysiol, 2015;38:558-64.
9. Thibault, B, Dubuc, M, Khairy, P, et al. Acute haemodynamic comparison of multisite and biventricular pacing with a quadripolar left ventricular lead. Europace, 2013;15:984-91.
10. Zanon, F, Baracca, E, Pastore, G, et al. Multipoint pacing by a left ventricular quadripolar lead improves the acute hemodynamic response to CRT compared with conventional biventricular pacing at any site. Heart Rhythm, 2015;12:975-81.
11. van Geldorp, IE, Vanagt, WY, Prinzen, FW, and Delhaas, T. Chronic ventricular pacing in children: toward prevention of pacing-induced heart disease. Heart Fail Rev, 2011;16:305-14.
12. Peschar, M, de Swart, H, Michels, KJ, Reneman, RS, and Prinzen, FW. Left ventricular septal and apex pacing for optimal pump function in canine hearts. J Am Coll Cardiol, 2003;41:1218-26.
13. Vanagt, WY, Prinzen, FW, and Delhaas, T. Reversal of pacing-induced heart failure by left ventricular apical pacing. N Engl J Med, 2007;357:2637-8.
14. Merchant, FM, Heist, EK, McCarty, D, Kumar, P, Das, S, Blendea, D, Ellinor, PT, Mela, T, Picard, MH, Ruskin, JN, and Singh, JP. Impact of segmental left ventricle lead position on cardiac resynchronization therapy outcomes. Heart Rhythm, 2010;7:639-44.
15. Russel, IK, Gotte, MJ, Bronzwaer, JG, Knaapen, P, Paulus, WJ, and van Rossum, AC. Left ventricular torsion: an expanding role in the analysis of myocardial dysfunction. JACC Cardiovasc Imaging, 2009;2:648-55.
16. Pedrizzetti, G, La Canna, G, Alfieri, O, and Tonti, G. The vortex--an early predictor of cardiovascular outcome? Nat Rev Cardiol, 2014;11:545-53.
17. Shetty, AK, Sohal, M, Chen, Z, et al. A comparison of left ventricular endocardial, multisite, and multipolar epicardial cardiac resynchronization: an acute haemodynamic and electroanatomical study. Europace, 2014;16:873-9.

18. Ginks, MR, Duckett, SG, Kapetanakis, S, Bostock, J, Hamid, S, Shetty, A, Ma, Y, Rhode, KS, Carr-White, GS, Razavi, RS, and Rinaldi, CA. Multi-site left ventricular pacing as a potential treatment for patients with postero-lateral scar: insights from cardiac magnetic resonance imaging and invasive haemodynamic assessment. Europace, 2012;14:373-9.

19. Sohal, M, Shetty, A, Niederer, S, et al. Mechanistic insights into the benefits of multisite pacing in cardiac resynchronization therapy: The importance of electrical substrate and rate of left ventricular activation. Heart Rhythm, 2015.

20. Whinnett, ZI, Davies, JE, Willson, K, Manisty, CH, Chow, AW, Foale, RA, Davies, DW, Hughes, AD, Mayet, J, and Francis, DP. Haemodynamic effects of changes in atrioventricular and interventricular delay in cardiac resynchronisation therapy show a consistent pattern: analysis of shape, magnitude and relative importance of atrioventricular and interventricular delay. Heart, 2006;92:1628-34.

21. Horowitz, LN, Kay, HR, Kutalek, SP, Discigil, KF, Webb, CR, Greenspan, AM, and Spielman, SR. Risks and complications of clinical cardiac electrophysiologic studies: a prospective analysis of 1,000 consecutive patients. J Am Coll Cardiol, 1987;9:1261-8.

L APPENDICES

L.1 Case Report Forms

A copy of the Case Report Form will be provided under a separate cover.

L.2 Foreseeable adverse event and anticipated adverse device effects

The information provided in this section pertains to foreseeable adverse events that may be observed in study subjects 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 two parts, events related to cardiac catheterization and events related to LV lead placement. An evaluation of potentially anticipated events, adverse device effects observed in previous clinical studies, and reported events in literature may be used in combination with device labeling, current event reporting information, and other published data to assess for an unexpected occurrence.

The EP study for the study 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 procedures under investigation.

Potential risks associated with the study procedures, as well as risk minimization are discussed within Section J.

Events related to cardiac catheterization

Potential adverse events and patient complications associated with the cardiac catherization procedure have been documented in the literature[21]. These events include, but are not limited to, the following:

- stimulation of more severe rhythm problems
- bleeding from the catheter insertion site(s)
- damage to the vessel at the catheter insertion site(s)
- infection of the catheter site(s)
- perforation of the heart (rare)
- Allergic reactions to medications or latex[21]

Additional adverse events associated with the use of the left ventricular pressure catheter are infection, bleeding, hematoma, lack of blood flow to the tissue supplied by the artery, injury to blood vessel, valve or heart and localized pain where the incision is made to insert the pressure catheter.

Events related to LV lead placement

The listings below provide examples of adverse events associated with the use of transvenous leads, pacing and defibrillation systems reported in previous Medtronic studies that included predicate LV leads, including Concerto AT, InSync III US study, Model 4194, 4195, 4196 and 4396 pre-market clinical studies. Table 7 displays adverse events classified as LV lead related. The incidence rate and 2-sided 95% Confidence Interval, for each event type are displayed to provide an estimate of percent of patients experienced such event in the historical dataset.

All events were collected and reviewed during the study phase and have been reclassified utilizing MedDRA, the Medical Dictionary for Regulatory Activities, to allow coding to a standard set of medical terms. The MedDRA Lowest Level Term (LLT) and the Preferred Terms (PT) are provided. The LLT is the specific granular term or verbatim term, and the PT is the linked parent term for the LLT that is the single medical concept.

Table 7: Observed LV Lead Related Adverse Events

Preferred Term	Lower Level Term	Number of Incidence	Number of Patients	Event Rate	95% Confidence Interval
Atrioventricular block		2	2	0.12%	(0.01% , 0.45%)
	Heart block	2	2	0.12%	(0.01%, 0.45%)
Cardiac perforation		1	1	0.06%	(0.00% , 0.34%)
	Cardiac perforation	1	1	0.06%	(0.00% , 0.34%)
Cardiac vein dissection		4	4	0.25%	(0.07% , 0.63%)
	Coronary sinus dissection	4	4	0.25%	(0.07% , 0.63%)
Cardiac vein perforation		1	1	0.06%	(0.00%, 0.34%)
	Coronary sinus perforation	1	1	0.06%	(0.00% , 0.34%)
Complication of device removal		4	4	0.25%	(0.07% , 0.63%)
	Complication of device removal	4	4	0.25%	(0.07% , 0.63%)
Decompensated heart failure		1	1	0.06%	(0.00% , 0.34%)
	Cardiac failure	1	1	0.06%	(0.00% , 0.34%)
Deep vein thrombosis		2	2	0.12%	(0.01% , 0.45%)
	Deep vein thrombosis	1	1	0.06%	(0.00% , 0.34%)
	Deep venous thrombosis arm	1	1	0.06%	(0.00% , 0.34%)
Device capturing issue		14	13	0.80%	(0.43% , 1.37%)
	Loss of capture	14	13	0.80%	(0.43% , 1.37%)
Device dislocation		58	55	3.40%	(2.57% , 4.41%)
	Lead dislodgement	58	55	3.40%	(2.57% , 4.41%)
Device electrical		1	1	0.06%	(0.00% , 0.34%)

Preferred Term	Lower Level Term	Number of Incidence	Number of Patients	Event Rate	95% Confidence Interval
impedance issue	Impedance increased	1	1	0.06%	(0.00% , 0.34%)
Device lead damage		2	2	0.12%	(0.01% , 0.45%)
	Lead conductor fracture	2	2	0.12%	(0.01% , 0.45%)
Device lead issue		1	1	0.06%	(0.00% , 0.34%)
	Device lead issue	1	1	0.06%	(0.00% , 0.34%)
Device pacing issue		37	36	2.23%	(1.57% , 3.07%)
	Elevated pacing threshold	37	36	2.23%	(1.57% , 3.07%)
Device stimulation issue		260	200	12.38%	(10.81% , 14.08%)
	Inappropriate device stimulation of tissue	9	8	0.50%	(0.21% , 0.97%)
	Inappropriate pectoral muscle stimulation	8	7	0.43%	(0.17% , 0.89%)
	Inappropriate phrenic nerve stimulation	17	13	0.80%	(0.43% , 1.37%)
	Inappropriate stimulation of diaphragm	226	176	10.89%	(9.41% , 12.51%)
Implant site infection		1	1	0.06%	(0.00% , 0.34%)
	Implant site infection	1	1	0.06%	(0.00% , 0.34%)
Implant site pain		1	1	0.06%	(0.00% , 0.34%)
	Implant site pain	1	1	0.06%	(0.00% , 0.34%)
Palpitations		3	3	0.19%	(0.04% , 0.54%)
	Palpitations	3	3	0.19%	(0.04% , 0.54%)
Pericardial effusion		1	1	0.06%	(0.00% , 0.34%)
	Pericardial effusion	1	1	0.06%	(0.00% , 0.34%)
Pneumothorax		1	1	0.06%	(0.00% , 0.34%)

Preferred Term	Lower Level Term	Number of Incidence	Number of Patients	Event Rate	95% Confidence Interval
	Pneumothorax	1	1	0.06%	(0.00% , 0.34%)
Septic shock		1	1	0.06%	(0.00% , 0.34%)
	Septic shock	1	1	0.06%	(0.00% , 0.34%)
Thrombosis		1	1	0.06%	(0.00% , 0.34%)
	Thrombosis	1	1	0.06%	(0.00% , 0.34%)

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

Cardiac rupture, cardiac tamponade, depression, dysplasia, electrical conduction disorders, emotional distress, implant tool delivery problem, tissue fibrosis, tissue necrosis, implant site seroma, inappropriate device therapy, inappropriate shocks, keloid scar, lead abrasion and discontinuity, insulation or conductor failure, mortality due to inability to deliver therapy, myocardial irritability or damage, nerve damage, pacemaker syndrome, pericardial rub, transient ischemic attack, valve damage, or venous stenosis.

L.3 Abbreviations

ADE	Adverse Device Effect
AE	Adverse Event
AEAC	Adverse Event Advisory Committee
AV	Atrioventricular
BiV	Biventricular
CIP	Clinical Investigation Plan
CRF	Case Report Form
CRT	Cardiac Resynchronization Therapy
DD	Device Deficiency
EC	Ethical Committee
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
EGM	Electrogram
EP	Electrophysiology
HF	Heart Failure
LBBB	Left Bundle Branch Block
LV	Left Ventricle
(M)EC	(Main)Ethical Committee
MRI	Magnetic Resonance Imaging
MSP	Multi Spot Pacing
RA	Right Atrium
RBBB	Right Bundle Branch Block

RV	Right Ventricle
SADE	Serious Adverse Device Effect
SAE	Serious Adverse Event
SOP	Standard Operating Procedure