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Medtronic

Clinical Investigation Plan

Clinical Investigation Plan/Study Title	REVAMP Study (REmodeling the Left Ventricle with Atrial Modulated Pacing)
Sponsor/Local Sponsor	Medtronic, Inc. Cardiac Rhythm and Heart Failure Clinical Research 8200 Coral Sea Street NE Mounds View, MN 55112 U.S.A. 1-800-328-2518
Document Version	3.0 27 APR 2018

Confidentiality Statement

Sponsor Contact

Medtronic, Inc. is sponsoring the REVAMP Clinical Research Study. Regional contact information is provided below. This information may be subject to change during the course of the clinical study. Periodic updates to study contact information will be sent to sites as needed.

Table 1: Study Sponsor Contact Information

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CROs/Core Laboratories

This information may be subject to change during the course of the clinical study. Periodic updates to study contact information will be sent to sites as needed.

Table 2: CRO and Core Laboratory Information

Contact Information	Role
Cognizant Technology Solutions 500 Frank W. Burr Blvd. Teaneck, NJ 07666 United States Direct Phone: (201) 801-0233 Direct Fax: (201) 801-0243	Review of electronic case report forms and management of discrepancies
Echocardiography Core Laboratory The Ohio State University 1960 Kenny Road, Columbus, Ohio 43210	Review of study echocardiograms
Blood Core Laboratory ACM Global Central Laboratory 160 Elmgrove Park | Rochester, NY 14624	Review of blood samples

1. Version History

Version	Summary of Changes	Author(s)/Title
1.0	• Not Applicable, New Document	Nancy Bennett, Prin. Field Clinical Site Specialist Jeff Lande, Prin. Statistician Teri Whitman, Sr. Prinicipal Scientist Matt Zmijewski, Distinguished Field Clinical Engineer
2.0	• Refer to Appendix G Table 17 for detailed changes	Andrea DeRoche, Prin. Clinical Research Specialist Teri Whitman, Sr. Prinicipal Scientist
3.0	• Refer to Appendix G Table 18 for detailed changes	Melinda Berg, Prin Field Clinical Engineer Jeff Lande, Prin Statistician Kristie Wallace, Sr Statistician Troy Jackson, Sr Prin Scientist

2. Investigator Statement

Investigators will be provided with a separate investigator agreement to document their obligation and commitment with respect to study conduct.

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3. Glossary

Term/Abbreviation	Definition
ACE	Angiotensin Converting Enzyme
ADE	Adverse Device Effect
ADL	Activities of Daily Living
AE	Adverse Event
ARB	Angiotensin Receptor Blocker
Bpm	Beats per minute
BNP	B-type Natriuretic Peptide
CIP	Clinical Investigation Plan
CH	Concentric Hypertrophy
CRF	Case Report Form
CTA	Clinical Trial Agreement
CV	Curriculum Vitae
Data protection authorization	A/an Authorization to Use and Disclose Personal Health Information/Research Authorization/other privacy language
DD	Device Deficiency
Echo	Echocardiography
eCRF	Electronic Case Report Form
ERI	Elective Replacement Indicator
Ethics Committee	MEC/IRB/HREB/Ethics Board
FAL	Foreseeable Adverse Event List
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act

Term/Abbreviation	Definition
GCP	Good Clinical Practice
Hall Walk	6 Minute Walk Test
HF	Heart Failure
HFpEF	Heart Failure With Preserved Ejection Fraction
HFrEF	Heart Failure With Reduced Ejection Fraction
IC Form	Informed Consent Form
IDE	Investigational Device Exemption
IRB	Institutional Review Board
LBBB	Left Bundle Branch Block
LV	Left Ventricular
LVEF	Left Ventricular Ejection Fraction
LVH	Left Ventricular Hypertrophy
MN	Minnesota
MNLWHF	Minnesota Living With Heart Failure
MMPs	Matrix Metalloproteinases
MRA	Mineralocorticoid Receptors Antagonist
MRI	Magnetic Resonance Imaging
NSR	Non-Significant Risk
NT-proBNP	N-terminal pro b-type Natriuretic Peptide
NYHA	New York Heart Association
OC	Oracle Clinical (electronic database)
QOL	Quality of Life
RA	Right Atrial

Term/Abbreviation	Definition
SADE	Serious Adverse Device Effect
SAE	Serious Adverse Event
SC	Steering Committee
SVT	Supraventricular Tachycardia
TIC	Tachycardia induced dilated cardiomyopathy
TIMPs	Tissue inibitors of metalloproteinases
TriV	Tri-ventricular
UR	Upper Rate
UADE	Unanticipated Adverse Device Effect
USADE	Unanticipated Serious Adverse Device Effect
WO	Work Order

4. Synopsis

Title	REVAMP Clinical Study (REmodeling the Left Ventricle with Atrial Modulated Pacing)
Clinical Study Type	Feasibility
Product Name	Medtronic dual chamber pacemakers with a Sleep function including: Kappa 700, Kappa 900, Adapta, Versa, Sensia, EnPulse, Advisa, Advisa MRI, and additional Medtronic dual chamber pacemakers with the Sleep Function as they become market released
Sponsor/Local Sponsor	Medtronic, Inc. Cardiac Rhythm and Heart Failure Clinical Research 8200 Coral Sea Street NE Mounds View, MN 55112 U.S.A. 1-800-328-2518
Indication under investigation	New therapy tested in heart failure with preserved ejection fraction (HFpEF) patients with approved indications for pacing
Investigation Purpose	The REVAMP Clinical Study is a feasibility study in heart failure with preserved ejection fraction (HFpEF) patients who have normal to small left ventricular volumes and evidence of hypertrophy. The pacemaker Sleep function will be used in order to deliver a 5 hour block of sustained pacing at 100 bpm during the night for 4-8 weeks. The purpose is to investigate whether this elevated pacing therapy is tolerated and whether there is a signal of efficacy.
Product Status	The study will be conducted using market-released Medtronic dual chamber pacemaker devices with a Sleep function and a Medtronic programmer. The protocol will specify the programming of the Sleep Rate and Pacing Parameters in order to deliver elevated atrial pacing rates during the time when the patient is sleeping.
Primary Objective(s)	The primary objective of this study is to assess the feasibility of using elevated night pacing as a therapy for heart failure with preserved ejection fraction.
Ancillary/Exploratory Objective(s)	Collect and characterize adverse events, quality of life, 6 Minute Walk Test, echo measurements and blood biomarker data at Baseline and follow-up visits
Study Design	The REVAMP Clinical Study will be a multi-center, prospective, randomized, single-blinded, clinical feasibility study.
Randomization	Subjects will be randomized at the 4 week follow-up visit to a 2:1 ratio to elevated night pacing ON or elevated night pacing OFF.

Sample Size	It is expected that up to 50 subjects may be enrolled to ensure 30 subjects undergo elevated night pacing at approximately 10 sites in the United States only.
Inclusion/Exclusion Criteria	Inclusion criteria: • Subject has had a market released dual chamber Medtronic Pacemaker with a Sleep function for at least 3 months • Subject is stable on current medications • Subject has dyspnea with exertion or diagnosed as NYHA Class II or III heart failure. • Subject has had a prior Echo in past 6 months with: EF ≥ 50% and Diastolic volume $\leq$80 ml/m^2 • Subject has evidence of hypertrophy (indexed to body surface area: men 115 g/m^2, women 95 g/m^2 or indexed to height: men 49.2 g/$m^{2.7}$, women 46.7 g/$m^{2.7}$) or Relative Wall thickness >0.42, or Wall Thickness$\geq$1.2cm (posterior wall) • Subject is willing to sign and date the study Informed Consent Form • Subject is 18 years of age or older, or of legal age to give informed consent per local law • Subject is expected to remain available for follow-up visits Exclusion criteria: • Subject has permanent AF or AF noted on baseline interrogation rhythm strip • Subject has uncontrolled BP; (systolic pressure needs to be >100mmHg and <160mmHg on medications) • Subject has severe stenosis of the aortic or mitral valve, defined as a valve area ≤ 1.0 cm^2 or subject has severe regurgitation of the aortic or mitral valve. • Subject has symptomatic COPD requiring oxygen • Subject's Pacemaker has less than 6 months of Pacemaker battery life • Subject had an aortic valve replacement (surgical or TAVR) procedure less than 9 months prior to enrollment • Subject's programmed upper rate limit is less than 100 bpm because of concerns of elevated pacing • Subject is unable or unwilling to perform the 6 Minute Walk Test at all scheduled study visits • Subject is currently enrolled or planning to enroll in a potentially confounding trial during the course of the study (co-enrollment in concurrent studies is only allowed when documented pre-approval is obtained from the Medtronic study manager) • Subject is pregnant • Subject meets any exclusion criteria required by local law

	• Subject's life expectancy is less than 12 weeks • Subject with a medical condition that precludes the patient from participation in the opinion of the investigator • Subject has known coronary disease with Class II angina
Study Procedures and Assessments	In Office Visits: Study procedures, assessments and in-clinic data collection will be at Enrollment/Baseline, 4 weeks, 8 weeks and 12 week visits. Telephone Call Follow Up Visits: Subjects will be called at regular intervals after their Baseline visit: 24 hours, 5 days, 2 weeks, 6 weeks, and 10 weeks to inquire about symptoms. Subjects will also be asked their heart rate which the subject can read using a finger pulse oximeter monitor that will be given to them at Baseline to use. Enrollment Baseline: • Informed Consent • Verification of Inclusion/Exclusion criteria • Subject Demographics • Medical History • Medications • Physical Assessment (including height, weight, heart rate and blood pressure) • NYHA classification • MN Living with Heart Failure Questionnaire • EQ-5D-5L Questionnaire • 6 Minute Walk Test • Blood Draw • Echo • Device Interrogation (initial) • Save to media (initial) • Program the sleep function to ON and program the pacing parameters • Subject observation of at least 30 minutes to ensure the subject can tolerate 100 bpm pacing post programming • Device Interrogation (final) - this needs to be completed at the end of the visit after programming has been completed • Save-to-Media (final) 24 Hour Telephone Call Follow Up Visit: • Symptom Assessment • Heart Rate 5 Day Telephone Call Follow Up Visit: • Symptom Assessment • Heart Rate 2 Week Telephone Call Follow Up Visit:

	• Symptom Assessment • Heart Rate 4 Week In-Clinic Follow Up Visit (Randomization): • Medications • Physical Assessment (including weight, heart rate and blood pressure) • NYHA classification • MN Living with Heart Failure Questionnaire • 6 Minute Walk Test • Blood Draw • Echo • Device Interrogation (initial) • Save-to-Media (initial) • Program the sleep function to OFF if randomization assignment is OFF (and program the pacing parameters) • Device Interrogation (final) - this needs to be completed at the end of the visit after programming has been completed • Save-to-Media (final) • Adverse Events (report new/assess ongoing AEs), Study Deviations, System Modifications, Device Deficiencies, Crossovers (as they occur) 6 Week Telephone Call Follow Up Visit: • Symptom Assessment • Heart Rate 8 Week In-Clinic Follow Up Visit: • Medications • Physical Assessment (including weight, heart rate and blood pressure) • NYHA classification • MN Living with Heart Failure Questionnaire • EQ-5D-5L Questionnaire • 6 Minute Walk Test • Blood Draw • Echo • Device Interrogation (initial) • Save-to-Media (initial) • Program the sleep function to OFF if subject still has sleep function ON (and program the pacing parameters) • Device Interrogation (final) - this needs to be completed at the end of the visit after programming has been completed • Save-to-Media (final)

	• Adverse Events (report new/assess ongoing AEs), Study Deviations, System Modifications, Device Deficiencies, Crossovers (as they occur) 10 Week Telephone Call Follow Up Visit: • Symptom Assessment • Heart Rate 12 Week In-Clinic Follow Up Visit (Exit): • Medications • Physical Assessment (including weight, heart rate and blood pressure) • NYHA classification • MN Living with Heart Failure Questionnaire • 6 Minute Walk Test • Blood Draw • Echo • Device Interrogation (initial) • Save-to-Media (initial) • Device Interrogation (final) - this needs to be completed at the end of the visit after programming has been completed • Save-to-Media (final) • Adverse Events (report new/assess ongoing AEs), Study Deviations, System Modifications, Device Deficiencies, Crossovers Early study exit (prior to 12 week visit): • Date of visit • Reason for exit • Adverse Events (report new/assess ongoing AEs), Study Deviations, System Modifications, Device Deficiencies, Crossovers • Complete a Scheduled/Unscheduled Follow Up eCRF, if applicable Unscheduled Follow Up: The following are recommended at the discretion of the investigator if deemed necessary: • Physical Assessment (including weight, heart rate and blood pressure) • Medications • Echo • Blood draw • Device Interrogation (initial) • Save-to-Media (initial) • Program the Sleep Function to protocol

	• Device Interrogation (final) - this needs to be completed at the end of the visit after programming has been completedSave to Media (final) The following are required: • Adverse Events (report new/assess ongoing AEs), Study Deviations, System Modifications, Device Deficiencies, Crossovers
Safety Assessments	Levels of Troponin and NT-proBNP will be monitored at all in office visits to assess for ischemia and elevated wall stress that may indicate worsening heart failure. All Adverse Events (AEs) that are potentially relevant will be collected which include system-related, programming-related, cardiovascular and serious adverse event information throughout the study duration, starting at the time of signing the Informed Consent Form. All new and/or worsening AE information, including all deaths will be collected throughout the clinical study duration. NT-pro BNP and Troponin will be collected at Baseline and at each subsequent in-office visit and changes will be assessed to ensure that the therapy is not leading to undue cardiac stress or ischemia. Documented pre-existing conditions are not considered an AE unless the nature or severity of the condition has worsened.
Endpoints	A number of measures of therapy safety, tolerability and efficacy will be explored as ancillary endpoints.
Statistics	As a feasibility study, this study is not powered to meet any specific endpoints.

5. Introduction

5.1. Background

An estimated 8.5 million people in the United States will have heart failure (HF) by 2030 [1], and approximately 50% of these HF patients will have a preserved ejection fraction (HFpEF) [2]. In contrast to HF with reduced EF (HFrEF), no effective drug or device therapies have been identified that improve the prognosis of the disease.

A large proportion of HFpEF patients have hypertension and have a concentric hypertrophic (CH) etiology described as an increased heart mass with increased relative wall thickness [3]. Cardiomyocytes in HFpEF are thicker than HFrEF, and collagen content is increased compared to controls [4]. Patients with concentric hypertrophy or evidence of increased wall thickness are characterized by an increase in end diastolic pressures and isovolumic relaxation time [5] compared to normal controls. HFpEF patients have relatively normal volumes and EF, but they have a reduced ability to adequately fill a stiffened left ventricle (LV). The impact of this diastolic dysfunction is more notable during exercise; HFpEF left ventricles are reliant on high left atrial pressures to fill the LV [4]. A search for a therapy that improves the compliance of the ventricle and improves early diastolic filling in these patients has not been successful.

We are proposing a pacing therapy that titrates a bolus of atrial pacing at 100 bpm delivered during sleeping hours with the hypothesis that raising heart rates can promote a beneficial LV dilation, which will reduce chamber stiffness and improve diastolic filling in HFpEF patients that have thickened ventricular walls and normal to small LV volumes. One challenge is finding a therapeutic heart rate dose that does not cause undesirable symptoms in ambulatory HF patients and a dose that achieves a desirable level of dilation to improve filling. Studies in animal models show that the dilatory effects of rapid pacing diminishes once the elevated pacing rates are discontinued [6-8] ; the study of dose response to elevated atrial pacing rate also includes monitoring the reaction of the heart to withdrawal of the pacing therapy.

Clinical studies of SupraVentricular Tachycardia (SVT) rates and durations that cause LV dilation are limited. An extreme example of elevated heart rates promoting significant dilation and LV dysfunction comes from the clinical observation of SVT induced cardiomyopathy. Medi et al [9] reported 10% incidence of tachycardia induced dilated cardiomyopathy (TIC) in N=345 patients undergoing ablation for atrial tachycardia. EF improved from 35 ± 11% to 59 ± 3% in the 2 months post-ablation. At the time of ablation treatment, the patients with LV dilation were characterized by slower ventricular response rates (117 ± 21 bpm vs 132 ± 33 bpm, p=0.05) and these patients reported that the duration of their symptoms started one or more years before seeking treatment. Conventional wisdom is that patients with more rapid ventricular responses are symptomatic and seek treatment more quickly before dilation and cardiomyopathy can occur from the rapid SVT.

Animal studies that have been used to study TIC have reported LV dilation and increased pulmonary capillary wedge pressures within 1 to 3 weeks when hearts are paced at extremely fast rates such as 240bpm [6]. However, the extent of dilation and symptoms can be titrated by choice of pacing rate and the duration of pacing. A study in a porcine model of concentric hypertrophy showed that 100% atrial pacing at 170bpm increased LV end-diastolic volumes by 246% in 4 weeks of pacing compared to an increase of 25% at a more modest rate of 125 bpm at 2 weeks of pacing (about 30bpm higher than normal sinus rhythm). The atrial pacing rate of 125bpm did not cause measurable changes in biomarkers including B-type natriuretic peptide [7].

Since this therapy is delivered in an ambulatory patient, the choice of pacing rate and duration to achieve a therapeutic dilation of the LV must not induce intolerable symptoms. A rate of 100bpm may be suitable for most HFpEF patients to respond favorably to stimulus rate, without symptoms. The nominal pacing rate setting for "Activities of Daily Living" (ADL) in Medtronic pacemakers is 95bpm and the upper pacing rate (UR) is 130 bpm, so a sustained pacing rate of 100bpm is well within normal pacing range [10]. The acute hemodynamic response to elevated pacing rates in supine patients with CH has been characterized to have a blunted inotropic response to pacing rates above 100bpm compared to normal subjects [5]. Stroke volumes have been shown to decrease from baseline as atrial pacing increases the rate above 120bpm in supine patients [5, 11, 12]. The force-frequency effect was reported to be positive at rates 20 and 40bpm above intrinsic rates in patients with left ventricular hypertrophy (LVH) [11]. However, Inagaki et al [13] showed that the force frequency relationship can be biphasic in some patients with severe LVH, with a decrease in LV max +dp/dt observed in some patients as pacing rates increased above a range of 100-130bpm. At a structural level, HFpEF is typically associated with concentric remodeling with an increased left ventricular (LV) mass-to-volume ratio or overt LV hypertrophy and fibrosis. A high prevalence of this structural phenotype in HFpEF was recently confirmed in the Treatment of Preserved Cardiac Function Heart Failure with an Aldosterone Antagonist (TOPCAT) trial [22]. Despite the inclusion of patients with LV chamber dilation in this trial, about a quarter of patients had below-normal chamber volumes.

Pacing at an elevated rate for 100% of the day may accelerate changes in cardiac structure, but could be symptomatic if elevated rates sustained for long periods of time. Elevating heart rate for 5 hours during sleep at night may reduce the sensation to elevated rates and minimize symptoms for the patients. However, a heart rate dose of 5 hours will increase the overall duration required to promote dilation in the LV chamber. A measurable change in LV volumes was measured at 2 weeks of 100% pacing at 125bpm in animals [7], so a reasonable therapy duration of 100bpm for 5 hours per day would be 4 to 8 weeks of pacing before changes in LV volume would be measured. Measurement of biomarkers including matrix metalloproteinases (MMPs) and tissue inibitors of metalloproteinases (TIMPs) may be useful in understanding the time course of changes that lead changes in geometry. The matrix metalloproteinases (MMPs) are part of an enzymatic system that contribute to the remodeling of the extracellular matrix during rapid pacing-induced cardiomyopathy [14]. MMP-1, MMP-2, and MMP-3 were shown to increase in abundance at 7 days following initiation of rapid pacing, and were temporally related to a measured decrease in the collagen content as well as a lengthening of cardiomyocytes. TIMPs are also involved in inhibiting MMPs enzymatic activity and elevated TIMP-1 with reduction in MMPs were reported in HFpEF patients with LV hypertrophy [15].

This proposed elevated atrial rate pacing therapy is aimed at improving exercise capacity in HFpEF patients. In order to safeguard patients, we propose measuring blood biomarkers including troponin and NT-proBNP in order to monitor indications that the therapy is not causing ischemia or worsening heart failure. Natriuretic peptide release occurs in response to myocardial stretch. BNP and NT-proBNP are moderately elevated in HFpEF patients and may drop to normal levels in symptom-free periods [16]. The European Society of Cardiology guidelines propose a cut-off of >35 pg/ml for BNP and >125 pg/ml for NT-proBNP to identify chronic, stable HFpEF patients [17]. Thresholds for acute HF have been reported as 100pg/ml for BNP and 300 pg/ml for NT-proBNP, which give sensitivity of 0.95 and 0.99 respectively, and negative predictive value of 0.94 and 0.98, respectively [18]. In a study of patients hospitalized for acute decompensated heart failure, a positive Troponin test for myocardial infarction was defined using a threshold of 1.0 µg/L or higher for cardiac Troponin I or 0.1 µg/L for cardiac Troponin T [19]. In an ambulatory chronic HFpEF population in 157 patients, the median value for Troponin I was 14 pg/mL (0.014 µg/L) [20]. A Troponin T threshold of 0.02 ng/mL (0.02 µg/L) was used in ambulatory HFpEF patients to detect myocardial injury; patients that had elevated Troponin T had an 78% rate of death or hospitalization at 18 months compared to 13% [21].

Metrics that will be used to evaluate whether there is a measurable therapeutic effect of the elevated atrial pacing rate therapy include serial measurements of quality of life, 6 Minute Walk Test, device-measured activity, echo measurements of volumes and diastolic function, and chronic changes in resting heart rate.

5.2. Purpose

Medtronic, Inc. is sponsoring the REVAMP study, a multi-center, prospective, randomized, single-blinded, clinical feasibility study. The REVAMP clinical study will include market-released pacemaker devices that incorporate the Sleep function. The purpose of the REVAMP Clinical Study is to assess whether elevating the atrial pacing rate for temporary periods of time is feasible. Data will be collected to characterize whether temporary atrial pacing rate elevation can lead to beneficial left ventricular (LV) chamber dilation, improvements in exercise capacity, and quality of life in a specific etiology of Heart Failure with Preserved Ejection Fraction (HFpEF) patients who have normal to small LV chambers and evidence of thickened walls.

6. Objectives and Endpoints

6.1 Objectives

6.1.1. Primary Objectives

The primary objective of this study is to assess the feasibility of using elevated night pacing as a therapy for HFpEF patients.

6.1.2. Ancillary/Exploratory Objectives

Adverse events, Minnesota Living With Heart Failure (MNLWHF) Questionnaire responses, EQ-5D-5L Questionnaire responses, 6 Minute Walk Test distances, resting heart rate, atrial fibrillation incidence, device-measured activity levels, echo measurements and blood samples will be collected at Baseline and follow-up visits as detailed in Section 10. Study Procedures. Adverse events will be collected as described in Section 12.1. Adverse Events and will be characterized to assess the overall safety and tolerability of the therapy, as described in Section 12.5.1. Adverse Event and Device Deficiency Classification. Changes in NT-proBNP and troponin concentrations from Baseline will also be used to assess patient safety. Early study patient withdrawals over the course of the study will be used to further assess therapy tolerability. Changes in quality of life, as assessed by the MN Living With Heart Failure and EQ-5D-5L, changes in 6 Minute Walk Test distance and change in activity levels will be compared from baseline to the various follow up time points to assess for therapy efficacy. Echo measurements and, optionally, peripheral blood concentrations of extracellular matrix biomarkers will be characterized and changes will be correlated with changes in the safety and efficacy assessments. End diastolic volume and mitral deceleration time could increase if the therapy works as hypothesized. If the quality of life, changes in 6 Minute Walk Test distance and/or activity levels improve, it will be of interest to see if the end diastolic volume and mitral deceleration time correlate with improvements. If the therapy works as hypothesized, other echo measurements, including left ventricular ejection fraction (LVEF), might also change over time, although the direction and magnitiude of these effects are difficult to predict. Characterizing these effects will be an important goal of the feasibility study.

6.2. Endpoints

As part of the exploratory/ancillary safety, tolerability and efficacy effects described in Section 14.1. Endpoint Definitions, it will be of interest to characterize changes in collected measurements from Baseline to 4 weeks, compare changes in collected measurements at 4 weeks to 8 weeks in the subjects randomized to the elevated night pacing ON arm to subjects randomized to the elevated night pacing OFF arm and compare changes in collected measurements at 12 weeks to Baseline, 4 and 8 weeks to see whether any therapeutic improvements are sustained after the therapy is discontinued.

6.2.1. Primary Endpoint

As a feasibility study, this study is not powered to meet any specific endpoints.

7. Study Design

The REVAMP Clinical Study will be a multi-center, prospective, randomized, single-blinded, clinical feasibility study. Subjects will be randomized in a 2:1 ratio to elevated night pacing ON or elevated night pacing OFF.

It is expected that up to 50 subjects may be enrolled to ensure approximately 30 subjects undergo elevated night pacing at approximately 10 sites in the United States to ensure enrollment completion within the pre-specified timeframe.

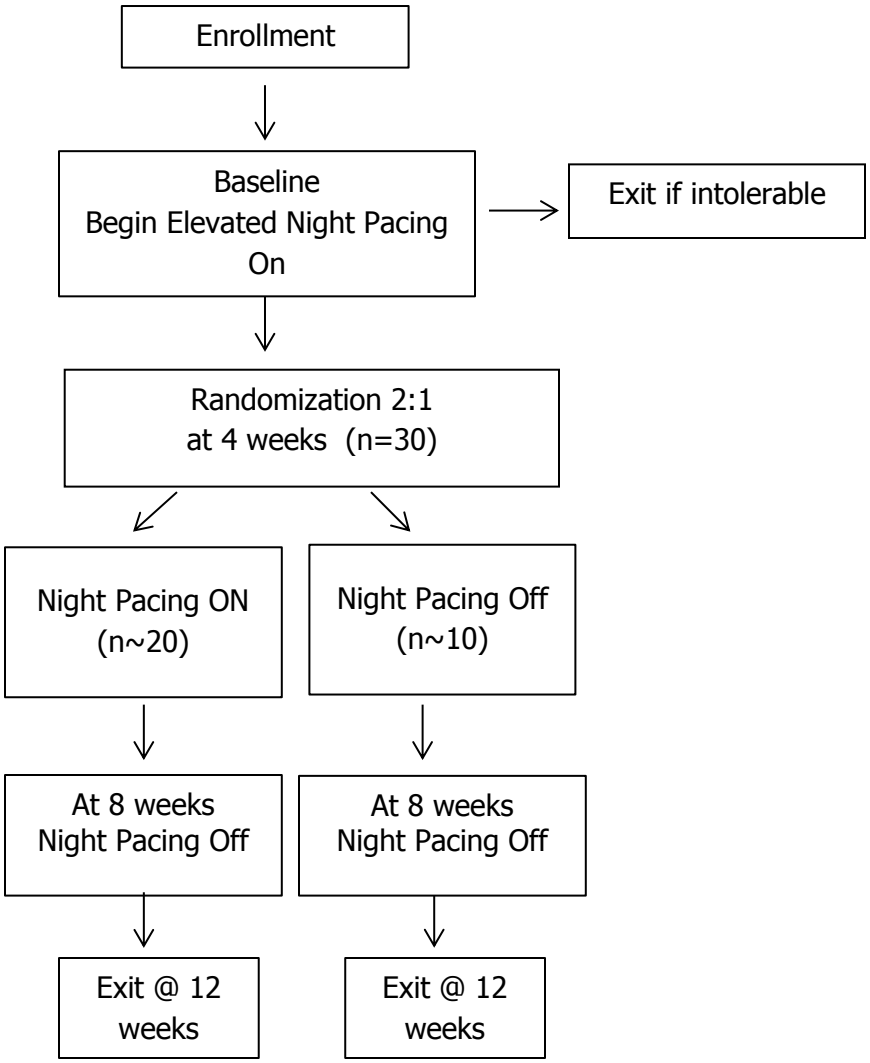
The REVAMP study will be conducted as a Non-Significant Risk (NSR) IDE study. The REVAMP Research System does not include an investigational device; the ability to program a lower rate of 100 bpm is available in market-released pacemakers, and the Sleep function (which allows a different rate to be programmed for part of a 24 hour clock) is an approved feature in market-released pacemakers that will be used in the clinical study. The study will be conducted in compliance with 21 CFR Parts 11, 50, 56, 812.2(b)(1). This study does not require an IDE submission to FDA.

The Sleep Function will be programmed so that the pacemaker can deliver an elevated pacing rate of 100 bpm during the night for 5 hours and lower the rate during the daytime hours. This is within the FDA-approved programmable parameters of the Sleep Function feature. The associated minimal risk will be minimized as described in Section 11.2. Risk Minimization.

The study will collect the following information: demographics, medical history, medications, standard physical, NYHA class, blood samples to measure NT-proBNP, Troponin and other biomarkers, echo measurements, MN Living with Heart Failure Questionnaire, EQ-5D-5L Questionnaire, 6 Minute Walk Test, implanted device information, device interrogations, save-to-media, adverse events (including death), system modifications, and exit information. The MN Living with Heart Failure Questionnaire was chosen to measure the quality of life for subjects with heart failure, which includes a question on how well the subject is sleeping at night.

See Section 10. Study Procedures. for further detail on study procedures and data collection as well as time-points for data collection.

Figure 1: In Office Study Visits



7.1. Duration

The study duration is expected to be approximately 24 months. This represents 21 months for subject enrollment and 3 months for subject follow-up after the last subject is randomized. Subjects are anticipated to be in the study for approximately 12 weeks completing in office visits at Enrollment/Baseline, 4 weeks, 8 weeks, and 12 weeks. Subject's device programming will be returned to standard pacemaker device settings per physician discretion at either 4 or 8 weeks after initiation of elevated night pacing, and subjects will be exited after completing the 12 week visit.

7.2. Rationale

It is expected that up to 50 subjects may be enrolled to ensure approximately 30 subjects will have elevated night pacing programmed ON for the first 4 weeks in order to evaluate whether the therapy is symptomatic. Limitations to the programming of the Sleep Function requires subjects to have a lower

rate of 100bpm programmed between the time they leave the Baseline visit and 5am the next morning when "Bed Time" will set the Sleep Rate at the pre-study lower rate of 60-70bpm. At the 4 week visit, there will be a safety assessment. Measurements of NT-proBNP will be used to assess whether dilation of the heart is signalling worsening heart failure. A Troponin assay will be used to ensure the elevated night pacing therapy isn't leading to ischemia. Subjects will be randomized at 4 weeks to elevated night pacing ON or OFF in order to gather data on the dose-response of the elevated night pacing therapy. Some patients may have sensation of an elevated heart rate from this programming, making blinded randomization difficult to achieve. All subjects will be followed for at least 4 weeks following termination of the elevated night pacing therapy in order to evaluate whether changes in quality of life, 6 minute walk tests and echo measurements persist after the therapy is discontinued. Previous work in animal studies have shown that cessation of elevated pacing rates can reverse the dilation of the LV chamber; this study will monitor the time course of that reversal by serial echo measurements, 6 minute walk tests and activity counts, and quality of life assessments.

7.3. Study Oversight

The study will utilize a Steering Committee (SC). The SC is responsible for the scientific content of the study and provides input for the execution. Members of the SC may be study site investigators. The purpose of the SC is to provide unbiased opinions and expertise to the clinical study design and process. The SC will support the execution of the REVAMP clinical study and provide guidance, feedback and direction to the clinical study. The SC is comprised of the members as indicated below.

Table 3: Steering Committee Members

Committee Member	Contact information
Eugene S. Chung, MD	CEO and President The Christ Hospital Cardiovascular Associates 2123 Auburn Ave, Ste 424 Cincinnati, OH 45219 (513) 585-1777 Eugene.Chung@thechristhospital.com
Markus Meyer, MD	Associate Professor of Medicine, Cardiovascular Medicine Department of Medicine Medicine-Cardiology, McClure Wing, 111 Colchester Avenue Burlington, VT 05401 (802) 847-3734 markus.meyer@uvm.edu
Michael Zile, MD	Professor of Medicine Medical University of South Carolina Department of Medicine Division of Cardiology 25 Courtenay Drive, ART 7063 MSC 592 Charleston, SC 29425 (843) 876-4761 zilem@musc.edu

The Echocardiography Core Laboratory (Echo Core Lab) will review and analyze all echo data collected for the study.

Further details for the Echo Core Lab are provided in CROs/Core Laboratories.

The Blood Core Laboratory (Lab) will review and analyze all blood data collected for the study.

Further details for the Blood Core Lab are provided in CROs/Core Laboratories.

8. Product Description

8.1. General

All Medtronic implantable pacemakers and associated programmer and monitoring equipment must be market-released. The Medtronic pacemakers must offer the Sleep Function feature. The pacing parameter Lower Rate will be programmed to 100bpm, and the Sleep Function will be used to lower the Sleep Rate to the pre-study lower rate (50-70 bpm) during 19 hours of the day. The Sleep Function will be programmed to deliver the Sleep Rate between 5a.m. and 11:30pm, using a Bed Time of 5a.m. and a Wake Time of 11:30pm. Subjects will receive 5 hours of elevated night pacing at 100bpm and 1 hour of a transition rate between 100bpm and the Sleep Rate. See Figure 2.

8.2. Intended Population

All subjects in this investigation have received a Medtronic dual chamber pacemaker for approved indications. HFpEF subjects who have a small to normal LV volume and evidence of LV hypertrophy and/or increased LV wall thickness will be selected for this study.

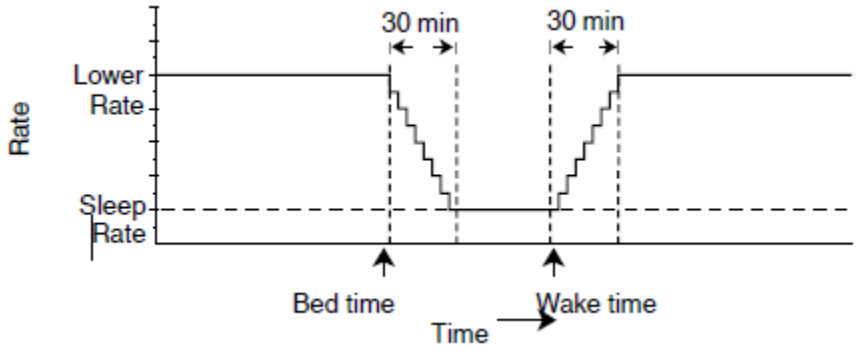
8.3. Study Components

- All Medtronic dual chamber pacemakers that have the Sleep Function
- Medtronic market-released programmers
- Compatible market-released leads
- Finger Pulse Oximeter Monitor (will be provided to the site)
- Echocardiography machine capable of recording and exporting echo data in digital format
- Access to dry ice to ship blood samples
- Computer with high speed internet access using a web browser compatible with the electronic data management system for electronic database entry

8.4. Product Use

The Sleep function in all Medtronic market-released devices was designed to temporarily substitute the programmed Lower Rate with a slower pacing rate (Sleep Rate) during the time of day that the patient normally sleeps. This feature can be programmed to lower the rate to the Sleep Rate at "Bed time" and to increase the rate back to the Lower Rate at "Wake time". The design intent of this feature was that the slower Sleep Rate can be programmed to occur during any window in the 24 hour clock; the difference between Bed Time and Wake Time must be a minimum of 2 hours. The REVAMP study proposes to use the lower Sleep Rate for 18 hours during the day, in order to elevate the Lower Rate to 100bpm and pace the atrium at an elevated rate at night. For the REVAMP study, we specify the Lower Rate programmed at 100bpm, with the Sleep Rate programmed to the pre-study value of the Lower Rate (e.g. 60bpm).

Figure 2: Sleep Function On During the Day



The Sleep Function will be programmed to deliver the Sleep Rate between 5a.m. and 11:30pm, using a Bed Time of 5a.m. and a Wake Time of 11:30pm.

The Sleep Function was designed to operate in conjunction with Rate Responsive pacing; however, the Rate Profile Optimization feature that automatically optimizes was not developed with 5 hours of 100bpm imposed on patients. Therefore, Rate Profile Optimization will be turned OFF while the Sleep Function is programmed ON.

The Sleep Function is suspended following any parameter programming operations. If the Sleep Function is suspended, the pacing rate will immediately return to the programmed Lower Rate (100bpm per this protocol) until the next Bed Time is reached. At the initial programming visit of this protocol, subjects will be evaluated for whether they are symptomatic at a Lower Rate of 100bpm. Subjects will leave the Baseline visit experiencing a Lower pacing rate of 100 bpm until 5am the next morning, when Bed Time for the Sleep Function is reached. After the elevated pacing has been turned ON, any telemetry activation, such as programming, magnet application or CareLink transmission will suspend the Sleep Function and the pacemaker will immediately return to the Lower Rate of 100 bpm until 5am.

If a pacemaker reaches Estimated Replacement Indicator (ERI), the device will automatically turn OFF the Sleep Function and reprogram the pacemaker to VVI 65 mode.

8.5. Product Receipt and Tracking

All product is market released and therefore does not need to be tracked.

9. Selection of Subjects

9.1. Study Population

This study will enroll patients who have a Medtronic dual chamber pacemaker system with the Sleep function per local guidelines and who meet all of the specific study inclusion criteria and none of the exclusion criteria.

9.2. Subject Enrollment

In order for subjects to be considered for enrollment, they must meet all of the inclusion criteria and none of the exclusion criteria. Notification of site activation from Medtronic, and approval from the IRB of the REVAMP Clinical Investigation Plan (CIP), Informed Consent Form (IC Form), Authorization to Use and Disclose Personal Health Information/Research Authorization/other privacy language (data protection authorization) as required by law, and any other applicable documents must be obtained prior to enrolling subjects in the study.

9.3. Inclusion Criteria

Subjects must meet all of the following inclusion criteria to be eligible to participate in the study:

INC 1: Subject has had a market released dual chamber Medtronic Pacemaker with a Sleep function for at least 3 months

INC 2: Subject is stable on current medications

INC 3: Subject has dyspnea with exertion or diagnosed as NYHA Class II or III heart failure.

INC 4: Subject has had a prior Echo in past 6 months with: EF ≥ 50% and Diastolic volume $\leq$80 ml/m^2

INC 5: Subject has evidence of hypertrophy (indexed to body surface area: men 115 g/m^2, women 95 g/m^2 or indexed to height: men 49.2 g/$m^{2.7}$, women 46.7 g/$m^{2.7}$) or Relative Wall thickness >0.42, or Wall Thickness$\geq$1.2cm (posterior wall)

INC 6: Subject is willing to sign and date the study Informed Consent Form (IC Form) and Authorization to Use and Disclose Personal Health Information/Research Authorization/other privacy language (data protection authorization) as required by law

INC 7: Subject is 18 years of age or older, or of legal age to give informed consent per local law

INC 8: Subject is expected to remain available for follow-up visits

9.4. Exclusion Criteria

Subjects must not meet any of the following exclusion criteria to be eligible to participate in the study:

EXC 1: Subject has permanent AF or AF noted on baseline interrogation rhythm strip

EXC 2: Subject has uncontrolled BP; (systolic pressure needs to be >100mmHg and <160mmHg on medications)

EXC 3: Subject has severe stenosis of the aortic or mitral valve, defined as a valve area less than or equal to 1.0 cm^2 or subject has severe regurgitation of the aortic or mitral valve.

EXC 4: Subject has symptomatic COPD requiring oxygen

EXC 5: Subject's Pacemaker has less than 6 months of Pacemaker battery life

EXC 6: Subject had an aortic valve replacement (surgical or TAVR) procedure less than 9 months prior to enrollment.

EXC 7: Subject's programmed upper rate limit is less than 100 bpm because of concerns of elevated pacing

EXC 8: Subject is unable or unwilling to perform the 6 Minute Walk Test at all scheduled study visits

EXC 9: Subject is currently enrolled or planning to enroll in a potentially confounding trial during the course of the study (co-enrollment in concurrent studies is only allowed when documented pre-approval is obtained from the Medtronic study manager)

EXC 10: Subject is pregnant

EXC 11: Subject meets any exclusion criteria required by local law

EXC 12: Subject's life expectancy is less than 12 weeks

EXC 13: Subject with medical condition that precludes the patient from participation in the opinion of the investigator

EXC 14: Subject has known coronary disease with Class II angina

9.5. Minimization of Bias

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

- Subjects will be evaluated at Baseline to confirm eligibility for enrollment with defined inclusion/exclusion criteria prior to randomization
- Subjects will be randomly assigned to their treatment assignment
- Subject demographics and medical history will be collected at Baseline and differences that may affect endpoints will be identified
- Subjects will be blinded to their randomization assignment
- Data collection requirements and study procedures will be standardized across all sites
- All study site personnel and Medtronic personnel will be trained on their respective aspects of the study using standardized training materials, and required to follow the CIP
- Monitoring visits will be conducted according to the study-specific monitoring plan.
- A single Echocardiography Core Lab will be used to analyze the echo data, and members of the core lab will be blinded to subject's randomization
- A single Blood Core Lab will be used to analyze the blood data
- Registration of the trial on ClinicalTrials.gov

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

10. Study Procedures

Prior to performing study related procedures, all sites must have IRB approval and documentation from Medtronic of site readiness.

Medtronic representatives may perform the following activities at the study sites during the study, if appropriately trained and under supervision of the Principal Investigator:

- Study training relevant and pertinent to the involvement of personnel conducting study activities and investigator responsibilities
- Technical support at all visits (e.g. programming of the pacemakers according to study requirements, performing device interrogations/save-to-media, etc.), but no CRF data entry shall be performed by Medtronic personnel
- Monitoring activities

At the request of the Principal Investigator or other authorized site personnel, Medtronic will use information from its device registration database to provide a study site a list of its patients whom the site had implanted with the Medtronic dual chamber pacemaker with Sleep Function, required by the inclusion criteria set out in Section 9.3. Study site, if permitted by its IRB, could further review the records of such patients to determine if they may be eligible to participate in the study.

10.1. Study Personnel Requirements

All clinical investigators managing the subject's heart failure must be qualified practitioners and experienced in the diagnosis and treatment of subjects with heart failure.

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

The principal investigator shall:

- Be qualified by education, training, and experience to assume responsibility for the proper conduct of the clinical investigation
- Be experienced in the field of application
- Disclose potential conflicts of interest that interfere with the conduct of the clinical investigation or interpretation of results

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

- Has the required number of eligible subjects needed within the recruitment period
- Has a qualified investigational site team and adequate facilities available for the foreseen duration of the clinical investigation

Site personnel training and delegation will be completed prior to participation in this clinical study.

10.2. Role of the Sponsor Representative

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

- Provide study training relevant and pertinent to the involvement of personnel conducting study activities and Investigator responsibilities
- Technical support at all visits under the supervision of a study Investigator, but no data entry, shall be performed by Medtronic personnel or their representatives at sites
- Monitoring activities

10.3. Site Activation

During the activation process (prior to subject enrollment), Medtronic will train site personnel on the CIP, relevant standards and regulations, obtaining informed consent, and on data collection and reporting tools. If new members join the study site team, they will receive training on the applicable clinical study requirements relevant to their role before contributing to the clinical study. For new members, local IRB notification requirements must be met, as well as Medtronic requirements.

A Clinical Trial Agreement (CTA) or Work Order (WO) shall be entered into effect by Medtronic, the participating investigation site and/or the principal clinical investigator at each investigational site as per local legal requirements, and returned, fully executed, to Medtronic prior to the commencement of any study activities. Financial aspects of conducting and reporting a study will be specified in the agreement. By signing and dating the agreement the investigation site indicates approval of the CIP.

Prior to performing study related activities, all sites must have IRB approval.

All local and regional regulatory requirements will be fulfilled prior to site activation and enrollment of subjects into the study. Each study site must have written documentation from Medtronic of site and investigator readiness before beginning any study-related activities. Requirements for activation may include, but are not limited to the following:

- Written documentation of IRB approval of the current version of the CIP, IC Form, Authorization to Use and Disclose Personal Health Information/Research Authorization/other privacy language (data protection authorization) as required by law, subject materials, and voting list (as required by local law)
- Fully executed CTA or WO on file with the sponsor
- Investigator Agreement
- Current Curriculum Vitae (CV)
- Financial Disclosure Agreement
- Documentation of delegated tasks
- Documentation of study site personnel training

Additional requirements imposed by the IRB shall be followed, if applicable.

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

10.4. Equipment Requirements

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

- Medtronic market-released programmers
- Echocardiography machine capable of recording and exporting echo data in digital format
- Access to dry ice for shipment of blood samples
- Computer with high speed internet access using a web browser compatible with the electronic data management system for electronic database entry

The maintenance and calibration of the programmers used for this study will be assessed outside of this clinical study. Sites are responsible for maintaining and calibrating non-programmer equipment used in the course of this study in accordance with established site practice. Records should be kept and able to be provided upon request by the Sponsor or regulatory agency.

10.5. Schedule of Events

Clinical data is collected at designated time points throughout the study as indicated in Table 4 below. Data will be collected using eCRFs, an electronic data management system for clinical studies. See Section 16.2. Data Management for more information. At the baseline, 4 week, 8 week, and 12 week visits subjects are to fill out the MN Living with Heart Failure Questionnaire and perform a 6 Minute Walk Test. At the same visits, an echocardiogram must be done, for which instructions are provided in an Echocardiography Handbook (provided under separate cover). A blood draw must also be done,

(instructions are provided under separate cover.) The device programming should occur after all other study procedures are complete, except for the final device interrogation and save-to-media. The EQ-5D-5L Questionnaire will only be collected at the Baseline and 8 week visits.

In addition to eCRF data, non-eCRF data will be collected to include device interrogation files/save-to-media and digital echo data.

Table 4: Study Procedures

Study Procedure	Enroll-ment	Baseline	Telephone Call Follow Up Visits (24 Hour, 5 days, 2 weeks, 6 weeks, 10 weeks)	4 week visit	8 week visit	12 week visit (Study Exit)	Early Study Exit	Unscheduled Visit
Informed consent	x							
Inclusion/exclusion	x	x						
Demographics		x						
Medical History		x						
Medications		x	X	x	X	x	X	x**
Physical Assessment		x		x	X	x		x**
NYHA class		x		x	X	x		
MN Living with Heart Failure Questionnaire		x		x	X	x		
EQ-5D-5L Questionnaire		x			X			
6 Minute Walk Test		x		x	X	x		
Echo		x		x	X	x		x**
Blood Draw		x		x	X	x		x**
Initial Device Interrogation/Save-to-media		x		x	X	x	x	x**
Device Programming		x		x*	x*		x**	x**
Final Device Interrogation/ Save-to-Media		x		x	X	x	x	x**
At least 30 minute observation period post device programming		x						
Symptom Assessment			X	x	X	x		x**

Study Procedure	Enroll-ment	Baseline	Telephone Call Follow Up Visits (24 Hour, 5 days, 2 weeks, 6 weeks, 10 weeks)	4 week visit	8 week visit	12 week visit (Study Exit)	Early Study Exit	Unscheduled Visit
Heart Rate (using finger oximeter)			X					
Crossover			As they occur					
System modifications	As they occur							
Adverse events (AEs)/Death	As they occur							
Device Deficiencies	As they occur							
Study deviations	As they occur							
Study Exits	As they occur							

* See programming recommendations for the follow up visit
** If deemed necessary by the investigator

Table 5 below specifies permitted time windows for the required subject visits. Should a subject miss a visit or the visit falls outside the pre-specified window, a study deviation must be reported and the original follow-up schedule maintained for subsequent visits. Data analyses will include follow-up visits, regardless of whether the visit occurs within the window. Therefore, a late visit is preferred over a missed visit but must be accompanied by a deviation.

Table 5: Visit windows

Visit	Must occur between	After reference visit
Baseline	0 - 30 days	Enrollment
24 Hour Phone Call	0-1 day	Baseline
5 Day Phone Call	2 - 8 days	Baseline
2 Week Phone Call	11 – 17 days	Baseline
Randomization – 4 week visit	21 – 35 days	Baseline
6 Week Phone Call	39 – 45 days	Baseline
8 Week Visit	49 – 63 days	Baseline
10 Week Phone Call	67 – 73 days	Baseline
12 Week Visit (Exit)	77 - 91 days	Baseline

10.6. Prior and Concomitant Medications

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

At baseline, 4, 8, and 12 week follow up visits, all telephone call follow up visits, unscheduled visits, and early exit visits, cardiovascular medications and the use of insulin will be collected. Cardiovascular medications include: ACE inhibitors, ARBs, MRAs, antiarrhythmics, anti-coagulants and antiplatelets, antihypertensives, antilipidemics (incl. statins), ß-blockers, calcium channel blockers, diuretics, digitalis, inotropes, nitrates, digoxin, and vasodilators.

10.7. Subject Consent

Informed consent is defined as a legally effective documented confirmation of a subject's voluntary agreement to participate in a particular clinical study after information has been given to the subject on all aspects of the clinical study that are relevant to the subject's decision to participate. This process includes obtaining an Informed Consent Form and an Authorization to Use and Disclose Personal Health Information/Research Authorization/other privacy language (data protection authorization) as required by law that has been approved by the study site's IRB, and Medtronic, and signed and dated by the subject and the Principal Investigator or an authorized designee. A subject may only consent after information has been given to the subject on all aspects of the clinical study that are relevant to the subject's decision to participate.

Prior to enrolling subjects, each site must have documented IRB approval of the Informed Consent Form (IC Form) and an Authorization to Use and Disclose Personal Health Information/Research Authorization/other privacy language (data protection authorization) as required by law. Any changes to a previously approved Informed Consent Form throughout the course of the study must be reviewed and approved by Medtronic and the IRB reviewing the application before being used to obtain consent or re-consent a study subject. The document(s) must be controlled (i.e. versioned and dated) to ensure it is clear which version(s) were approved by Medtronic and the IRB. All important new information should be provided in written form to new and existing subjects throughout the study. If relevant, all affected subjects must be asked to confirm their continuing informed consent in writing.

Prior to initiation of any study-specific procedures, informed consent must be obtained from the subject. Likewise, privacy or health information protection regulation may require subjects to sign additional forms to authorize sites to submit subject information to the study sponsor. Obtaining informed consent must be conducted by the principal investigator or an authorized designee, and the Informed Consent Form and an Authorization to Use and Disclose Personal Health Information/Research Authorization/other privacy language (data protection authorization), as required by law, must be given to the subject in a language he/she is able to read and understand.

The process of obtaining informed consent shall:

- Ensure that the principal investigator or an authorized designee obtains the informed consent process.
- Include all aspects of the clinical study that are relevant to the subject's decision to participate throughout the clinical study.
- Avoid any coercion or undue improper influence on, or inducement of the subject to participate.
- Not waive or appear to waive the subject's legal rights.
- Ensure the Informed Consent Form and an Authorization to Use and Disclose Personal Health Information/Research Authorization/other privacy language, (data protection authorization) as required by law, are given to the subject in a non-technical language the subject is able to read and understand.
- Provide ample time and opportunity for the subject to read and understand the Informed Consent Form to inquire about details of the study, and to consider participation. All questions about the study should be answered to the satisfaction of the subject.
- Include a personally dated signature of the subject acknowledging that their participation in the study is voluntary.
- Include a personally dated signature by the principal investigator or authorized designee responsible for obtaining the informed consent, as required by local law.
- Provide the subject with a copy of the Informed Consent Form and an Authorization to Use and Disclose Personal Health Information/Research Authorization/other privacy language (data protection authorization) as required by law.
- Ensure subjects are notified of any significant new findings about the study that become available during the course of the study which are pertinent to the safety and well-being of the subject, as this could impact a subject's willingness to participate in the study.

If the informed consent is obtained the same day the subject begins participating in study-related procedures, it must be documented that consent was obtained prior to participation in any study-related procedures. It is best practice for the process of obtaining the informed consent to be documented in the subject's case history, regardless of circumstance.

In the event the subject cannot read and/or write, witnessed (impartial third party) informed consent will be allowed, provided detailed documentation of the process of obtaining the informed consent is recorded in the subject's case history and the witness signs and dates the Informed Consent Form. Informed consent shall be obtained through a supervised oral process. An independent witness must be present throughout the process. The IC Form and any other information must be read aloud and explained to the prospective subject, if allowed by local law. The witness signs and personally dates the Informed Consent Form attesting that the information was accurately explained and that informed consent was freely given. The subject should "make his mark" (sign or otherwise physically mark the document so as to indicate consent) on the Informed Consent Form as well. The Informed Consent Form

should document the method used for communication with the prospective subject and the specific means by which the prospective subject communicated agreement to participate in the study.

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

The Informed Consent Form and an Authorization to Use and Disclose Personal Health Information/Research Authorization/other privacy language (data protection authorization) as required by law, must be available for monitoring, auditing and regulatory inspections. Any Medtronic personnel who support the initial programming of the elevated night pacing must be able to review the subject's signed and dated Informed Consent Form and verify its completeness prior to proceeding with the programming. In the event the designated Medtronic personnel identify the IC Form as being incomplete, the programming will not be allowed to occur until the consent of the subject can be adequately and appropriately obtained.

10.8. Enrollment

A subject is considered enrolled when the Informed Consent Form has been signed and dated. The date the subject signed the Informed Consent Form and an Authorization to Use and Disclose Personal Health Information/Research Authorization/other privacy language (data protection authorization) as required by law, must be documented in the subject's medical records. Enrollment can be a stand-alone visit or can occur on the same day as the Baseline Visit. Once consent is obtained, report adverse events/deaths, study deviations and subject exits as they occur.

10.9. Baseline Visit

The Baseline Visit must occur within 30 days after subject enrollment. The Baseline visit can be a stand-alone visit or can be performed on the same day as consent is obtained and documented in the subject's medical chart. If eligibility verification at the Baseline visit shows that the subject does not meet all inclusion and exclusion criteria the subject must be exited. The device programming should occur after all other study procedures are complete, except for the final device interrogation and save-to-media.

The subject will be provided at the Baseline Visit with a finger pulse oximeter monitor to use at home during the telephone follow-up visits to measure their heart rate. The finger pulse oximeter should be returned to the site at the study exit visit.

In the event a subject experiences symptoms at home after the Baseline visit, the subject will be instructed to seek medical help to determine the cause of the symptoms.

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

- Verification of Inclusion/Exclusion criteria
- Subject Demographics
- Medical History
- Medications
- Physical Assessment (including height, weight, heart rate and blood pressure)
- NYHA Class
- MN Living with Heart Failure Questionnaire
- EQ-5D-5L Questionnaire
- 6 Minute Walk Test
- Echo*
- Blood Draw**

- Device Interrogation (initial)
- Save-to-Media (initial)
- Device Programming, see Table 6.
- Subject observation of at least 30 minutes to ensure the subject can tolerate 100 bpm pacing post programming
- Device Interrogation (final) - this needs to be completed at the end of the visit after programming has been completed
- Save-to-Media (final)

*The Baseline echo must be sent to the Echocardiography Core Laboratory (echo core lab) for analysis, with a copy of the echo remaining at the site. Details of the echo core lab, type of echo to be performed, and the review process will be provided in an Echocardiography Handbook (provided under separate cover).

** The baseline blood sample must be sent to the Blood Core Laboratory for analysis. Details of the blood core lab and the blood draw process will be provided under separate cover.

10.9.1. Programming Recommendations at Baseline

Table 6 lists the programming recommendations applicable to all study subjects. At the Baseline visit, when the Sleep Function is turned ON, the pacing rate will remain at the 100 bpm setting until 5:00 am the next day. Use of AAI (R) programming is not recommended due to the possibility of AV block occurring at higher rate pacing.

Table 6: Programming Recommendations at Baseline

Parameter	Elevated Night Pacing ON
Sleep function	On[†]
Sleep Rate	Whatever was previously programmed as Lower Rate
Bed Time	05:00 (5am) [††]
Wake Time	23:30 (11:30pm) [††]
Pacing Parameter: Lower Rate	100 bpm
Rate response	ON (if previously programmed ON)
ADL	$\geq$ 105 bpm
Rate Profile Optimization	Off
ADL Setpoint	Previously programmed value as ADL Setpoint plus 5
UR Setpoint	Previously programmed value as UR Setpoint plus 5

[†] After the Sleep Function is turned ON, any telemetry activation, such as programming, magnet application or CareLink transmission – the ongoing sleep function will be terminated which means the programmed rate will jump to 100 bpm. If ERI is detected, the pacemaker will turn the Sleep function to Off and the Lower Rate will be reprogrammed to VVI 65 automatically.

[††]If the subject's normal sleep hours are not during 11:30 pm – 5:00 am, adjust the Bed Time and Wake Time to keep the 5 hours of pacing aligned with the time that the subject will likely be sleeping.

10.10. Scheduled Follow-Up Phone Calls

The participating investigator/study coordinator will attempt to reach the subject for phone calls at regular intervals after the Baseline visit (24 hours, 5 days, 2 weeks, 6 weeks, 10 weeks) to inquire about symptoms and medications. A standard set of questions to use when inquiring about symptoms and medications will be provided to the sites. Subjects will also be asked their heart rate, which the subject can read using a finger pulse oximeter monitor that will be given to them at Baseline to use.

10.11. Randomization (4 Week Follow-Up)

Subjects will be assigned to a group at random during the randomization visit. Randomization will occur at 4 weeks.

Subjects will be randomized in a 2:1 ratio to the Elevated Night Pacing ON or to the Elevated Night Pacing OFF group.

Sites will receive this randomization assignment from the randomization schedule, which is automatically populated on the eCRF.

Procedures to be performed and data to be collected at Randomization include:

- Physical Assessment (including weight, heart rate, symptoms, and blood pressure)
- Medications
- NYHA Class
- MN Living with Heart Failure Questionnaire
- 6 Minute Walk Test
- Echo*
- Blood Draw**
- Randomization assignment
- Device Interrogation/ (initial)
- Save-to-Media (initial)
- Device Programming, see Table 7: Programming Recommendations at 4 Week Follow-Up
- Device Interrogation (final) - this needs to be completed at the end of the visit after programming has been completed
- Save-to-Media (final)
- Adverse Events (report new/assess ongoing AEs), Study Deviations, System Modifications, Device Deficiencies, Crossovers (as they occur)

*The echo must be sent to the Echo Core Laboratory for analysis, with a copy of the echo remaining at the site. Details of the Echo Core Laboratory, type of echo to be performed, and the review process will be provided in an Echocardiography Handbook (provided under separate cover).

** The blood sample must be sent to the Blood Core Laboratory for analysis. Details of the blood core lab and the blood draw process will be provided under separate cover.

For any subject who has an abnormal NT-proBNP, troponin or LVEF measurement as defined in the Safety Assessment (Section 10.19. Assessment of Safety) and the investigator elects to discontinue elevated night pacing, a subsequent visit will be necessary for the elevated night pacing to be programmed OFF if the subject was randomized to the elevated pacing ON arm. The subject should continue to be followed through the 12 week visit.

10.11.1. Blinding

The study will be single blinded (i.e., subjects are blinded to their group) to reduce bias for the duration of the study. It is essential that sites, including echocardiography staff, take special precaution to maintain the blind for the entire portion of the subject's participation in the study. Other options to maintain the blind may be applied per investigational site research procedure. Refer to the Randomization and Blinding Plan for specific details.

10.11.2. Programming Recommendations at 4 Week Follow-Up

Table 7 lists the programming recommendations applicable to study subjects, according to their respective randomization assignment.

Table 7: Programming Recommendations at 4 Week Follow-Up

Parameter	Elevated Night Pacing ON	Elevated Night Pacing OFF
Sleep function	ON†	Per physician discretion
Sleep Rate	Whatever was previously programmed as Lower Rate	Per physician discretion
Bed Time	05:00 (5am) ††	Per physician discretion
Wake Time	23:30 (11:30pm) ††	Per physician discretion
Pacing Parameter: Lower Rate	100 bpm	Per physician discretion
Rate response	ON (if previously programmed ON)	Per physician discretion
ADL	≥ 105 bpm	Per physician discretion
Rate Profile Optimization	OFF	Per physician discretion
ADL Setpoint	Previously programmed value as ADL Setpoint plus 5	Per physician discretion
UR Setpoint	Previously programmed value as UR Setpoint plus 5	Per physician discretion

† After the Sleep Function is turned ON, any telemetry activation, such as programming, magnet application or CareLink transmission – the ongoing sleep function will be terminated which means the programmed rate will jump to 100 bpm.
If ERI is detected, the pacemaker wil automatically turn the Sleep function to Off and program the pacing mode and rate to VVI 65.
††If the subject's normal sleep hours are not during 11:30 pm – 5:00 am, adjust the Bed Time and Wake Time to keep the 5 hours of pacing aligned with the time that the subject will likely be sleeping.

10.12. 8 Week Follow-Up

The following procedures must be performed / data are required to be collected at the 8 week visit:

- Physical Assessment (including weight, heart rate, symptoms and blood pressure)
- Medications
- NYHA Class
- MN Living with Heart Failure Questionnaire
- EQ-5D-5L Questionnaire
- 6 Minute Walk Test
- Echo*
- Blood Draw**

- Device Interrogation (initial)
- Save to media (initial)
- Device Programming, see Table 8.
- Device Interrogation (final) - this needs to be completed at the end of the visit after programming has been completed
- Save-to-Media (final)
- Adverse Events (report new/assess ongoing AEs), Study Deviations, System Modifications, Device Deficiencies, Crossovers (as they occur)

*The echo must be sent to the Echo Core Laboratory for analysis, with a copy of the echo remaining at the site. Details of the Echo Core Laboratory, type of echo to be performed, and the review process will be provided in an Echocardiography Handbook (provided under separate cover).

** The blood sample must be sent to the Blood Core Laboratory for analysis. Details of the blood core lab and the blood draw process will be provided under separate cover.

10.12.1. Programming Recommendations

Table 8 lists the programming recommendations applicable to study subjects who still have elevated night pacing ON. (All subjects should have elevated night pacing OFF by the end of the 8 week visit.)

Table 8: Programming Recommendations at 8 Week Follow-Up

Parameter	Elevated Night Pacing OFF
Sleep function	Per physician discretion
Sleep Rate	Per physician discretion
Bed Time	Per physician discretion
Wake Time	Per physician discretion
Pacing Parameter: Lower Rate	Per physician discretion
Rate response	Per physician discretion
ADL	Per physician discretion
Rate Profile Optimization	Per physician discretion
ADL Setpoint	Per physician discretion
UR Setpoint	Per physician discretion

10.13. Unscheduled Follow-Up Visits

An unscheduled visit is defined as any unplanned visit by the subject to the study site. Routine visits or other planned visits are not collected.

The following information is recommended to be collected at an unscheduled follow-up visit at the discretion of the investigator if deemed necessary:

- Physical Assessment (including weight, heart rate, symptoms and blood pressure)
- Medication changes
- Echo*
- Blood draw**
- Device Interrogation (initial)
- Save-to-Media (initial)
- Program the Sleep Function and parameters to protocol
- Device Interrogation (final) - this needs to be completed at the end of the visit after programming has been completed
- Save to Media (final)

The following is required:

- Adverse Events (report new/assess ongoing AEs)
- Study Deviations
- System Modifications
- Device Deficiencies
- Crossovers

*The echo must be sent to the Echo Core Laboratory for analysis, with a copy of the echo remaining at the site. Details of the Echo Core Laboratory, type of echo to be performed, and the review process will be provided in an Echocardiography Handbook (provided under separate cover).

** The blood sample must be sent to the Blood Core Laboratory for analysis. Details of the blood core lab and the blood draw process will be provided under separate cover.

10.14. 12 Week Visit (Study Exit)

At the completion of the 12 week follow-up visit, subjects will be exited from the study since this is the final visit. The 12 week follow-up visit and exit visit should be combined, and both a 12 week follow-up eCRF and a Study Exit eCRF need to be completed.The following procedures must be performed / data are required to be collected at the 12 week visit:

- Medications
- Physical Assessment (including weight, heart rate, symptoms and blood pressure)
- NYHA Class
- MN Living with Heart Failure Questionnaire
- 6 Minute Walk Test
- Echo*
- Blood Draw**
- Device Interrogation (initial)
- Save to Media (initial)
- Program the sleep function and pacing parameters to elevated night pacing OFF (see Table 8) for subjects who still have their pacemaker programmed to elevated night pacing ON.

- Device Interrogation (final) - this needs to be completed at the end of the visit after programming has been completed
- Save-to-Media (final)
- Adverse Events (report new/assess ongoing AEs), Study Deviations, System Modifications, Device Deficiencies

* The echo must be sent to the Echo Core Laboratory for analysis, with a copy of the echo remaining at the site. Details of the Echo Core Laboratory, type of echo to be performed, and the review process will be provided in an Echocardiography Handbook (provided under separate cover).

** The blood sample must be sent to the Blood Core Laboratory for analysis. Details of the blood core lab and the blood draw process will be provided under separate cover.

10.15. Study Exit

Subjects will be exited from the study for any of the following situations:

- Study completed
- Subject death
- Subject lost to follow-up
- Subject chooses to exit (i.e. revokes informed consent)
- Investigator withdraws subject
- Subject has intolerable symptoms that cannot be alleviated by reprogramming

A Study Exit eCRF needs to be completed for all subjects with the date and reason for the exit. The following should also be collected if applicable:

- Scheduled/Unscheduled Follow Up eCRF, if applicable
- Adverse Events, Study Deviations, System Modifications, Device Deficiencies

The finger pulse oximeter should be returned to the stie at the study exit visit. After all study tests and procedures have been completed and just prior to subject exit from the study, the subject may be informed (verbally or in written form) of the subject's randomization assignment.

Following exit, subjects will continue to receive standard medical care and should be managed and followed per physician discretion. There will be no further required study-related follow-up visits for these subjects.

10.15.1. Lost to Follow-Up

In the case that the subject is determined to be lost to follow-up, details of a minimum of two attempts to contact the subject, and the method of attempt (e.g., one letter and one phone record, or two letters) must be recorded.

10.15.2. Subject Does Not Meet Eligibility Criteria

If eligibility is not met, the subject must be exited prior to study procedures and device programming.

10.15.3. Subject chooses to exit (i.e. revokes informed consent)

A subject can withdraw from the study at any time. If the subject wishes to exit from the study (i.e. the subject revokes informed consent), the site is required to document the reason for exit on the Study Exit eCRF.

10.15.4. Investigator Withdraws Subject

No subjects should be withdrawn by investigators unless compelling medical justification is present. It is recommended investigators discuss any withdrawals with the study team prior to exiting subjects. If the subject was randomized, it is preferred to keep the subject in the study and perform study procedures / collect data to the extent possible. If an Investigator withdrawal is necessary, the site is required to document the reason for exit on the Study Exit eCRF.

10.16. Device Interrogation / Save-to-Media

For the Baseline, Randomization and in clinic follow-up visits, an initial interrogation and final device interrogation file (since last session) must be obtained (.pdd) and saved in a digital format (Save-to-Media). Store one copy of the save-to-media at the site and send a copy to Medtronic. It is recommended that data are not cleared during any interrogation.

An initial interrogation and final device interrogation (since last session) and Save-to-Media should also be completed at the time of study exit, for a crossover, a system modification, and in the case of a death (where possible).

10.17. System Modification

A system modification will be reported in the event the device and/or leads require invasive modification (e.g. generator or lead explant, generator or lead replacement, lead repositioning, etc.). In the event of a system modification, regardless of outcome of the modification, subjects should remain in the study when possible and the follow-up visit schedule for the subject will remain unchanged. For a system modification the following information/activities are required to be collected:

- Report the reason for the system modification
- Report the details of the system modification procedure
- Device interrogation (initial and final)
- Save-to-Media (a copy of the interrogation files must be sent to Medtronic with a copy also being maintained at the site)
- Report the associated AE or Device Deficiency, if applicable

It is recommended that all explanted Medtronic products (device, leads, etc.) are returned to Medtronic for analysis per local process and when permissible by local laws and regulations.

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

10.18. Deviation Handling

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

Prior approval by Medtronic is expected in situations where the investigator anticipates, contemplates, or makes a conscious decision to deviate. Prior approval is not required when a deviation is necessary to protect the safety, rights or well-being of a subject in an emergency or in unforeseen situations beyond the investigator's control (e.g. subject failure to attend scheduled follow-up visits, inadvertent loss of data due to computer malfunction, inability to perform required procedures due to subject illness, blood sample or echo lost at Core Lab).

For medically justifiable conditions which preempt a subject's ability to complete a study-required procedure, it may be permitted to report only one deviation which will apply to all visits going forward. This may also apply for other unforeseen situations (e.g. the subject permanently refuses to complete a study required procedure and the data will not contribute to the primary end point analysis). However, prior approval from Medtronic is required for such situations.

All study deviations must be reported to Medtronic regardless of whether they are medically justifiable, pre-approved by Medtronic, an inadvertent occurrence, or taken to protect the subject in an emergency. The deviation must be recorded in Oracle Clinical (see Section 10.18. Deviation Handling) with an explanation for the deviations.

In the event the deviation involves a failure to obtain a subject's informed consent, or is made to protect the life or physical well-being of a subject in an emergency, the deviation must be reported to the IRB as well as Medtronic as soon as possible but no later than five (5) working days, or according to local requirements. Reporting of all other study deviations should comply with the IRB policies and/or local laws and deviations must be reported to Medtronic as soon as possible upon the site becoming aware of the deviation.

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

10.19. Assessment of Safety

As a feasibility study, the primary objective is to assess the feasibility of using elevated night pacing as a therapy for heart failure with preserved ejection fraction. This includes assessing the safety and tolerability of elevated night pacing, as described in Section 5.1. Background. Subjects who experience intolerable symptoms from the elevated pacing therapy and whose symptoms cannot be reconciled by reprogramming may have the elevated night pacing programmed OFF. NT-proBNP, troponin, assessed from peripheral blood samples and LVEF, as assessed by the echo, will be collected at Baseline and at the 4 week visit. Subjects with increases in NT-proBNP and troponin from Baseline to the 4 week visit should be monitored by the investigator for accompanying symptoms, including worsening heart failure and cardiac ischemia. Symptoms should be reported as adverse events and subjects will be considered for withdrawal from the study, at the discretion of the investigator. Subjects with 4 week LVEF < 45% whose baseline LVEF was at least 55% may also be considered for withdrawal from the study at the discretion of the investigator. NT-proBNP, troponin and LVEF will be further assessed as discussed in Section 10.11. Randomization (4 Week Follow-Up) and Section 14.1.2. Ancillary Safety Endpoint – NT-proBNP, troponin, LVEF. Further information on the collection of Adverse Events is discussed in Section 12.5. Reporting of Adverse Events.

10.20. Assessment of Efficacy

Assessment of efficacy will be done on an exploratory basis. Quality of life, mobility and echo measurements will be collected and assessed as discussed in Sections 6.1 Objectives and 14.1. Endpoint Definitions.

10.21. Recording Data

The study will collect data using Oracle Clinical, an electronic data management system for clinical studies. Sites will enter data onto eCRFs within an Oracle Clinical database.

Data reported on the eCRFs shall be derived from source documents, which may include worksheets, QOL questionnaires, patient medical records, echo data, blood lab data, programmer printouts and device interrogation/save-to-media files. These source documents must be created and maintained by the investigational site team. Further detail on data management is provided in Section 16.2. Data Management.

11.1. Potential Risks

Medtronic follows rigorous Quality Assurance and Control procedures throughout the life of the product, from the research and development phase through the study phase and market release.

There are risks associated with the elevated night pacing:

Table 9: Risks Related to Elevated Pacing

Risk	Potential Patient Harm	Mitigation
Pacing at a sustained elevated rate that causes symptoms during the day or night	Increased risk of Dizziness, palpitations, heart racing, shortness of breath, difficulty sleeping	At the time of enrollment, subjects will be evaluated to whether they can tolerate a pacing rate of 100bpm Subjects will be instructed to call study team if they are experiencing symptoms Symptoms will be gathered from subjects using phone calls following enrollment, 4 week, and 8 week clinic visits A programming checklist will be used at enrollment, 4 week, 8 week, and Exit visits to ensure appropriate programming of the Sleep Function parameters
Pacing at a sustained elevated rate may initiate or make heart failure or AF or ischemia worse	Increased risk of chest pain, atrial arrhythmia, or ischemia	We are monitoring troponin and NT-proBNP levels for worsening heart failure and troponin for ischemia. If levels worsen the subject will have their elevated pacing therapy programmed Off
Mode-switch during atrial arrhythmia results in a higher ventricular non-tracking pacing rate because the lower rate is programmed to 100bpm	Increased risk of Dizziness, palpitations, heart racing, shortness of breath	Symptoms will be gathered from subjects using phone calls following enrollment, 4 week, and 8 week clinic visits

Pacing at a sustained elevated rate that causes symptoms following unscheduled clinic visits. (Any minor telemetry activation, such as reprogramming, magnet application, or CareLink transmission will suspend the Sleep Function and the pacer will start pacing at the programmed Lower Rate.)	Increased risk of Dizziness, palpitations, heart racing, shortness of breath	Subjects will be instructed to call study team if they are experiencing symptoms Subjects will also be asked their heart rate, which the subject can read using a finger pulse oximeter monitor that will be given to them at Baseline to use Centers will be trained to instruct subjects to come to center for unscheduled visits
Misleading information that could reasonably lead to incorrect pacing therapy. (Rate histograms will show a higher percentage of pacing at 100bpm. Clinicians not aware of the subject's participation in the study may program the Lower Rate back to pre-study values.)	No risk to the patient. May result in loss of usable data for the study.	Subjects will be given a REVAMP study ID card
Negative impact to device longevity due to change in the pacing rate to 100 bpm	Failure to come in for exit visit for device reprogramming may negatively impact device longevity by 20% over remaining lifetime of device. Premature battery depletion which could lead to early Explant/ revision procedure related harm (Infection, Thrombus, Embolus, Hematoma, Stroke,Pneumothorax, Hemothorax, Nerve Damage)	The Patient informed Consent will include warnings about the impact to battery life of the device, if the patient does not adhere to thestudy protocol for the 12 week follow up and exit visit
Missing or Misleading information leading to adverse operation of the device when used in combination with other features or devices within its system	Risk of additional unnecessary elevated pacing rates.	The Clinical Investigation Protocol and training material will include details about the device interactions and programming recommendations for this study

Additional information can be found in the Foreseeable Adverse Event List (FAL) in **APPENDIX C**.

Subjects who are pregnant are excluded from study participation. If a subject becomes pregnant during the study, she must notify the physician immediately.

There may be other discomforts and risks related to elevated night pacing and this study that are not foreseen at this time. The adverse event collection requirements in this study will ensure that risks associated with the study are adequately monitored.

11.2. Risk Minimization

Medtronic has minimized the risks to the subject by the following:

- Performing required laboratory and pre-clinical testing prior to the REVAMP clinical study.
- Implementing quality control measures into development and production processes.
- Providing guidelines for subject selection and evaluation, and subject inclusion and exclusion criteria.
- Providing adequate instructions and training.
- Selecting investigators that have demonstrated previous experience with the programming, interrogation, and monitoring of pacemaker devices.
- After enrollment in the REVAMP clinical study, at each protocol required follow-up, the investigator must evaluate the subject's health, assess for any adverse events, and interrogate the study device to verify appropriate study device function.

11.3. Potential Benefits

Elevated pacing rates may offer no benefit. The potential benefits of having the elevated pacing ON for this 12 week study include:

- Improvement in exercise capacity
- Improvement in symptoms

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

11.4. Risk-Benefit Rationale

The risk for harm is minimal with this study as the pacing rate is within the FDA-approved programmable parameters of the Lower Rate and the Sleep Function, and pacing rates of 100 bpm can occur with activities of daily living. There are potential benefits to the subject, as listed in Section 11.3. Potential Benefits. Therefore, the study risk-benefit is acceptable.

12. Adverse Event Assessments

Timely, accurate, and complete reporting and analysis of safety information for clinical studies are crucial for the protection of subjects. Medtronic has established procedures to ensure appropriate reporting of safety information.

12.1. Adverse Events

Adverse Event definitions are provided in Table 10. To ensure that all AEs that are potentially relevant are collected, the following will be collected throughout the study duration, starting at the time of signing the Informed Consent Form:

- All system related AEs
- All programming related AEs
- All cardiovascular related AEs
- All Serious Adverse Events (SAEs), regardless of relatedness

In order to fully understand intolerable symptoms and mitigate any safety concerns about elevated night pacing, for any subject that exits the study because of intolerable symptoms, the enrolling site should report any associated programming related AEs. Reporting of these events to Medtronic will occur on an Adverse Event (AE) eCRF. Documented pre-existing conditions are not considered AEs unless the nature or severity of the condition has worsened.

For AEs that require immediate reporting (see Table 12), initial reporting may be done by phone, fax, or on the eCRF completing as much information as possible. The original completed AE eCRF must be submitted to Medtronic as soon as possible.

Each adverse event must be reported separately. Any medication, whether cardiovascular or not, associated with the treatment of an adverse event must be reported.

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

12.2. Device Deficiencies

Device Deficiency is defined as an inadequacy of a medical device with respect to its identity, quality, durability, reliability, safety or performance. Device Deficiencies will need to be collected in the study. Device Deficiency information will be collected throughout the study and reported to Medtronic.

12.3. Processing Updates and Resolution

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

At the time of study exit, all collected adverse events with an outcome of "Unresolved" must be reviewed and an update to the original AE eCRF must be reported. At a minimum, if there are no changes to the description, relatedness, test and procedures or actions taken, the outcome must be updated to reflect "Unresolved at time of study exit".

12.4. Definitions/Classifications

Where the definition indicates "device", it refers to any device used in the study.

Table 10: Adverse Event and Device Deficiency Definitions

General	
Adverse Event (AE)	Any untoward medical occurrence, unintended disease or injury, or untoward clinical signs (including abnormal laboratory findings) in subjects, users or other persons, whether or not related to the investigational medical device 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. (ISO 14155:2011, 3.2)
Adverse Device Effect (ADE)	Adverse event related to the use of an investigational medical device NOTE 1: This definition includes adverse events resulting from insufficient or inadequate instructions for use, deployment, implantation, installation, or operation, or any malfunction of the investigational medical device. NOTE 2: This definition includes any event resulting from an error use or from intentional misuse of the investigational medical device. (ISO 14155:2011, 3.1)
Device Deficiency (DD)	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 labeling (ISO 14155:2011, 3.15)
Relatedness	
System Related	An adverse event that results from the presence or performance of any component of the system. Device-related: An adverse event that results from the presence or performance (intended or otherwise) of the device. RA lead-related: An adverse event that results from the presence or performance (intended or otherwise) of the RA lead. RV lead-related: An adverse event that results from the presence or performance (intended or otherwise) of the RV lead.
Programming Related	An adverse event that results from the CIP required programming for elevated night pacing therapy.
Cardiovascular Related	An Adverse Event relating to the heart and the blood vessels or the circulation, e.g. Atrial Fibrillation, Myocardial Infarction, stroke, perivascular disease.

Seriousness	
Serious Adverse Event (SAE)	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 fetal distress, fetal death or a congenital abnormality or birth defect NOTE 1: Planned hospitalization for a pre-existing condition, or a procedure required by the CIP, without serious deterioration in health, is not considered a serious adverse event. (ISO 14155:2011, 3.37)
Unanticipated Adverse Device Effect (UADE)	Any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death, was not previously identified in a nature, severity, or degree of incidence in the investigational plan or application (including a supplementary plan or application), or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects. (21 CFR 812.3(s))

12.5. Reporting of Adverse Events

12.5.1. Adverse Event and Device Deficiency Classification

All reported Adverse Events and Device Deficiencies will be reviewed by a Medtronic representative. AEs will be classified according to the definitions provided.

Upon receipt of Adverse Events at Medtronic, a Medtronic representative will review the Adverse Event/Device Deficiency for completeness and accuracy and when necessary will request clarification and/or additional information from the Investigator. Medtronic will utilize MedDRA, the Medical Dictionary for Regulatory Activities, to assign a MedDRA term for each adverse event based on the information provided by the investigator.

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

APPENDIX C contains the Foreseeable Adverse Event List (FAL), which is a list of adverse events that may be experienced by subjects. This list may help to assess if an adverse event is unanticipated in nature.

For emergency contact regarding a UADE, contact a clinical study representative immediately (refer to the study contact list provided in the site's study documents binder/investigator site file or refer to the Sponsor Contact Information section provided in the CIP).

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

Table 11: Adverse Event Classification Responsibilities

What is classified?	Who classifies?	Classification Parameters
Relatedness	Investigator	Device, RA Lead, RV Lead, Programming, Cardiovascular
	Sponsor	Device, RA Lead, RV Lead, Programming
Seriousness	Investigator	SAE
	Sponsor	SAE, UADE
Diagnosis	Investigator	Based on presenting signs and symptoms and other supporting data
	Sponsor	MedDRA term assigned based on the data provided by Investigator
Death Classification	Investigator	Sudden Cardiac, Non-sudden Cardiac, Non-Cardiac, Unknown

12.5.2. Adverse Event and Device Deficiency Reporting Requirements

Regulatory reporting of AEs and device deficiencies will be recorded and reported according to local regulatory requirements. It is the responsibility of the Investigator to abide by the adverse event reporting requirements stipulated by local law and the site's IRB.

Table 12: Reporting Requirements

Unanticipated Adverse Device Effects (UADEs)	
Investigator submit to:	
Medtronic	Submit as soon as possible, but no later than within 10 working days after the investigator first learns of the event. (21 CFR 812.150(a)(1))
IRB	Submit as soon as possible, but no later than within 10 working days after the investigator first learns of the event. (21 CFR 812.150(a)(1))
Sponsor submit to:	
Regulatory authorities	Submit as soon as possible, but no later than within 10 working days after the sponsor first learns of the event. (21 CFR 812.150(b)(1))
IRB	Submit as soon as possible, but no later than within 10 working days after the sponsor first learns of the event. (21 CFR 812.150(b)(1))
Investigators	Submit as soon as possible, but no later than within 10 working days after the sponsor first learns of the event. (21 CFR 812.150(b)(1))

12.6. Subject Death

12.6.1. Death Data Collection

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

In the event of a subject's death, it is recommended that the implanted system be explanted and returned to Medtronic for analysis whenever possible per local process. Local laws and procedures must be followed where applicable.

System Interrogation Data Recommendations:

- After the subject has died but prior to explant, it is strongly recommended that the system be interrogated and a full summary interrogation (Interrogate All) performed when possible, and saved in a digital format (Save-to-Media). Store one copy of the save-to-media at the site and send a copy to Medtronic.
- Make the device interrogation/save-to-media file before any programming to prevent overwriting information in the device's memory and/or distinguishing between events detected during versus before the explant procedure.
- Recommend obtaining the exact date and time of death as lower temperatures after death can cause ERI and other "event flags" to be stored in the device memory.

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 site's responsibility to attempt retrieval of information about the death. Additionally, device disposition information should be updated. In summary, the following data will be collected:

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

12.6.2. Death Classification and Reporting

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

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

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

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

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

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

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

Table 13: Subject Death Classification Responsibilities

What is classified?	Who classifies?	Classification Parameters
Relatedness	Investigator	Device, RA Lead, RV Lead, Programming
Death Classification	Investigator	Sudden Cardiac, Non-sudden Cardiac, Non-cardiac, Unknown

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

12.7. Product Complaint Reporting

All devices used in the study will be market released at study start. Therefore, product complaint reporting is applicable and AEs related to any market-released device during the study must be reported. The reporting of product complaints is not part of the clinical study and should be done in addition to the Adverse Event reporting requirements. Refer to local regulations for reporting requirements.

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

13. Data Review Committees

13.1. Echocardiography Core Laboratory

The study will utilize an Echocardiography Core Laboratory (echo core lab). The echo core lab will complete data analysis on all study echoes required to be performed (Baseline, 4 week, 8 week, and 12 week). An echocardiogram will be performed as described in the Echocardiography Handbook (provided under separate cover).

The echo core lab will be blinded to subjects' randomization assignment. Echoes sent to the core lab for analysis will be labeled in such a way to maintain the blind and not provide information that would inform which visit the echo was collected.

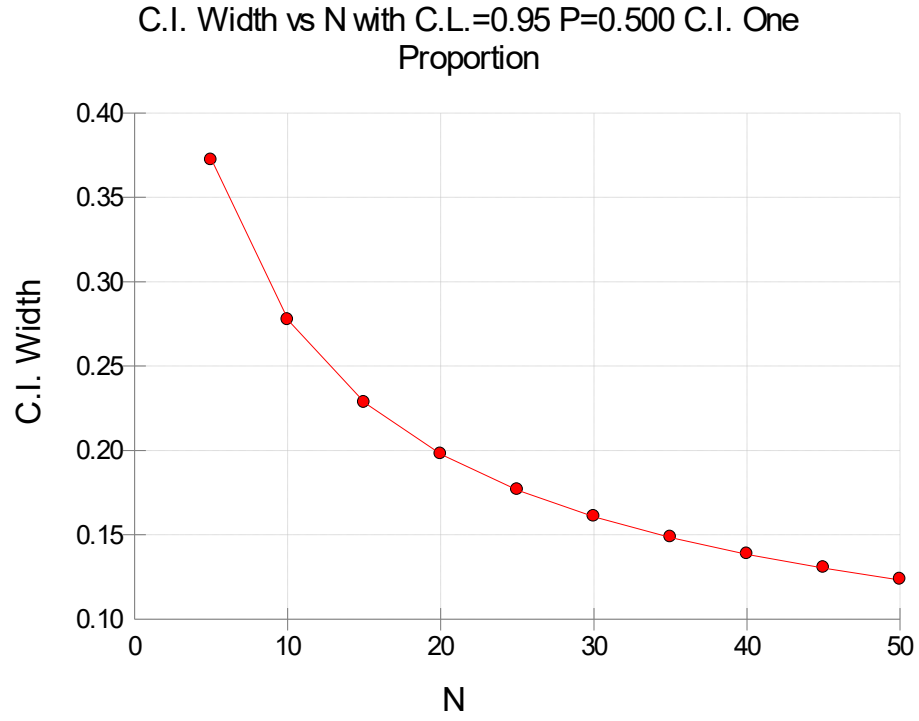
13.2. Blood Core Laboratory

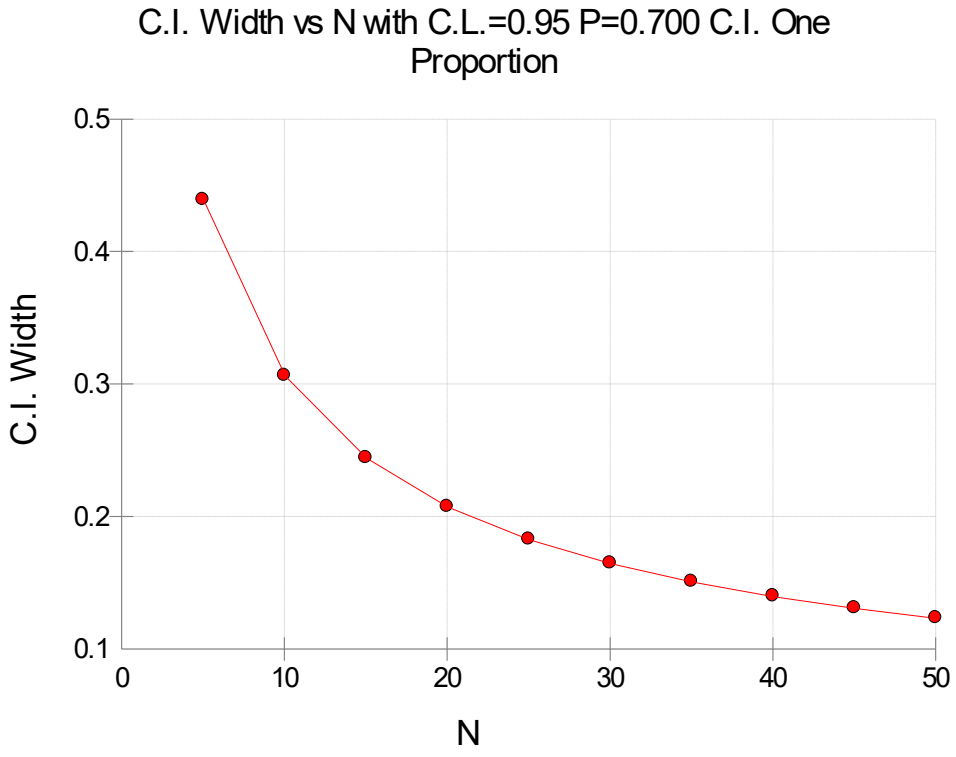
The study will utilize a Blood Core Laboratory (blood core lab). The blood core lab will complete data analysis on all study blood samples required to be performed (Baseline, 4 week, 8 week, and 12 week). Details of the blood core lab and the blood draw process will be provided under separate cover.

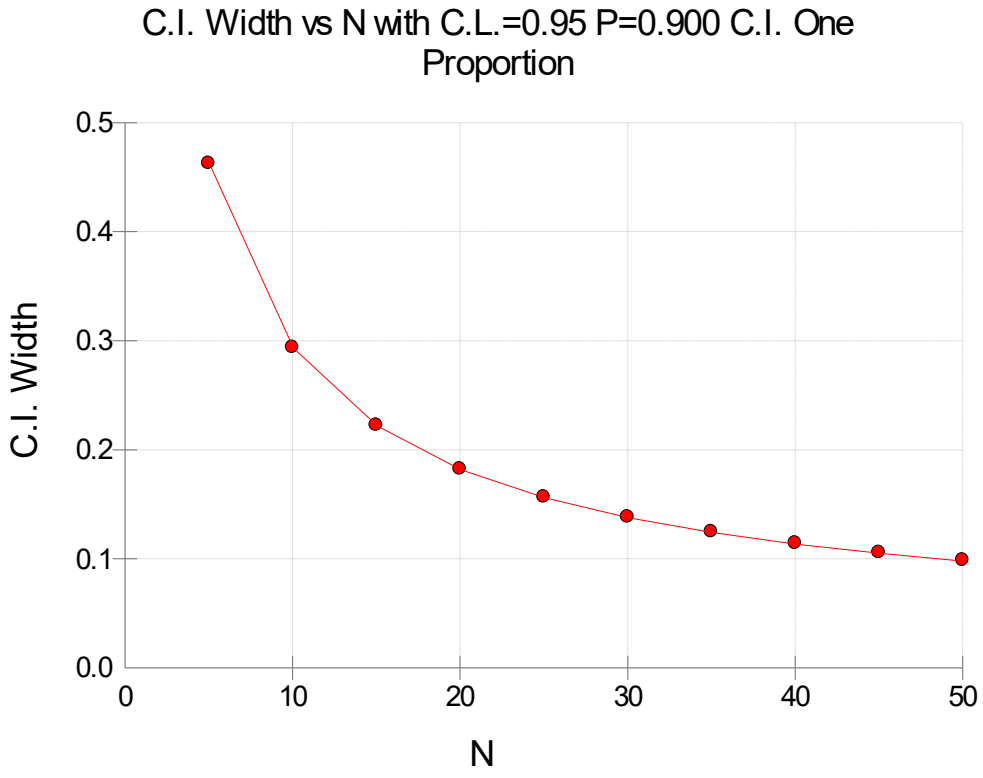
14. Statistical Design and Methods

This feasibility study is not powered to formally test a hypothesis. However, it is expected that a sample of up to 30 subjects will be sufficient to determine whether this approach warrants further study. The 4 week safety and tolerability objective described in Section 14.1.1. Ancillary Safety and Tolerability Endpoint will help determine whether to move forward with this therapy. Figure 3 indicates that improvements in the confidence interval width at various proportions of subjects meeting the 4 week safety and tolerability endpoint beyond 30 subjects are relatively small.

Figure 3: 95% Confidence Interval Widths for Various Proportions of 4 Week Safety and Tolerability Endpoint







This section presents statistical considerations for the study design and provides a high-level description of planned analysis and reporting. More details will be given in a separate Statistical Analysis Plan (SAP) that will be completed before data freeze and unblinding for the primary objective analysis. Any deviation to the pre-specified statistical analyses will be noted in the study report.

As part of the exploratory/ancillary safety, tolerability and efficacy effects described in 10.20. Assessment of Efficacy, it will be of interest to characterize changes in collected measurements from baseline to 4 weeks, compare changes in collected measurements at 4 weeks to 8 weeks in the subjects randomized to the elevated night pacing ON arm to subjects randomized to the elevated night pacing OFF arm and compare changes in collected measurements at 12 weeks to Baseline, 4 and 8 weeks to see whether any therapeutic improvements are sustained after the therapy is discontinued.

The 4 week endpoints will characterize the magnitude of change as a result of the therapy. For MNLWHF and the 6 Minute Walk Test, positive changes could be due to placebo-related effects, since this phase of the study is single arm and unblinded. Efficacy changes from the 4 week to the 8 week visit in the ON arm versus the OFF arm would be indicative of actual therapeutic effects of elevated night pacing, as blinding would help mitigate any placebo effect. Safety and tolerability changes from the 4 week to the 8 week visit in the ON arm versus the OFF arm would be indicative of long term safety and tolerability of elevated night pacing for subjects for which the first 4 weeks of therapy were safe and tolerable.

If there are changes in any of the efficacy measurements from baseline to week 4 and/or improvements in any of the efficacy measurements in the ON arm compared to the OFF arm from week 4 to week 8, there may be additional analyses on the extracellular matrix biomarkers to correlate to the efficacy improvements.

14.1. Endpoint Definitions

14.1.1. Ancillary Safety and Tolerability Endpoint

Safety and Tolerability – 4 weeks

Hypothesis
A 4 week period of elevated night pacing is safe and tolerable.

Analysis Methods
The proportion of subjects who remain in the study up until the 4 week visit without exiting due to intolerable symptoms, increase in NT-proBNP levels, decrease in LVEF or increase in troponin will be calculated along with the lower bound of the one-sided 95% confidence interval

Determination of Subjects for Analysis
All enrolled subjects that are programmed with elevated night pacing.

Safety and Tolerability – 8 weeks

Hypothesis
Following a 4 week period of elevated night pacing, compare the safety and tolerability of subjects in the ON and OFF arm for an additional 4 weeks of elevated night pacing

Analysis Methods
The proportion of subjects who remain in the study from the 4 week visit to the 8 week visit without exiting due to intolerable symptoms, increase in NT-proBNP levels, decrease in LVEF or increase in troponin will be calculated along with the lower bound of the one-sided 95% confidence interval for both arms (elevated night pacing left ON versus elevated night pacing programmed OFF).

Determination of Subjects for Analysis

All subjects that completed 4 weeks of elevated night pacing. Subjects that were unable to tolerate or withdrew from the treatment during the first 4 weeks because of safety or other issues will not be included in this analysis.

14.1.2. Ancillary Safety Endpoint – NT-proBNP, troponin, LVEF

NT-proBNP, troponin, LVEF – 4 weeks

Hypothesis
For each of the main safety measures (NT-proBNP, troponin and LVEF), comparisons will be done to see if there are changes from baseline after a 4 week period of elevated night pacing.

Analysis Methods
A paired comparison of the value at the end of the period compared to the value at the start of the period will be calculated. A two-sided paired t-test will be performed testing the hypothesis

H_o: $\mu = 0$

H_a: $\mu \neq 0$

Where μ = difference in measurement from baseline to week 4 visit

Determination of Subjects for Analysis

All subjects that completed 4 weeks of elevated night pacing. Subjects that were unable to tolerate or withdrew from the treatment during the first 4 weeks because of safety or other issues will not be included in this efficacy analysis.

NT-proBNP, troponin, LVEF – 8 weeks

Hypothesis
For each of the main safety measures (NT-proBNP, troponin and LVEF), it will be assessed whether there is a difference in the change of the measurement following an additional 4 week period of elevated night pacing after an initial 4 week period of elevated night pacing compared to that period of 4 weeks with the elevated night pacing programmed OFF after the initial 4 weeks period of elevated night pacing.

Analysis Methods
A paired comparison of the measurement at the 8 week visit compared to the scored at the 4 week visit period compared to the value at the start of the period will be calculated. A two-sided paired t-test will be performed testing the hypothesis

H_o: $\mu_{ON} = \mu_{OFF}$

H_a: $\mu_{ON} \neq \mu_{OFF}$

Where μ_{ON} = difference in NT-proBNP, troponin or LVEF from week 4 to week 8 for subjects in the ON arm and μ_{OFF} = difference in those measurements in subjects in the OFF arm

Determination of Subjects for Analysis

All subjects that completed 4 weeks of elevated night pacing. NT-proBNP, troponin or LVEF at time of exit will be used for subjects that do not complete the full 4 weeks of participation in the study from week 4 to week 8.

14.1.3. Ancillary Safety Endpoint – Adverse Events

Adverse Events – 4 weeks

Hypothesis
Not applicable. This endpoint is to characterize adverse events during the first 4 weeks of elevated night pacing.

Analysis Methods

Summarization of adverse events by MedDRA preferred term. Summarization may include pertinent subgroups, including all potentially related events and all CV-related events.

Determination of Subjects for Analysis

All adverse events reported for subjects actively receiving elevated night pacing will be included.

Adverse Events – 8 weeks

Hypothesis
There are differential rates of adverse event reporting between subjects randomized to receive elevated night pacing and subjects randomized to elevated night pacing OFF. In addtion, adverse events for subjects continuing to receive elevated night pacing will be characterized and extended from the AE's collected during the first 4 weeks.

Analysis Methods
The adverse reporting rate during the period from week 4 to week 8 in subjects in the ON arm and OFF arm will be compared and characterized.

Determination of Subjects for Analysis
Rates of adverse events for subjects randomized to OFF will be calculated over the full period of follow-up, while rates of adverse events for subjects randomized to ON will be calculated only during the period that subjects were actually receiving elevated night pacing.

14.1.4. Ancillary Efficacy Endpoint - Quality of Life

MNLWHF Questionnaire – 4 weeks

Hypothesis
There is an improvement in quality of life from baseline after a 4 week period of elevated night pacing, as assessed by the MNLWHF Questionnaire.

Analysis Methods
A paired comparison of the value at the end of the period compared to the value at the start of the period will be calculated. A one-sided paired t-test will be performed testing the hypothesis

H_o: $\mu \leq 0$

H_a: $\mu > 0$

Where μ = difference in MNLWHF score from baseline to week 4 visit

Determination of Subjects for Analysis

All subjects that completed 4 weeks of elevated night pacing. Subjects that were unable to tolerate or withdrew from the treatment during the first 4 weeks because of safety or other issues will not be included in this efficacy analysis.

MNLWHF Questionnaire – 8 weeks

Hypothesis
There is an improvement in quality of life of an additional 4 week period of elevated night pacing after an initial 4 week period of elevated night pacing compared to that period of 4 weeks with the elevated night pacing programmed OFF after the initial 4 weeks period of elevated night pacing, as assessed by the MNLWHF Questionnaire.

Analysis Methods
A paired comparison of the scores at the 8 week visit compared to the scores at the 4 week visit period will be calculated. A one-sided paired t-test will be performed testing the hypothesis

H_o: $\mu_{ON} \leq \mu_{OFF}$

H_a: $\mu_{ON} > \mu_{OFF}$

Where μ_{ON} = difference in MNLWHF score from week 4 to week 8

Determination of Subjects for Analysis

All subjects that completed 4 weeks of elevated night pacing. MNLWHF score at time of exit will be used for subjects that do not complete the full 4 weeks of participation in the study from week 4 to week 8.

EQ-5D-5L Questionnaire – 8 weeks

Hypothesis
There is an improvement in quality of life from baseline after an 8 week period of elevated night pacing, as assessed by the EQ-5D-5L Questionnaire. This assumes the effect is the same whether or not elevated nice pacing is turned off at week 4.

Analysis Methods
A paired comparison of the value at the end of the period compared to the value at the start of the period will be calculated. A one-sided paired t-test will be performed testing the hypothesis

H_o: $\mu \leq 0$

H_a: $\mu > 0$

Where μ = difference in EQ-5D-5L score from baseline to week 8 visit

Determination of Subjects for Analysis

All subjects that completed 8 weeks of elevated night pacing. Subjects that were unable to tolerate or withdrew from the treatment during the first 4 weeks because of safety or other issues will not be included in this efficacy analysis. EQ-5D-5L score at time of exit will be used for subjects that do not complete the full 4 weeks of participation in the study from week 4 to week 8.

Hypothesis
There is more of an improvement in quality of life after an 8 week period of elevated night pacing than for a 4 week period of elevated night pacing followed by 4 weeks with the elevated night pacing programmed OFF after the initial 4 weeks period of elevated night pacing, as assessed by the EQ-5D-5L Questionnaire.

Analysis Methods
A paired comparison of the scores at the 8 week visit compared to the scored at the baseline visit will be calculated. A one-sided paired t-test will be performed testing the hypothesis

H_o: $\mu_{ON} \leq \mu_{OFF}$

H_a: $\mu_{ON} > \mu_{OFF}$

Where μ_{ON} = difference in EQ-5D-5L score from baseline to week 8

Determination of Subjects for Analysis

All subjects that completed 8 weeks of elevated night pacing. Subjects that were unable to tolerate or withdrew from the treatment during the first 4 weeks because of safety or other issues will not be included in this efficacy analysis. EQ-5D-5L score at time of exit will be used for subjects that do not complete the full 4 weeks of participation in the study from week 4 to week 8.

14.1.5. Ancillary Efficacy Endpoint - Mobility and Activity

6 Minute Walk Test Distance – 4 weeks

Hypothesis
There is an improvement in the 6 Minute Walk Test distance from baseline after a 4 week period of elevated night pacing.

Analysis Methods
A paired comparison of the value at the end of the period compared to the value at the start of the period will be calculated. A one-sided paired t-test will be performed testing the hypothesis

H_o: $\mu \leq 0$

H_a: $\mu > 0$

Where μ = difference in 6 Minute Walk Test distance from baseline to week 4 visit

Determination of Subjects for Analysis

All subjects that completed 4 weeks of elevated night pacing. Subjects that were unable to tolerate or withdrew from the treatment during the first 4 weeks because of safety or other issues will not be included in this efficacy analysis.

6 Minute Walk Test Distance – 8 weeks

Hypothesis
There is an improvement in the 6 Minute Walk Test distance from an additional 4 week period of elevated night pacing after an initial 4 week period of elevated night pacing compared to that period of 4 weeks with the elevated night pacing programmed OFF after the initial 4 weeks period of elevated night pacing.

Analysis Methods
A paired comparison of the scores at the 8 week visit compared to the scored at the 4 week visit period compared to the value at the start of the period will be calculated. A one-sided paired t-test will be performed testing the hypothesis

H_o: $\mu_{ON} \leq \mu_{OFF}$

H_a: $\mu_{ON} > \mu_{OFF}$

Where μ_{ON} = difference in MNLWHF score from week 4 to week 8 in subjects randomized to the ON arm and μ_{OFF} = difference in 6 Minute Hall Walk Test distance from week 4 to week 8 in subjects randomized to the OFF arm

Determination of Subjects for Analysis

All subjects that completed 4 weeks of elevated night pacing. 6 Minute Walk Test distance at time of exit will be used for subjects that do not complete the full 4 weeks of participation in the study from week 4 to week 8.

Device-measured activity levels – 4 weeks

Hypothesis
There is an improvement in daytime activity levels from baseline over a 4 week period of elevated night pacing.

Analysis Methods
Activity levels over time will be characterized over time from baseline to the 4 week visit.

Determination of Subjects for Analysis

All subjects that completed 4 weeks of elevated night pacing. Subjects that were unable to tolerate or withdrew from the treatment during the first 4 weeks because of safety or other issues will not be included in this efficacy analysis.

Device-measured activity levels – 8 weeks

Hypothesis
There is an improvement in daytime activity levels over an additional 4 week period of elevated night pacing after an initial 4 week period of elevated night pacing compared to that period of 4 weeks with the elevated night pacing programmed OFF after the initial 4 weeks period of elevated night pacing.

Analysis Methods
Activity levels over time will be characterized over time from the 4 week visit to the 8 week visit and compared between the subjects with the elevated pacing programmed ON versus OFF.

Determination of Subjects for Analysis

All subjects that completed 4 weeks of elevated night pacing. Daytime activity levels up to time of exit will be used for subjects that do not complete the full 4 weeks of participation in the study from week 4 to week 8.

14.1.6. Ancillary Efficacy Endpoint – Echo Measurements

Echo measurements – 4 weeks

Hypothesis
All echo measurements will be assessed to see if there are changes from baseline after a 4 week period of elevated night pacing.

Analysis Methods
A paired comparison of the value at the end of the period compared to the value at the start of the period will be calculated. A two-sided paired t-test will be performed testing the hypothesis

H_o: $\mu = 0$

H_a: $\mu \neq 0$

Where μ = difference in measurement from baseline to week 4 visit

Determination of Subjects for Analysis
All subjects that completed 4 weeks of elevated night pacing. Subjects that were unable to tolerate or withdrew from the treatment during the first 4 weeks because of safety or other issues will not be included in this efficacy analysis.

Echo measurements – 8 weeks

Hypothesis
All echo measurements will be assessed to determine whether there is a difference in the change of the measurement following an additional 4 week period of elevated night pacing after an initial 4 week period of elevated night pacing compared to that period of 4 weeks with the elevated night pacing programmed OFF after the initial 4 weeks period of elevated night pacing.

Analysis Methods
A paired comparison of the measurement at the 8 week visit compared to the scored at the 4 week visit period compared to the value at the start of the period will be calculated. A two-sided paired t-test will be performed testing the hypothesis

H_o: $\mu_{ON} = \mu_{OFF}$

H_a: $\mu_{ON} \neq \mu_{OFF}$

Where μ_{ON} = difference in echo measurement from week 4 to week 8 in subjects randomized to the ON arm and μ_{OFF} = difference in echo measurement from week 4 to week 8 in subjects randomized to the OFF arm

Determination of Subjects for Analysis
All subjects that completed 4 weeks of elevated night pacing. Echo measurement at time of exit will be used for subjects that do not complete the full 4 weeks of participation in the study from week 4 to week 8.

14.1.7. Ancillary Efficacy Endpoint – Collagen Degradation Biomarker Measurements

Biomarker measurements – 4 weeks

Hypothesis
If the results of the safety, tolerability and efficacy of elevated night pacing appear to be promising, additional work may be done to assess collagen degradation biomarker measurements to see if there are changes from baseline after a 4 week period of elevated night pacing.

Analysis Methods
A paired comparison of the value at the end of the period compared to the value at the start of the period will be calculated. A two-sided paired t-test will be performed testing the hypothesis

H_o: $\mu = 0$

H_a: $\mu \neq 0$

Where μ = difference in measurement from baseline to week 4 visit

Determination of Subjects for Analysis

All subjects that completed 4 weeks of elevated night pacing. Subjects that were unable to tolerate or withdrew from the treatment during the first 4 weeks because of safety or other issues will not be included in this efficacy analysis.

Biomarker measurements – 8 weeks

Hypothesis
If the results of the safety, tolerability and efficacy of elevated night pacing appear to be promising, additional work may be done to determine whether there is a difference in the change in the collagen degradation biomarker measurements following an additional 4 week period of elevated night pacing after an initial 4 week period of elevated night pacing compared to that period of 4 weeks with the elevated night pacing programmed OFF after the initial 4 weeks period of elevated night pacing.

Analysis Methods
A paired comparison of the measurement at the 8 week visit compared to the scored at the 4 week visit period compared to the value at the start of the period will be calculated. A two-sided paired t-test will be performed testing the hypothesis

H_o: $\mu_{ON} = \mu_{OFF}$

H_a: $\mu_{ON} \neq \mu_{OFF}$

Where μ_{ON} = difference in collagen degradation biomarker measurement from week 4 to week 8 in subjects randomized to the ON arm and μ_{OFF} = difference in collagen degradation biomarker measurement from week 4 to week 8 in subjects randomized to the OFF arm

Determination of Subjects for Analysis

All subjects that completed 4 weeks of elevated night pacing. Biomarker measurement at time of exit will be used for subjects that do not complete the full 4 weeks of participation in the study from week 4 to week 8.

14.1.8. Ancillary Efficacy Endpoint – Sustained effects of elevated night pacing

Hypothesis
it will be explored whether there are sustained effects of elevated night pacing.

Analysis Methods
These analyses will be exploratory in nature, involving characterizing changes from baseline and end of therapy to the last follow-up visit.

Determination of Subjects for Analysis

All subjects that have follow-up visits after elevated night pacing was programmed OFF. This will include subjects completed 12 weeks of follow-up and subjects that had elevated night pacing programmed OFF at 4 weeks and completed 8 weeks of follow-up.

15. Ethics

15.1. Statement(s) of Compliance

REGULATORY COMPLIANCE

This REVAMP study will be conducted in compliance with international ethical and scientific quality standards, known as good clinical practice (GCP). The study was designed to reflect the GCP principles outlined in ISO 14155:2011. GCP includes review and approval by an independent IRB before initiating and obtaining and documenting the freely given patient informed consent of a subject before initiating the study.

The study will be conducted according to federal, national and local laws, regulations, standards, and requirements where the study is being conducted. The principles of the Declaration of Helsinki have been implemented through the patient informed consent process, IRB approval, study training, clinical trial registration, preclinical testing, risk-benefit assessment and publication policy.

The REVAMP study will be conducted as a Non-Significant Risk (NSR) IDE study. The study will be conducted in compliance with 21 CFR Parts 11, 50, 56, 812.2(b)(1). This study does not require an IDE submission to FDA.

The study will be publicly registered prior to first enrollment in accordance with the 2007 Food and Drug Administration Amendments Act FDAAA and Declaration of Helsinki on http://www.clinicaltrials.gov (PL 110-85, section 810(a)).

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

- Medtronic
- An Institutional Review Board at each individual study center

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

16. Study Administration

16.1. Monitoring

It is the responsibility of Medtronic to ensure proper monitoring of this clinical study. Trained Medtronic personnel or delegates appointed by Medtronic may perform study monitoring at the study site in order to ensure that the study is conducted in accordance with the CIP, the Clinical Trial Agreement or Work Order, and applicable regulatory and local requirements. Medtronic, or delegates, must therefore be allowed access to the subjects' case histories (clinic and hospital records, and other source data/documentation) upon request as per the Informed Consent Form and Authorization to Use and Disclose Personal Health Information/Research Authorization/other privacy language (data protection authorization) as required by law and Clinical Trial Agreement or Work Order. The principal investigator should also be available during monitoring visits.

Monitoring for the study will be done in accordance to the study-specific monitoring plan.

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

Frequency of monitoring visits may be based upon subject enrollment, duration of the study, study compliance, number of adverse events, number of deviations, findings from previous monitoring visits and any suspected inconsistency in data that requires investigation.

16.2. Data Management

Data will be collected using Oracle Clinical, an electronic data management system for clinical studies. CRF data will be stored in a secure, password-protected database which will be backed up nightly. Data will be reviewed using programmed and manual data checks. Data queries will be made available to sites for resolution. Study management reports may be generated to monitor data quality and study progress. At the end of the study, the data will be frozen and will be retained indefinitely by Medtronic.

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

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

The data reported on the eCRFs shall be derived from source documents and be consistent with these source documents, and any discrepancies shall be explained in writing. Save-to-media data collected at

office visits will be sent to Medtronic. Upon receipt, device data will be maintained within a Medtronic device database and retrieved for analysis and reporting.

16.3. Direct Access to Source Data/Documents

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

16.4. Confidentiality

All records and other information about subjects participating in this study will be treated as confidential. See Section 16.2. Data Management for further information.

16.5. CIP Amendments

Approval of subsequent revisions to the CIP is required at each study site from the following groups prior to implementation of the revised CIP at the site:

- Medtronic
- Principal Investigators (where required by local law)
- An independent institutional review board.

If a CIP amendment occurs, site personnel will need to be re-trained as necessary, and will need to submit any changes to their IRB.

16.6. Warranty/Insurance Information

16.6.1. Warranty

Warranty information is provided in the product packaging for the commercially released pacemaker devices and leads, and additional copies are available upon request.

16.7. Record Retention

16.7.1. Investigator Records

The investigator is responsible for the preparation and retention of the records including, but not limited to, those cited below. All of the below records, with the exception of case history records and case report forms, should be kept in the Investigator Site File (i.e., the study binder provided to the investigator) or Subject Study Binder. eCRFs must be maintained and signed electronically by an investigator within the electronic data capture system during the study. The following records are subject to inspection and must be retained for a period of two years (or longer as local law/regulation or hospital administration requires) after product approval. Measures shall be taken to avoid loss or premature destruction.

- All correspondence between the IRB, sponsor, monitor, and/or the investigator that pertains to the investigation, including required reports.
- Subject's case history records, including:
    - Signed and dated Informed Consent Form, in accordance with local requirements

  - Observations of adverse events/adverse device effects/device deficiencies
  - Medical history
  - Baseline and follow-up data (if applicable)
  - Documentation of the dates and rationale for any deviation from the protocol
- Electronically signed and dated eCRFs and a blank set of eCRFs where required by local law
- All approved versions of the CIP and IC Form
- Signed and dated Clinical Trial Agreement or Work Order
- IRB approval documentation. Written information that the investigator or other study staff, when member of the IRB, did not participate in the approval process. Approval documentation must include the IRB composition, where required per local law.
- List of investigation sites
- Randomization list
- Current curriculum vitae of principal investigators
- Documentation of delegated tasks
- Study training records for site staff
- Final Study Report including the statistical analysis

16.7.2. Investigator Reports

The investigator is responsible to prepare and submit the following complete, accurate, and timely reports:

Table 14: Investigator Reports for the United States

Report	Submit to	Description/Constraints
Unanticipated adverse device effects	Sponsor and IRB/MEC	The investigator shall submit to the sponsor and reviewing IRB as soon as possible, but no later than 10 working days after the investigator first learns of the effect. (21 CFR 812.150 (a)(1))
Withdrawal of IRB/MEC approval (either suspension or termination)	Sponsor	The investigator must report a withdrawal of approval by the reviewing IRB/MEC of the investigator's part of the investigation within 5 working days. *(21 CFR 812.150(a)(2))*
Failure to obtain informed consent	IRB	Investigator's report will be submitted to IRB within five working days of notification. (21 CFR 812.150(a)(5))
Other	IRB/MEC and FDA	An investigator shall, upon request by a reviewing IRB/MEC, FDA or any other regulatory agency, provide accurate, complete, and current information about any aspect of the investigation. *(21 CFR 812.150(a)(7))*

Reports are subject to inspection and to the retention requirements as described above for investigator records.

Investigator reporting requirements for safety data are listed in Section 12. Adverse Event Assessments.

16.7.3. Sponsor Records

Medtronic shall maintain the following accurate, complete, and current records that includes, but is not limited to:

- All correspondence which pertains to the clinical study
- Executed Clinical Trial Agreement
- Randomization List
- Current curriculum vitae of principal investigators
- Electronically signed and dated eCRFs
- All approved informed consent templates, and other information provided to the subjects and advertisements, including translations
- Copies of all IRB approval letters and relevant IRB correspondence and IRB voting list/roster/letter of assurance
- Names of the institutions in which the clinical study will be conducted
- Names/contact addresses of monitors
- Monitoring reports (interim monitoring visit reports, follow-up letters and close-out visit reports)
- Site qualification visit reports
- Statistical analyses and underlying supporting data
- Final report of the clinical study
- The approved Clinical Investigation Plan, study related reports, and revisions
- Documentation of delegated tasks
- Study training records for site personnel and Medtronic personnel involved in the study
- Sample of CRFs
- Any other records that local regulatory agencies require to be maintained

16.7.4. Sponsor Reports

Medtronic shall prepare and submit the following complete, accurate, and timely reports listed in the tables below. In addition to the reports listed below, Medtronic shall, upon request of reviewing IRB or FDA, provide accurate, complete and current information about any aspect of the clinical study. Safety data Medtronic reporting requirements are listed in Section 12. Adverse Event Assessments.

Table 15: Sponsor Reports for the United States

Report	Submit to	Description/Constraints
Withdrawal of IRB approval	Investigators, IRB	Notification within five working days after receipt of the withdrawal of approval. *(21 CFR 812.150(b)(2))*
Progress Reports	IRB	Progress reports will be submitted at least annually. *(21 CFR 812.150(b)(5), 812.36(f)*
Failure to obtain informed consent	MDT, IRB	Investigator's report will be submitted to IRB within five working days of notification. *(21 CFR 812.150(b)(8))*
Final report	Investigators and IRB	A final report will be submitted to investigators, and IRBs/MECs within six months after completion or termination of this study. *(21 CFR 812.150(b)(7))*
Study deviation	Investigators	Ensure that all deviations from the Clinical Investigation Plan are reviewed with the appropriate clinical investigator(s), are reported on the case report forms and the final report of the clinical investigation. Site specific study deviations will be submitted to investigators periodically.

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

16.8. Publication and Use of Information

Publications from the REVAMP clinical study will be handled according to Medtronic Policies and Standard Operating Procedures and as indicated in the Clinical Trial Agreement or Work Order.

16.8.1. Publication Committee

The REVAMP clinical study will utilize a Publication Committee which will include the Steering Committee members as well as Medtronic personnel. This committee will manage study publications with the goal of publishing findings from the data. The Publication Committee may develop the final Publication Plan as a separate document.

The Publication Committee's role is to:

- manage elements addressed in the publication plan as outlined in this section
- develop the final Publication Plan under separate cover, as needed
- execute the Publication Plan
- oversee the publication of primary, secondary and ancillary study results
- review and prioritize publication proposals
- provide input on publication content, and
- determine authorship

In addition, the committee will apply and reinforce the authorship guidelines set forth in the Publication Plan. Membership in the Publication Committee does not guarantee authorship. The committee will meet as needed.

16.8.2. Management of Primary, Secondary, and Ancillary Publications

The Publication Committee reviews, prioritizes and manages all publications including primary, secondary and ancillary publications. Primary and secondary publications are those that address analyses of any or all primary objectives or secondary/ancillary objectives, respectively, as specified in the Clinical Investigation Plan. An ancillary publication is any publication that does not address the study objectives identified in the Clinical Investigation Plan. They include publications proposed and developed by other Medtronic departments or entities, clinicians participating in this clinical study and clinicians not participating in this clinical study. The committee will work with Medtronic to ensure that requests do not present conflicts with other proposals, are not duplicative and to determine which ancillary publication proposals, if any, will be supported.

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

16.8.3. Criteria for Determining Authorship

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

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

- Substantial contribution to conception and design, or acquisition of data, or analysis and interpretation of data
- Drafting the article or revising it critically for important intellectual content
- Final approval of the version to be published

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

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

16.8.4. Transparency

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

- a final report, describing the results of all objectives and analysis, will be distributed to all investigators and IRBs.
- registering and posting the study results on ClinicalTrials.gov based on the posting rules stipulated
- submitting for publication the primary study results after the study ends
- disclosing conflicts of interest (e.g. financial) of the co-authors of publications according to the policies set forth by the corresponding journals and conferences

- making an individual sites study data accessible to the corresponding investigator after the completion of the study, if requested

16.9. Suspension or Early Termination

16.9.1. Planned Study Closure

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

16.9.2. Early Termination or Suspension

Early Termination of the Study is the closure of a clinical study that occurs prior to meeting defined endpoints. This is possible for the whole study or a single site. Study Suspension is a temporary postponement of study activities related to enrollment and distribution of the product. This is possible for the whole study or a single site. In the event the whole study or a single site is terminated, subjects will be exited.

Study-Wide Termination or Suspension

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

- Adverse events associated with the system or product under investigation which might endanger the safety or welfare of the subject
- Observed/suspected performance different from the product's design intent
- Decision by Medtronic

Investigator/Site Termination or Suspension

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

- Failure to obtain initial IRB approval or annual renewal of the study
- Persistent non-compliance to the clinical investigation (e.g. failure to adhere to inclusion/exclusion criteria, failure to follow subjects per scheduled follow-ups)
- Lack of enrollment
- Noncompliance to regulations and the terms of the Clinical Trial Agreement or Work Order (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.)
- IRB suspension of the site
- Fraud or fraudulent misconduct is discovered (as defined by local law and regulations)
- Investigator request (e.g. no longer able to support the study)

16.9.3. Procedures for Termination or Suspension

Medtronic-Initiated and Regulatory Authority-Initiated

- Medtronic will promptly inform the clinical investigators of the (early) termination or suspension and the reasons and inform the regulatory authority(ies) where required
- In the case of study termination or suspension for reasons other than a temporary IRB approval lapse, the investigator will promptly inform the IRB
- In the case of study termination, the investigator must inform the subjects and may inform the personal physician of the subjects to ensure appropriate care and follow-up is provided
- In the case of a study suspension, subject enrollment must stop until the suspension is lifted by Medtronic
- In the case of a study suspension, enrolled subjects should continue to be followed out of consideration of their safety, rights and welfare

Investigator-Initiated

- The investigator will inform Medtronic and provide a detailed written explanation of the termination or suspension
- The investigator will promptly inform the institution (where required per regulatory requirements)
- The investigator will promptly inform the IRB
- The investigator will promptly inform the subjects and/or the personal physician of the subjects to ensure appropriate care and follow-up is provided
- In the case of a study suspension, subjects enrolled should continue to be followed out of consideration of their safety, rights and welfare

IRB-Initiated

- The investigator will inform Medtronic and provide a detailed written explanation of the termination or suspension within 5 business days
- Subject enrollment must stop until the suspension is lifted
- Subjects already enrolled should continue to be followed in accordance with IRB policy or its determination that an overriding safety concern or ethical issue is involved
- The investigator will inform his/her institution (where required per local requirements)
- The investigator will promptly inform the subjects, and/or the personal physician of the subjects, with the rationale for the study termination or suspension

17. Appendices

APPENDIX A: DATA COLLECTION ELEMENTS (ELECTRONIC CASE REPORT FORMS)

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

APPENDIX B: INFORMED CONSENT TEMPLATE(S)

Informed Consent Form templates will be provided under separate cover.

APPENDIX C: FORESEEABLE ADVERSE EVENT LIST

The information provided in this section pertains to foreseeable adverse events that may be observed in the REVAMP Study and may assist in identifying those events that are unexpected in nature. Potential risks and associated adverse events related to the patients implanted market-released device are in alignment with the product labeling. This section address in more detail those events that are foreseeable due to participation in the REVAMP Study in those patients with a dual chamber pacemaker.

Potential risks associated with elevated night pacing as well as risk minimization are discussed within Section 11. Treatment required for programming related adverse events may include device reprogramming, medications, or other surgical and medical remedies. The foreseeable adverse event information includes rates of adverse events reported from previous Medtronic studies evaluating traditional pacemaker systems. Evaluation of potentially anticipated events may involve data in this Clinical Investigation Plan as well as a thorough review of all available information (e.g. labeling, current event reporting, published data, etc.).

Adverse Events Reported in Previous Clinical Studies with Dual Chamber Pacing Systems

Table 16 provides examples of adverse events associated with the use of traditional dual chamber pacemaker systems reported in six previous Medtronic studies between 1999 and 2012. The six predicate Medtronic studies include the EnRhythm pre-market evaluation study, 3830 IDE study, 5076 IDE study, EnRhythm MRI IDE study, Advisa MRI IDE study, and the SAVEPACe post-market study. These six studies collected all adverse events and include data from 2667 subjects that underwent a device implant. The average follow-up time across the six studies ranged from 5.9 to 30.8 months. Table 16 displays the adverse event rates classified as related to the implanted system and/or procedure. Kaplan-Meier estimates and associated 95% confidence intervals of the adverse event rates are provided in the table below at 30-days and 12-months (365 days) post-implant to characterize both peri-procedural and long-term adverse events related to the procedure or implanted system.

Table 16: Previous Clinical Study Data - System and/or Procedure Related Adverse Events (n=2667)

	Within 30-days of Implant		Within 12-months of Implant	
MedDRA Preferred Term Lowest Level Term	**No. Events (No. Subjects, %)[1]**	**95% CI[1]**	**No. Events (No. Subjects, %)[1]**	**95% CI[1]**
ADVERSE DRUG REACTION	**9 (9, 0.34%)**	**0.18% - 0.65%**	**10 (10, 0.39%)**	**0.21% - 0.72%**
ADVERSE DRUG REACTION	9 (9, 0.34%)	0.18% - 0.65%	10 (10, 0.39%)	0.21% - 0.72%
AIR EMBOLISM	**4 (4, 0.15%)**	**0.06% - 0.40%**	**4 (4, 0.15%)**	**0.06% - 0.40%**

Table 16: Previous Clinical Study Data - System and/or Procedure Related Adverse Events (n=2667)				
	Within 30-days of Implant		Within 12-months of Implant	
MedDRA Preferred Term Lowest Level Term	**No. Events (No. Subjects, %)[1]**	**95% CI[1]**	**No. Events (No. Subjects, %)[1]**	**95% CI[1]**
AIR EMBOLISM	4 (4, 0.15%)	0.06% - 0.40%	4 (4, 0.15%)	0.06% - 0.40%
ANAEMIA	**1 (1, 0.04%)**	**0.01% - 0.27%**	**1 (1, 0.04%)**	**0.01% - 0.27%**
ANEMIA	1 (1, 0.04%)	0.01% - 0.27%	1 (1, 0.04%)	0.01% - 0.27%
ANXIETY	**1 (1, 0.04%)**	**0.01% - 0.27%**	**1 (1, 0.04%)**	**0.01% - 0.27%**
ANXIETY	1 (1, 0.04%)	0.01% - 0.27%	1 (1, 0.04%)	0.01% - 0.27%
ATELECTASIS	**3 (3, 0.11%)**	**0.04% - 0.35%**	**3 (3, 0.11%)**	**0.04% - 0.35%**
ATELECTASIS	3 (3, 0.11%)	0.04% - 0.35%	3 (3, 0.11%)	0.04% - 0.35%
ATRIAL FIBRILLATION	**59 (59, 2.25%)**	**1.75% - 2.90%**	**63 (63, 2.43%)**	**1.90% - 3.10%**
ATRIAL FIBRILLATION	54 (54, 2.06%)	1.58% - 2.68%	57 (57, 2.18%)	1.69% - 2.82%
PAROXYSMAL ATRIAL FIBRILLATION	5 (5, 0.19%)	0.08% - 0.46%	6 (6, 0.25%)	0.11% - 0.55%
ATRIAL FLUTTER	**9 (9, 0.35%)**	**0.18% - 0.66%**	**9 (9, 0.35%)**	**0.18% - 0.66%**
ATRIAL FLUTTER	8 (8, 0.31%)	0.15% - 0.61%	8 (8, 0.31%)	0.15% - 0.61%
PAROXYSMAL ATRIAL FLUTTER	1 (1, 0.04%)	0.01% - 0.27%	1 (1, 0.04%)	0.01% - 0.27%
ATRIAL TACHYCARDIA	**11 (11, 0.42%)**	**0.23% - 0.76%**	**11 (11, 0.42%)**	**0.23% - 0.76%**
ATRIAL TACHYCARDIA	11 (11, 0.42%)	0.23% - 0.76%	11 (11, 0.42%)	0.23% - 0.76%
ATRIOVENTRICULAR BLOCK FIRST DEGREE	**0 (0, 0%)**	**--**	**1 (1, 0.04%)**	**0.01% - 0.28%**
ATRIOVENTRICULAR BLOCK FIRST DEGREE	0 (0, 0%)	--	1 (1, 0.04%)	0.01% - 0.28%
BASILAR MIGRAINE	**1 (1, 0.04%)**	**0.01% - 0.27%**	**1 (1, 0.04%)**	**0.01% - 0.27%**
BASILAR MIGRAINE	1 (1, 0.04%)	0.01% - 0.27%	1 (1, 0.04%)	0.01% - 0.27%
CARDIAC FAILURE	**0 (0, 0%)**	**--**	**1 (1, 0.04%)**	**0.01% - 0.31%**
DECOMPENSATED HEART FAILURE	0 (0, 0%)	--	1 (1, 0.04%)	0.01% - 0.31%
CARDIAC FAILURE CONGESTIVE	**13 (11, 0.42%)**	**0.23% - 0.76%**	**17 (15, 0.61%)**	**0.37% - 1.02%**
CONGESTIVE HEART FAILURE	13 (11, 0.42%)	0.23% - 0.76%	17 (15, 0.61%)	0.37% - 1.02%
CARDIAC PERFORATION	**14 (14, 0.53%)**	**0.31% - 0.89%**	**15 (15, 0.58%)**	**0.35% - 0.96%**
CARDIAC PERFORATION	14 (14, 0.53%)	0.31% - 0.89%	15 (15, 0.58%)	0.35% - 0.96%
CARDIAC TAMPONADE	**5 (5, 0.19%)**	**0.08% - 0.45%**	**5 (5, 0.19%)**	**0.08% - 0.45%**
CARDIAC TAMPONADE	5 (5, 0.19%)	0.08% - 0.45%	5 (5, 0.19%)	0.08% - 0.45%
CARDIOMYOPATHY	**0 (0, 0%)**	**--**	**1 (1, 0.04%)**	**0.01% - 0.31%**
CARDIOMYOPATHY	0 (0, 0%)	--	1 (1, 0.04%)	0.01% - 0.31%
CAROTID ARTERY DISEASE	**1 (1, 0.04%)**	**0.01% - 0.28%**	**1 (1, 0.04%)**	**0.01% - 0.28%**
CAROTID ARTERY DISEASE	1 (1, 0.04%)	0.01% - 0.28%	1 (1, 0.04%)	0.01% - 0.28%
CELLULITIS	**1 (1, 0.04%)**	**0.01% - 0.27%**	**2 (2, 0.08%)**	**0.02% - 0.31%**
CELLULITIS	1 (1, 0.04%)	0.01% - 0.27%	2 (2, 0.08%)	0.02% - 0.31%
CHEST DISCOMFORT	**1 (1, 0.04%)**	**0.01% - 0.27%**	**1 (1, 0.04%)**	**0.01% - 0.27%**
CHEST PRESSURE	1 (1, 0.04%)	0.01% - 0.27%	1 (1, 0.04%)	0.01% - 0.27%

Table 16: Previous Clinical Study Data - System and/or Procedure Related Adverse Events (n=2667)				
	Within 30-days of Implant		Within 12-months of Implant	
MedDRA Preferred Term Lowest Level Term	**No. Events (No. Subjects, %)[1]**	**95% CI[1]**	**No. Events (No. Subjects, %)[1]**	**95% CI[1]**
CHEST PAIN	**11 (10, 0.38%)**	**0.20% - 0.71%**	**14 (13, 0.52%)**	**0.30% - 0.90%**
CHEST PAIN	11 (10, 0.38%)	0.20% - 0.71%	12 (11, 0.42%)	0.23% - 0.76%
RETROSTERNAL PAIN	0 (0, 0%)	--	1 (1, 0.06%)	0.01% - 0.42%
THORACIC PAIN	0 (0, 0%)	--	1 (1, 0.04%)	0.01% - 0.28%
CHRONOTROPIC INCOMPETENCE	**3 (3, 0.12%)**	**0.04% - 0.36%**	**4 (4, 0.16%)**	**0.06% - 0.42%**
CHRONOTROPIC INCOMPETENCE	3 (3, 0.12%)	0.04% - 0.36%	4 (4, 0.16%)	0.06% - 0.42%
COMPLICATION OF DEVICE INSERTION	**17 (17, 0.64%)**	**0.40% - 1.02%**	**17 (17, 0.64%)**	**0.40% - 1.02%**
COMPLICATION OF DEVICE INSERTION	17 (17, 0.64%)	0.40% - 1.02%	17 (17, 0.64%)	0.40% - 1.02%
CONFUSIONAL STATE	**1 (1, 0.04%)**	**0.01% - 0.27%**	**1 (1, 0.04%)**	**0.01% - 0.27%**
CONFUSION	1 (1, 0.04%)	0.01% - 0.27%	1 (1, 0.04%)	0.01% - 0.27%
CORONARY ARTERY DISEASE	**11 (11, 0.42%)**	**0.23% - 0.76%**	**11 (11, 0.42%)**	**0.23% - 0.76%**
CORONARY ARTERY DISEASE	11 (11, 0.42%)	0.23% - 0.76%	11 (11, 0.42%)	0.23% - 0.76%
DEVICE CAPTURING ISSUE	**16 (16, 0.61%)**	**0.37% - 0.99%**	**22 (22, 0.90%)**	**0.59% - 1.36%**
LOSS OF CAPTURE	16 (16, 0.61%)	0.37% - 0.99%	22 (22, 0.90%)	0.59% - 1.36%
DEVICE COMPUTER ISSUE	**4 (4, 0.15%)**	**0.06% - 0.41%**	**9 (7, 0.28%)**	**0.13% - 0.59%**
INAPPROPRIATE DEVICE PROGRAMMING	4 (4, 0.15%)	0.06% - 0.41%	9 (7, 0.28%)	0.13% - 0.59%
DEVICE CONNECTION ISSUE	**5 (5, 0.19%)**	**0.08% - 0.46%**	**5 (5, 0.19%)**	**0.08% - 0.46%**
CONNECTOR BLOCK PROBLEM	2 (2, 0.08%)	0.02% - 0.30%	2 (2, 0.08%)	0.02% - 0.30%
INADEQUATE LEAD CONNECTION	3 (3, 0.11%)	0.04% - 0.35%	3 (3, 0.11%)	0.04% - 0.35%
DEVICE DAMAGE	**5 (5, 0.19%)**	**0.08% - 0.45%**	**5 (5, 0.19%)**	**0.08% - 0.45%**
CATHETER DAMAGE	5 (5, 0.19%)	0.08% - 0.45%	5 (5, 0.19%)	0.08% - 0.45%
DEVICE DISLOCATION	**63 (59, 2.26%)**	**1.75% - 2.91%**	**84 (78, 3.06%)**	**2.46% - 3.81%**
DEVICE MIGRATION	0 (0, 0%)	--	2 (2, 0.08%)	0.02% - 0.32%
LEAD DISLODGEMENT	63 (59, 2.26%)	1.75% - 2.91%	82 (76, 2.98%)	2.39% - 3.72%
DEVICE EXTRUSION	**0 (0, 0%)**	**--**	**1 (1, 0.04%)**	**0.01% - 0.29%**
DEVICE PROTRUSION	0 (0, 0%)	--	1 (1, 0.04%)	0.01% - 0.29%
DEVICE INTOLERANCE	**1 (1, 0.04%)**	**0.01% - 0.27%**	**2 (2, 0.08%)**	**0.02% - 0.32%**
DEVICE INTOLERANCE	1 (1, 0.04%)	0.01% - 0.27%	2 (2, 0.08%)	0.02% - 0.32%
DEVICE ISSUE	**4 (3, 0.12%)**	**0.04% - 0.36%**	**4 (3, 0.12%)**	**0.04% - 0.36%**
DEVICE ISSUE	4 (3, 0.12%)	0.04% - 0.36%	4 (3, 0.12%)	0.04% - 0.36%
DEVICE LEAD DAMAGE	**2 (2, 0.07%)**	**0.02% - 0.30%**	**3 (3, 0.13%)**	**0.04% - 0.39%**
DEVICE LEAD DAMAGE	1 (1, 0.04%)	0.01% - 0.27%	1 (1, 0.04%)	0.01% - 0.27%
DEVICE LEAD FRACTURE	0 (0, 0%)	--	1 (1, 0.05%)	0.01% - 0.36%
LEAD INSULATION FAILURE	1 (1, 0.04%)	0.01% - 0.27%	1 (1, 0.04%)	0.01% - 0.27%
DEVICE MALFUNCTION	**2 (2, 0.07%)**	**0.02% - 0.30%**	**3 (3, 0.12%)**	**0.04% - 0.37%**
DEVICE MALFUNCTION	2 (2, 0.07%)	0.02% - 0.30%	3 (3, 0.12%)	0.04% - 0.37%

Table 16: Previous Clinical Study Data - System and/or Procedure Related Adverse Events (n=2667)				
	Within 30-days of Implant		Within 12-months of Implant	
MedDRA Preferred Term Lowest Level Term	**No. Events (No. Subjects, %)[1]**	**95% CI[1]**	**No. Events (No. Subjects, %)[1]**	**95% CI[1]**
DEVICE PACING ISSUE	**27 (25, 0.95%)**	**0.65% - 1.41%**	**63 (57, 2.41%)**	**1.86% - 3.12%**
ELEVATED PACING THRESHOLD	27 (25, 0.95%)	0.65% - 1.41%	63 (57, 2.41%)	1.86% - 3.12%
DEVICE POWER SOURCE ISSUE	**0 (0, 0%)**	**--**	**3 (3, 0.12%)**	**0.04% - 0.39%**
DEVICE POWER SOURCE ISSUE	0 (0, 0%)	--	3 (3, 0.12%)	0.04% - 0.39%
DEVICE STIMULATION ISSUE	**14 (14, 0.53%)**	**0.32% - 0.90%**	**19 (17, 0.66%)**	**0.41% - 1.06%**
INAPPROPRIATE DEVICE STIMULATION OF MUSCLE	0 (0, 0%)	--	1 (1, 0.04%)	0.01% - 0.29%
INAPPROPRIATE EXTRA-CARDIAC DEVICE STIMULATION	2 (2, 0.08%)	0.02% - 0.31%	2 (2, 0.08%)	0.02% - 0.31%
INAPPROPRIATE PECTORAL MUSCLE STIMULATION	0 (0, 0%)	--	1 (1, 0.05%)	0.01% - 0.33%
INAPPROPRIATE PHRENIC NERVE STIMULATION	5 (5, 0.19%)	0.08% - 0.46%	7 (7, 0.27%)	0.13% - 0.57%
INAPPROPRIATE STIMULATION OF DIAPHRAGM	7 (7, 0.27%)	0.13% - 0.56%	8 (7, 0.27%)	0.13% - 0.56%
DIARRHOEA	**1 (1, 0.04%)**	**0.01% - 0.28%**	**1 (1, 0.04%)**	**0.01% - 0.28%**
DIARRHEA	1 (1, 0.04%)	0.01% - 0.28%	1 (1, 0.04%)	0.01% - 0.28%
DIZZINESS	**4 (4, 0.15%)**	**0.06% - 0.41%**	**7 (7, 0.29%)**	**0.14% - 0.62%**
DIZZINESS	4 (4, 0.15%)	0.06% - 0.41%	7 (7, 0.29%)	0.14% - 0.62%
DRESSLER'S SYNDROME	**1 (1, 0.04%)**	**0.01% - 0.27%**	**1 (1, 0.04%)**	**0.01% - 0.27%**
DRESSLER'S SYNDROME	1 (1, 0.04%)	0.01% - 0.27%	1 (1, 0.04%)	0.01% - 0.27%
DYSPNOEA	**1 (1, 0.04%)**	**0.01% - 0.28%**	**3 (3, 0.12%)**	**0.04% - 0.38%**
DYSPNEA	1 (1, 0.04%)	0.01% - 0.28%	3 (3, 0.12%)	0.04% - 0.38%
ECCHYMOSIS	**2 (2, 0.08%)**	**0.02% - 0.31%**	**2 (2, 0.08%)**	**0.02% - 0.31%**
ECCHYMOSIS	2 (2, 0.08%)	0.02% - 0.31%	2 (2, 0.08%)	0.02% - 0.31%
EJECTION FRACTION DECREASED	**0 (0, 0%)**	**--**	**1 (1, 0.05%)**	**0.01% - 0.36%**
EJECTION FRACTION DECREASED	0 (0, 0%)	--	1 (1, 0.05%)	0.01% - 0.36%
ERYTHEMA MIGRANS	**1 (1, 0.04%)**	**0.01% - 0.28%**	**1 (1, 0.04%)**	**0.01% - 0.28%**
ERYTHEMA CHRONICUM MIGRANS	1 (1, 0.04%)	0.01% - 0.28%	1 (1, 0.04%)	0.01% - 0.28%
EXTRAVASATION	**1 (1, 0.04%)**	**0.01% - 0.27%**	**1 (1, 0.04%)**	**0.01% - 0.27%**
EXTRAVASATION	1 (1, 0.04%)	0.01% - 0.27%	1 (1, 0.04%)	0.01% - 0.27%
FALL	**1 (1, 0.04%)**	**0.01% - 0.27%**	**1 (1, 0.04%)**	**0.01% - 0.27%**
FALL	1 (1, 0.04%)	0.01% - 0.27%	1 (1, 0.04%)	0.01% - 0.27%
FATIGUE	**2 (2, 0.08%)**	**0.02% - 0.31%**	**3 (3, 0.12%)**	**0.04% - 0.37%**
FATIGUE	2 (2, 0.08%)	0.02% - 0.31%	3 (3, 0.12%)	0.04% - 0.37%
HAEMATOMA	**1 (1, 0.04%)**	**0.01% - 0.27%**	**1 (1, 0.04%)**	**0.01% - 0.27%**
HEMATOMA	1 (1, 0.04%)	0.01% - 0.27%	1 (1, 0.04%)	0.01% - 0.27%
HAEMOGLOBIN DECREASED	**1 (1, 0.04%)**	**0.01% - 0.27%**	**1 (1, 0.04%)**	**0.01% - 0.27%**

Table 16: Previous Clinical Study Data - System and/or Procedure Related Adverse Events (n=2667)				
	Within 30-days of Implant		Within 12-months of Implant	
MedDRA Preferred Term Lowest Level Term	**No. Events (No. Subjects, %)[1]**	**95% CI[1]**	**No. Events (No. Subjects, %)[1]**	**95% CI[1]**
HEMOGLOBIN DECREASED	1 (1, 0.04%)	0.01% - 0.27%	1 (1, 0.04%)	0.01% - 0.27%
HEART RATE INCREASED	**0 (0, 0%)**	**--**	**2 (2, 0.08%)**	**0.02% - 0.33%**
HEART RATE HIGH	0 (0, 0%)	--	2 (2, 0.08%)	0.02% - 0.33%
HEART RATE IRREGULAR	**1 (1, 0.04%)**	**0.01% - 0.27%**	**1 (1, 0.04%)**	**0.01% - 0.27%**
HEART RATE IRREGULAR	1 (1, 0.04%)	0.01% - 0.27%	1 (1, 0.04%)	0.01% - 0.27%
HEPARIN-INDUCED THROMBOCYTOPENIA	**1 (1, 0.04%)**	**0.01% - 0.27%**	**1 (1, 0.04%)**	**0.01% - 0.27%**
HEPARIN-INDUCED THROMBOCYTOPENIA	1 (1, 0.04%)	0.01% - 0.27%	1 (1, 0.04%)	0.01% - 0.27%
HYPERTENSION	**2 (2, 0.08%)**	**0.02% - 0.30%**	**2 (2, 0.08%)**	**0.02% - 0.30%**
HYPERTENSION	2 (2, 0.08%)	0.02% - 0.30%	2 (2, 0.08%)	0.02% - 0.30%
HYPOTENSION	**7 (7, 0.27%)**	**0.13% - 0.56%**	**7 (7, 0.27%)**	**0.13% - 0.56%**
HYPOTENSION	7 (7, 0.27%)	0.13% - 0.56%	7 (7, 0.27%)	0.13% - 0.56%
IMPAIRED HEALING	**1 (1, 0.04%)**	**0.01% - 0.27%**	**1 (1, 0.04%)**	**0.01% - 0.27%**
WOUND HEALING DELAYED	1 (1, 0.04%)	0.01% - 0.27%	1 (1, 0.04%)	0.01% - 0.27%
IMPLANT SITE DISCHARGE	**0 (0, 0%)**	**--**	**1 (1, 0.04%)**	**0.01% - 0.28%**
IMPLANT SITE DISCHARGE	0 (0, 0%)	--	1 (1, 0.04%)	0.01% - 0.28%
IMPLANT SITE HAEMATOMA	**21 (21, 0.80%)**	**0.52% - 1.22%**	**23 (23, 0.88%)**	**0.59% - 1.32%**
IMPLANT SITE HEMATOMA	21 (21, 0.80%)	0.52% - 1.22%	23 (23, 0.88%)	0.59% - 1.32%
IMPLANT SITE INFECTION	**18 (18, 0.69%)**	**0.44% - 1.10%**	**27 (26, 1.01%)**	**0.69% - 1.48%**
IMPLANT SITE INFECTION	7 (7, 0.27%)	0.13% - 0.56%	9 (8, 0.31%)	0.15% - 0.62%
IMPLANT SITE POCKET INFECTION	11 (11, 0.42%)	0.23% - 0.76%	18 (18, 0.70%)	0.44% - 1.11%
IMPLANT SITE PAIN	**9 (9, 0.35%)**	**0.18% - 0.66%**	**19 (19, 0.81%)**	**0.51% - 1.27%**
IMPLANT SITE PAIN	2 (2, 0.08%)	0.02% - 0.30%	3 (3, 0.12%)	0.04% - 0.36%
IMPLANT SITE POCKET PAIN	7 (7, 0.27%)	0.13% - 0.57%	16 (16, 0.69%)	0.42% - 1.13%
IMPLANT SITE PARAESTHESIA	**0 (0, 0%)**	**--**	**3 (3, 0.12%)**	**0.04% - 0.38%**
IMPLANT SITE PARAESTHESIA	0 (0, 0%)	--	3 (3, 0.12%)	0.04% - 0.38%
IMPLANT SITE SWELLING	**1 (1, 0.04%)**	**0.01% - 0.27%**	**1 (1, 0.04%)**	**0.01% - 0.27%**
IMPLANT SITE SWELLING	1 (1, 0.04%)	0.01% - 0.27%	1 (1, 0.04%)	0.01% - 0.27%
IMPLANT SITE WARMTH	**0 (0, 0%)**	**--**	**1 (1, 0.04%)**	**0.01% - 0.29%**
IMPLANT SITE WARMTH	0 (0, 0%)	--	1 (1, 0.04%)	0.01% - 0.29%
INCISION SITE COMPLICATION	**0 (0, 0%)**	**--**	**1 (1, 0.04%)**	**0.01% - 0.29%**
INCISION SITE INFLAMMATION	0 (0, 0%)	--	1 (1, 0.04%)	0.01% - 0.29%
INCISION SITE ERYTHEMA	**1 (1, 0.04%)**	**0.01% - 0.27%**	**1 (1, 0.04%)**	**0.01% - 0.27%**
INCISION SITE ERYTHEMA	1 (1, 0.04%)	0.01% - 0.27%	1 (1, 0.04%)	0.01% - 0.27%
INCISION SITE HAEMORRHAGE	**2 (2, 0.08%)**	**0.02% - 0.31%**	**2 (2, 0.08%)**	**0.02% - 0.31%**
INCISION SITE BLEEDING	2 (2, 0.08%)	0.02% - 0.31%	2 (2, 0.08%)	0.02% - 0.31%
INCISION SITE PAIN	**0 (0, 0%)**	**--**	**1 (1, 0.05%)**	**0.01% - 0.32%**

Table 16: Previous Clinical Study Data - System and/or Procedure Related Adverse Events (n=2667)				
	Within 30-days of Implant		Within 12-months of Implant	
MedDRA Preferred Term Lowest Level Term	**No. Events (No. Subjects, %)[1]**	**95% CI[1]**	**No. Events (No. Subjects, %)[1]**	**95% CI[1]**
INCISION SITE PAIN	0 (0, 0%)	--	1 (1, 0.05%)	0.01% - 0.32%
INCISIONAL DRAINAGE	**1 (1, 0.04%)**	**0.01% - 0.27%**	**1 (1, 0.04%)**	**0.01% - 0.27%**
INCISIONAL DRAINAGE	1 (1, 0.04%)	0.01% - 0.27%	1 (1, 0.04%)	0.01% - 0.27%
INFECTION	**1 (1, 0.04%)**	**0.01% - 0.27%**	**2 (2, 0.08%)**	**0.02% - 0.32%**
INFECTION	1 (1, 0.04%)	0.01% - 0.27%	2 (2, 0.08%)	0.02% - 0.32%
INTENTIONAL DEVICE MISUSE	**0 (0, 0%)**	**--**	**1 (1, 0.05%)**	**0.01% - 0.35%**
INAPPROPRIATE DEVICE THERAPY FOR ATRIAL ARRHYTHMIA	0 (0, 0%)	--	1 (1, 0.05%)	0.01% - 0.35%
INTRACARDIAC THROMBUS	**1 (1, 0.04%)**	**0.01% - 0.27%**	**1 (1, 0.04%)**	**0.01% - 0.27%**
INTRACARDIAC THROMBUS	1 (1, 0.04%)	0.01% - 0.27%	1 (1, 0.04%)	0.01% - 0.27%
JOINT RANGE OF MOTION DECREASED	**1 (1, 0.04%)**	**0.01% - 0.27%**	**1 (1, 0.04%)**	**0.01% - 0.27%**
JOINT RANGE OF MOTION DECREASED	1 (1, 0.04%)	0.01% - 0.27%	1 (1, 0.04%)	0.01% - 0.27%
LEAD DISLODGEMENT	**7 (6, 0.23%)**	**0.10% - 0.51%**	**15 (14, 0.56%)**	**0.33% - 0.94%**
LEAD DISLODGEMENT	7 (6, 0.23%)	0.10% - 0.51%	15 (14, 0.56%)	0.33% - 0.94%
LOSS OF CONSCIOUSNESS	**1 (1, 0.04%)**	**0.01% - 0.27%**	**1 (1, 0.04%)**	**0.01% - 0.27%**
LOSS OF CONSCIOUSNESS	1 (1, 0.04%)	0.01% - 0.27%	1 (1, 0.04%)	0.01% - 0.27%
MEDICAL DEVICE DISCOMFORT	**3 (2, 0.08%)**	**0.02% - 0.30%**	**3 (2, 0.08%)**	**0.02% - 0.30%**
MEDICAL DEVICE DISCOMFORT	3 (2, 0.08%)	0.02% - 0.30%	3 (2, 0.08%)	0.02% - 0.30%
MEDICAL DEVICE SITE REACTION	**0 (0, 0%)**	**--**	**1 (1, 0.04%)**	**0.01% - 0.29%**
TISSUE BREAKDOWN ASSOCIATED WITH DEVICE	0 (0, 0%)	--	1 (1, 0.04%)	0.01% - 0.29%
MUSCULOSKELETAL PAIN	**3 (3, 0.11%)**	**0.04% - 0.35%**	**4 (4, 0.15%)**	**0.06% - 0.41%**
SHOULDER PAIN	3 (3, 0.11%)	0.04% - 0.35%	4 (4, 0.15%)	0.06% - 0.41%
MYOCARDIAL INFARCTION	**1 (1, 0.04%)**	**0.01% - 0.27%**	**1 (1, 0.04%)**	**0.01% - 0.27%**
MYOCARDIAL INFARCTION	1 (1, 0.04%)	0.01% - 0.27%	1 (1, 0.04%)	0.01% - 0.27%
NAUSEA	**1 (1, 0.04%)**	**0.01% - 0.27%**	**1 (1, 0.04%)**	**0.01% - 0.27%**
NAUSEA	1 (1, 0.04%)	0.01% - 0.27%	1 (1, 0.04%)	0.01% - 0.27%
NECK PAIN	**1 (1, 0.04%)**	**0.01% - 0.28%**	**1 (1, 0.04%)**	**0.01% - 0.28%**
NECK PAIN	1 (1, 0.04%)	0.01% - 0.28%	1 (1, 0.04%)	0.01% - 0.28%
NIPPLE PAIN	**1 (1, 0.04%)**	**0.01% - 0.27%**	**1 (1, 0.04%)**	**0.01% - 0.27%**
NIPPLE PAIN	1 (1, 0.04%)	0.01% - 0.27%	1 (1, 0.04%)	0.01% - 0.27%
NON-CARDIAC CHEST PAIN	**1 (1, 0.04%)**	**0.01% - 0.27%**	**1 (1, 0.04%)**	**0.01% - 0.27%**
NON-CARDIAC CHEST PAIN	1 (1, 0.04%)	0.01% - 0.27%	1 (1, 0.04%)	0.01% - 0.27%
OEDEMA	**6 (6, 0.23%)**	**0.10% - 0.51%**	**6 (6, 0.23%)**	**0.10% - 0.51%**
EDEMA	6 (6, 0.23%)	0.10% - 0.51%	6 (6, 0.23%)	0.10% - 0.51%
ORTHOSTATIC HYPOTENSION	**3 (3, 0.11%)**	**0.04% - 0.35%**	**3 (3, 0.11%)**	**0.04% - 0.35%**
ORTHOSTATIC HYPOTENSION	2 (2, 0.08%)	0.02% - 0.30%	2 (2, 0.08%)	0.02% - 0.30%

Table 16: Previous Clinical Study Data - System and/or Procedure Related Adverse Events (n=2667)				
	Within 30-days of Implant		Within 12-months of Implant	
MedDRA Preferred Term Lowest Level Term	**No. Events (No. Subjects, %)[1]**	**95% CI[1]**	**No. Events (No. Subjects, %)[1]**	**95% CI[1]**
POSTURAL HYPOTENSION	1 (1, 0.04%)	0.01% - 0.27%	1 (1, 0.04%)	0.01% - 0.27%
OVERSENSING	**0 (0, 0%)**	**--**	**4 (4, 0.18%)**	**0.07% - 0.48%**
OVERSENSING	0 (0, 0%)	--	4 (4, 0.18%)	0.07% - 0.48%
PACEMAKER GENERATED ARRHYTHMIA	**3 (3, 0.11%)**	**0.04% - 0.35%**	**4 (4, 0.16%)**	**0.06% - 0.42%**
PACEMAKER MEDIATED TACHYCARDIA	3 (3, 0.11%)	0.04% - 0.35%	4 (4, 0.16%)	0.06% - 0.42%
PACEMAKER SYNDROME	**1 (1, 0.04%)**	**0.01% - 0.27%**	**1 (1, 0.04%)**	**0.01% - 0.27%**
PACEMAKER SYNDROME	1 (1, 0.04%)	0.01% - 0.27%	1 (1, 0.04%)	0.01% - 0.27%
PAIN	**1 (1, 0.04%)**	**0.01% - 0.27%**	**2 (2, 0.08%)**	**0.02% - 0.31%**
PAIN	1 (1, 0.04%)	0.01% - 0.27%	2 (2, 0.08%)	0.02% - 0.31%
PAIN IN EXTREMITY	**3 (3, 0.11%)**	**0.04% - 0.35%**	**3 (3, 0.11%)**	**0.04% - 0.35%**
PAIN IN ARM	2 (2, 0.08%)	0.02% - 0.30%	2 (2, 0.08%)	0.02% - 0.30%
PAIN OF EXTREMITIES	1 (1, 0.04%)	0.01% - 0.27%	1 (1, 0.04%)	0.01% - 0.27%
PALPITATIONS	**10 (10, 0.38%)**	**0.21% - 0.71%**	**12 (12, 0.48%)**	**0.27% - 0.85%**
HEART RACING	1 (1, 0.04%)	0.01% - 0.27%	1 (1, 0.04%)	0.01% - 0.27%
PALPITATIONS	9 (9, 0.35%)	0.18% - 0.66%	11 (11, 0.44%)	0.24% - 0.80%
PANIC ATTACK	**1 (1, 0.04%)**	**0.01% - 0.27%**	**1 (1, 0.04%)**	**0.01% - 0.27%**
PANIC ATTACK	1 (1, 0.04%)	0.01% - 0.27%	1 (1, 0.04%)	0.01% - 0.27%
PERICARDIAL EFFUSION	**18 (17, 0.65%)**	**0.40% - 1.04%**	**20 (19, 0.73%)**	**0.46% - 1.14%**
CARDIAC PERFORATION	1 (1, 0.04%)	0.01% - 0.27%	1 (1, 0.04%)	0.01% - 0.27%
PERICARDIAL EFFUSION	17 (16, 0.61%)	0.37% - 0.99%	19 (18, 0.69%)	0.43% - 1.09%
PERICARDITIS	**4 (4, 0.15%)**	**0.06% - 0.41%**	**5 (4, 0.15%)**	**0.06% - 0.41%**
PERICARDITIS	4 (4, 0.15%)	0.06% - 0.41%	5 (4, 0.15%)	0.06% - 0.41%
PLEURAL EFFUSION	**11 (11, 0.42%)**	**0.23% - 0.75%**	**11 (11, 0.42%)**	**0.23% - 0.75%**
PLEURAL EFFUSION	11 (11, 0.42%)	0.23% - 0.75%	11 (11, 0.42%)	0.23% - 0.75%
PNEUMONIA	**2 (2, 0.08%)**	**0.02% - 0.31%**	**2 (2, 0.08%)**	**0.02% - 0.31%**
PNEUMONIA	2 (2, 0.08%)	0.02% - 0.31%	2 (2, 0.08%)	0.02% - 0.31%
PNEUMOTHORAX	**43 (43, 1.62%)**	**1.20% - 2.18%**	**43 (43, 1.62%)**	**1.20% - 2.18%**
PNEUMOTHORAX	43 (43, 1.62%)	1.20% - 2.18%	43 (43, 1.62%)	1.20% - 2.18%
POSTOPERATIVE WOUND COMPLICATION	**1 (1, 0.04%)**	**0.01% - 0.27%**	**1 (1, 0.04%)**	**0.01% - 0.27%**
POSTOPERATIVE WOUND COMPLICATION	1 (1, 0.04%)	0.01% - 0.27%	1 (1, 0.04%)	0.01% - 0.27%
POSTOPERATIVE WOUND INFECTION	**0 (0, 0%)**	**--**	**1 (1, 0.05%)**	**0.01% - 0.39%**
SUTURE LINE INFECTION	0 (0, 0%)	--	1 (1, 0.05%)	0.01% - 0.39%
PRESYNCOPE	**2 (2, 0.08%)**	**0.02% - 0.30%**	**2 (2, 0.08%)**	**0.02% - 0.30%**
NEAR SYNCOPE	1 (1, 0.04%)	0.01% - 0.27%	1 (1, 0.04%)	0.01% - 0.27%
VASOVAGAL REACTION	1 (1, 0.04%)	0.01% - 0.27%	1 (1, 0.04%)	0.01% - 0.27%
PRURITIS	**1 (1, 0.04%)**	**0.01% - 0.27%**	**1 (1, 0.04%)**	**0.01% - 0.27%**

Table 16: Previous Clinical Study Data - System and/or Procedure Related Adverse Events (n=2667)				
	Within 30-days of Implant		Within 12-months of Implant	
MedDRA Preferred Term Lowest Level Term	**No. Events (No. Subjects, %)[1]**	**95% CI[1]**	**No. Events (No. Subjects, %)[1]**	**95% CI[1]**
PRURITIS	1 (1, 0.04%)	0.01% - 0.27%	1 (1, 0.04%)	0.01% - 0.27%
PULMONARY EMBOLISM	**1 (1, 0.04%)**	**0.01% - 0.27%**	**1 (1, 0.04%)**	**0.01% - 0.27%**
PULMONARY EMBOLUS	1 (1, 0.04%)	0.01% - 0.27%	1 (1, 0.04%)	0.01% - 0.27%
PULMONARY OEDEMA	**1 (1, 0.04%)**	**0.01% - 0.27%**	**1 (1, 0.04%)**	**0.01% - 0.27%**
PULMONARY EDEMA	1 (1, 0.04%)	0.01% - 0.27%	1 (1, 0.04%)	0.01% - 0.27%
PYREXIA	**2 (2, 0.08%)**	**0.02% - 0.30%**	**2 (2, 0.08%)**	**0.02% - 0.30%**
FEVER	2 (2, 0.08%)	0.02% - 0.30%	2 (2, 0.08%)	0.02% - 0.30%
RASH	**3 (3, 0.11%)**	**0.04% - 0.35%**	**3 (3, 0.11%)**	**0.04% - 0.35%**
RASH	3 (3, 0.11%)	0.04% - 0.35%	3 (3, 0.11%)	0.04% - 0.35%
RENAL FAILURE	**1 (1, 0.04%)**	**0.01% - 0.27%**	**1 (1, 0.04%)**	**0.01% - 0.27%**
RENAL INSUFFICIENCY	1 (1, 0.04%)	0.01% - 0.27%	1 (1, 0.04%)	0.01% - 0.27%
RESTLESSNESS	**1 (1, 0.04%)**	**0.01% - 0.27%**	**1 (1, 0.04%)**	**0.01% - 0.27%**
RESTLESSNESS	1 (1, 0.04%)	0.01% - 0.27%	1 (1, 0.04%)	0.01% - 0.27%
SINUS TACHYCARDIA	**1 (1, 0.04%)**	**0.01% - 0.27%**	**3 (3, 0.13%)**	**0.04% - 0.42%**
SINUS TACHYCARDIA	1 (1, 0.04%)	0.01% - 0.27%	3 (3, 0.13%)	0.04% - 0.42%
SUBCLAVIAN ARTERY STENOSIS	**1 (1, 0.04%)**	**0.01% - 0.27%**	**1 (1, 0.04%)**	**0.01% - 0.27%**
SUBCLAVIAN ARTERY STENOSIS	1 (1, 0.04%)	0.01% - 0.27%	1 (1, 0.04%)	0.01% - 0.27%
SUBCLAVIAN VEIN THROMBOSIS	**1 (1, 0.04%)**	**0.01% - 0.28%**	**1 (1, 0.04%)**	**0.01% - 0.28%**
SUBCLAVIAN VEIN THROMBOSIS	1 (1, 0.04%)	0.01% - 0.28%	1 (1, 0.04%)	0.01% - 0.28%
SUBCUTANEOUS EMPHYSEMA	**1 (1, 0.04%)**	**0.01% - 0.27%**	**1 (1, 0.04%)**	**0.01% - 0.27%**
SUBCUTANEOUS EMPHYSEMA	1 (1, 0.04%)	0.01% - 0.27%	1 (1, 0.04%)	0.01% - 0.27%
SUPRAVENTRICULAR EXTRASYSTOLES	**2 (2, 0.08%)**	**0.02% - 0.31%**	**2 (2, 0.08%)**	**0.02% - 0.31%**
PREMATURE ATRIAL CONTRACTION	2 (2, 0.08%)	0.02% - 0.31%	2 (2, 0.08%)	0.02% - 0.31%
SUPRAVENTRICULAR TACHYCARDIA	**3 (3, 0.11%)**	**0.04% - 0.35%**	**3 (3, 0.11%)**	**0.04% - 0.35%**
SUPRAVENTRICULAR TACHYCARDIA	3 (3, 0.11%)	0.04% - 0.35%	3 (3, 0.11%)	0.04% - 0.35%
SUTURE RELATED COMPLICATION	**1 (1, 0.04%)**	**0.01% - 0.28%**	**2 (2, 0.08%)**	**0.02% - 0.31%**
SUTURE RELATED COMPLICATION	1 (1, 0.04%)	0.01% - 0.28%	2 (2, 0.08%)	0.02% - 0.31%
SWELLING	**0 (0, 0%)**	**--**	**2 (2, 0.08%)**	**0.02% - 0.33%**
SWELLING	0 (0, 0%)	--	2 (2, 0.08%)	0.02% - 0.33%
SYNCOPE	**4 (4, 0.15%)**	**0.06% - 0.40%**	**5 (5, 0.20%)**	**0.08% - 0.47%**
SYNCOPE	4 (4, 0.15%)	0.06% - 0.40%	5 (5, 0.20%)	0.08% - 0.47%
THROMBOPHLEBITIS	**1 (1, 0.04%)**	**0.01% - 0.27%**	**1 (1, 0.04%)**	**0.01% - 0.27%**
THROMBOPHLEBITIS	1 (1, 0.04%)	0.01% - 0.27%	1 (1, 0.04%)	0.01% - 0.27%
THROMBOSIS	**2 (2, 0.08%)**	**0.02% - 0.31%**	**4 (4, 0.18%)**	**0.07% - 0.47%**
THROMBOSIS	2 (2, 0.08%)	0.02% - 0.31%	4 (4, 0.18%)	0.07% - 0.47%
TRANSIENT ISCHAEMIC ATTACK	**2 (2, 0.08%)**	**0.02% - 0.30%**	**2 (2, 0.08%)**	**0.02% - 0.30%**

Table 16: Previous Clinical Study Data - System and/or Procedure Related Adverse Events (n=2667)				
	Within 30-days of Implant		Within 12-months of Implant	
MedDRA Preferred Term Lowest Level Term	**No. Events (No. Subjects, %)[1]**	**95% CI[1]**	**No. Events (No. Subjects, %)[1]**	**95% CI[1]**
TRANSIENT ISCHAEMIC ATTACK	1 (1, 0.04%)	0.01% - 0.27%	1 (1, 0.04%)	0.01% - 0.27%
TRANSIENT ISCHEMIC ATTACKS	1 (1, 0.04%)	0.01% - 0.27%	1 (1, 0.04%)	0.01% - 0.27%
UNDERSENSING	**9 (9, 0.34%)**	**0.18% - 0.65%**	**13 (13, 0.53%)**	**0.31% - 0.92%**
LOSS OF SENSING	2 (2, 0.07%)	0.02% - 0.30%	3 (3, 0.11%)	0.04% - 0.35%
UNDERSENSING	7 (7, 0.27%)	0.13% - 0.56%	10 (10, 0.42%)	0.22% - 0.78%
VASCULAR PSEUDOANEURYSM	**0 (0, 0%)**	**--**	**1 (1, 0.04%)**	**0.01% - 0.28%**
VASCULAR PSEUDOANEURYSM	0 (0, 0%)	--	1 (1, 0.04%)	0.01% - 0.28%
VENOUS INSUFFICIENCY	**1 (1, 0.04%)**	**0.01% - 0.27%**	**1 (1, 0.04%)**	**0.01% - 0.27%**
VENOUS EDEMA	1 (1, 0.04%)	0.01% - 0.27%	1 (1, 0.04%)	0.01% - 0.27%
VENOUS THROMBOSIS	**8 (8, 0.31%)**	**0.15% - 0.61%**	**8 (8, 0.31%)**	**0.15% - 0.61%**
VENOUS THROMBOSIS	8 (8, 0.31%)	0.15% - 0.61%	8 (8, 0.31%)	0.15% - 0.61%
VENTRICULAR EXTRASYSTOLES	**10 (10, 0.38%)**	**0.21% - 0.71%**	**11 (11, 0.42%)**	**0.23% - 0.76%**
FUSION BEAT	0 (0, 0%)	--	1 (1, 0.04%)	0.01% - 0.28%
PREMATURE VENTRICULAR CONTRACTIONS	10 (10, 0.38%)	0.21% - 0.71%	10 (10, 0.38%)	0.21% - 0.71%
VENTRICULAR TACHYCARDIA	**2 (2, 0.08%)**	**0.02% - 0.31%**	**2 (2, 0.08%)**	**0.02% - 0.31%**
VENTRICULAR TACHYCARDIA	2 (2, 0.08%)	0.02% - 0.31%	2 (2, 0.08%)	0.02% - 0.31%
VIRAL INFECTION	**1 (1, 0.04%)**	**0.01% - 0.27%**	**1 (1, 0.04%)**	**0.01% - 0.27%**
VIRAL INFECTION	1 (1, 0.04%)	0.01% - 0.27%	1 (1, 0.04%)	0.01% - 0.27%

APPENDIX D: PARTICIPATING INVESTIGATORS AND INSTITUTIONS

A complete list of participating investigators and institutions (including names, titles/professional positions, address(es), and telephone numbers) where study activities will be conducted will be provided upon request under a separate cover.

APPENDIX E: ETHICS COMMITTEE (IRB)

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

APPENDIX F: LABELING

Labeling and packaging for all products used in this study will follow the local regulatory requirements. Labeling for all system components market released at study start in the respective geographies can be found with each package insert and/or will be available on http://manuals.medtronic.com. In the event a non-Medtronic lead is used, governing labeling for that lead should be consulted.

APPENDIX G: CIP Change History

Table 17: Change History CIP V1.0 to CIP V2.0

Applicable Sections	Change	Rationale
Title Page, Appendix D & E, header/footer	Update to Version 2.0 from 1.0 Updated date to April 2017 from Dec 2016	CIP update
Sponsor Contact Information	Clinical Study Leader now Andrea DeRoche, previously Scott Sarazin	Role change
CROs/Core Laboratories	Added The Ohio State University as the echocardiographu core lab and ACM Glabal Central Lanoratory as the blood core lab	Formally adding contact information of the core laboratories
1. Version History	Added version 2.0	CIP Update
4. Synopsis	Removed "Ensura MRI" in the Product Name section	Available OUS only
4. Synopsis; Exclusion Criteria, 9.4	Changed criteria from "Subject has permanent AF or AF at time of enrollment visit" to Subject has permanent AF or AF noted on baseline interrogation rhythm strip"	Provide clairifcation to criteria
4. Synopsis; Exclusion Criteria, 9.4	Added " prior to enrollment" for exclusion criteria regarding aortic valve replacement procedure less than 1 year	Provide clairifcation to criteria
4. Synopsis; Exclusion Criteria, 9.4	Added "Subject has know coronary disease with Class II angina"	Added per Steering Committee recommendation
4. Synopsis; Study Procedures and Assessments, 10.8	Added "Subject observation of at least 30 minutes to ensure that they can tolerate 100 bpm pacing post programming"	Added per Steering Committee recommendation
4. Synopsis; Study Procedures and Assessments, 10.9	Added a 24 Hour Telephone call Follow-Up Visit	Added per Steering Committee recommendation

Applicable Sections	Change	Rationale
7. Study Design	Removed "This study is a Non-Significant Risk (NSR) Investigational Device Examption (IDE) study as subjects will already have implanted market-approved Medtronic pacemakers that have the Sleep Function." And added "The REVAMP study will be conducted as a Non-Significant Risk (NSR) IDE study. The REVAMP Research System does not include an investigational device; the ability to program a lower rate of 100 bpm is available in market-released pacemakers, and the Sleep function (which allows a different rate to be programmed for part of a 24 hour clock) is an approved feature in market-released pacemakers that will be used in the clinical study. The study will be conducted in compliance with 21 CFR Parts 11, 50, 56, 812.2 (b)(1). This study does not require an IDE submission to FDA."	Provide further clearity around the meaning of a Non-Significant Risk IDE study
7.1 Duration	Removed sentence regarding study start date	Not required
8.3 Study Componets, 10.3	Added "Access to dry ice to ship blood samples"	Provide clarity around shipping samples

Applicable Sections	Change	Rationale
10. Study Procedures	Added the following "At the request of the Principal Investigator or other authorized site personnel, Medtronic will use information from its device registration database to provide a study site a list of its patients whom the site had implanted with the Medtronic dual chamber pacemaker with Sleep Function, required by the inclusion criteria set out in Section 9.3. Study site, if permitted by its IRB, could further review the records of such patients to determine if they may be eligible to participate in the study."	To allow Medtronic access to potential study subjects at the study site using device database
10.2 Site Activation	Added a bullet to include Financial Disclosure Agreement	To include all required documents
10.4 Schedule of Events	Added the 24 hour post baseline call, medications to be collected at the early study visit, and at least 30 minute observation person post programming	Added per Steering Committee recommendation
10.5 Prior and Concomitant Medications	Added "all telephone call follow up visits" to the second sentence in the paragraph	To be consistant with schedule of events table
10.8 Baseline Visit	Added "In the event a subject experiences symptoms once sent home after the Baseline visit, the subject should be instructd to seek medical help for device reprogramming if they cannot or do not tolerate elevated pacing."	Added per Steering Committee recommendation
10.10.1 Blinding	Added "Refer to the Randomization and Blinding Plan for specific details."	Provide further clearity as to where to find this detailed information

Applicable Sections	Change	Rationale
10.12 unscheduled Follow-Up Visits	Changed "An unscheduled visit is defined as a visit not required by the follow up visit schedule in the CIP." To now read "An unscheduled visit is defined as any unplanned visit by the subject to the study site. Routine visits or other planned visits are not collected."	Provide clearity for how this visit is defined
10.13 12 Week Visit (Study Exit)	Added "NYHA" as a bullet	To be consistant with schedule of events table
15.1 Statement(s) of Compliance	Added the following sentence " The study was designed to reflect the GCP principles outlined in ICO 14155:2011."	Required per Medtroinc CIP checklist
16.1 Monitoring	Changed "Monitoring for the study, including site initiation visits, interim monitoring visits, and closeout visits, will be done in accordance to the study-specific plan." To now read "Monitoring for the study will be done in accordance to the study-specific plan	Specific details to be outlined in the Monitoring Plan

Applicable Sections	Change	Rationale
16.2 Data Management	Revised this paragraph from "Procedures in the CIP require source documentation. Source documentation will be maintained at the site. Source documents, which may include worksheets, patient medical records, echo data, programmer printouts, device interrogation files, must be created and maintained by the investigational site team." To "Procedures in the CIP require source documentation. Source documentation will be maintained at the site. Source may include worksheets, patient medical records, echo data, programmer printouts, device interrogation files, and certain CRF fields which must be created and maintained by the investigational site team."	Provide clearity that only certain CRF fields will need source documents created

Table 18: Change History CIP V2.0 to CIP V3.0

Applicable Sections	Change	Rationale
1. Version History	Added Version 3.0 Table 18	CIP Update
1. Version History	Added Table 17 to V2.0	Clarification of changes
3. Glossary	Added ADL (Activities of Daily Living) and UR (Upper Rate)	Consistency within protocol
4. Synopsis; Sample Size	Increased number of subjects from 40 to 50 and number of sites from approximately 5 sites to 10 sites	Recommended by Steering Committee
4. Synopsis; Inclusion/Exclusion Criteria and 9. Selection of Subjects 9.3. Inclusion Criteria	Changed Subject has had a marked released dual chamber Medtronic Pacemaker with Sleep Function for at 6 months to for at least 3 months.	Change recommended by Steering Committee
4. Synopsis; Inclusion/Exclusion Criteria and 9. Selection of Subjects 9.3. Inclusion Criteria	Changed from Subject has dyspnea with exertion to Subject has dyspnea with exertion or diagnosed as NYHA Class II or III heart Failure	Clarification recommended by Steering Committee
4. Synopsis; Inclusion/Exclusion Criteria and 9. Selection of Subjects 9.4. Exclusion Criteria	Changed from Subject has more than moderate valve disease to Subject has severe stenosis of the aortic or mitral valve, defined as a valve area less than or equal to 1.0cm² or subject has severe regurgitation of the aortic or mitral valve.	Clarification recommended by Steering Committee

Applicable Sections	Change	Rationale
4. Synopsis; Inclusion/Exclusion Criteria 9. Selection of Subjects 9.4. Exclusion Criteria	Changed from Subject has had an aortic valve replacement (surgical or TAVR) procedure less than 1 year to Subject has had an aortic valve replacement (surgical or TAVR) procedure less than 9 months.	Recommended by Steering Committee
Section 7. Study Design 7.1. Duration	Increased duration of study from 12 months to 24 months	Necessary for additional site selections and enrollments
5.1 Background and 8.4 Product Use	Added acronym or definition of acronym first time used	Consistency within protocol
7. Study Design Sites and Subjects 7.2. Rationale	Increased number of subjects from 40 to 50	Recommended by Steering Committee
14. Statistical Design and Methods	Removed list of analyses	Removal of redundant information; can see in Section 14.1 Endpoint Definitions
14.1 Endpoint Definitions 14.1.2. Ancillary Safety Endpoint – NT-proBNP, troponin, LVEF 14.1.4. Ancillary Efficacy Endpoint – Quality of Life 14.1.5. Ancillary Efficacy Endpoint – Mobility and Activity 14.1.6. Ancillary Efficacy Endpoint – Echo Measurements 14.1.7. Ancillary Efficacy Endpoint – Collagen Degration Biomarker Measurements	Updated symbols to show µ instead of a square	Consistency within protocol
14.1.4. Ancillary Efficacy Endpoint – Quality of Life	Added EQ-5D-5L Questionnaire – 8 weeks section	Clarify the quality of life analyses
14.1.5. Ancillary Efficacy Endpoint – Mobility and Activity	Updated ‘:’ to ‘-‘ in section header; Updated MNLWHF for week 8 to 6 Minute Hall Walk Test distance	Consistency within protocol

Applicable Sections	Change	Rationale
14.1.7. Ancillary Efficacy Endpoint – Collagen Degradation Biomarker Measurements	Updated echo to collagen degration biomarker at week 8	Consistency within protocol
10. Study Procedure 10.2. Rose of Sponsor Representative	Added to specify MDT field role	Clarify MDT field role
Appendix G: CIP Change Table 17 History V1 to V2	Inclusion updated to Exclusion	Consistency within protocol
Sponsor Contact Sponsor's Medical Expert	David Steinhaus removed Robert Kowal added	Change in staff
Table of Contents	Added Table 18 CIP Changes V2 to V3	Capture changes in CIP
Appendix G: CIP Change Added Table 18 CIP Changes V2 to V3	Addition of Table of Changes	Capture changes V2 to V3
Throughout CIP	Formatting & grammatical changes	Format change & grammatical errors
Table 15: Sponsor Reports for the United States	Removed: Recall and Disposition Other	Not required for NSR IDE
APPENDIX D: Participating Investigators and Institutions APPENDIX E: Ethics Committee (IRB)	Removed: At the time of REVAMP CIP V2 completion were not finalized	Site selections have been made for 5 sites since V2
10: Study Procedure 10.9.1. Programming Recommendations at Baseline	Added: Use of AAI (R) programming is not recommended due to the possibility of AV block occurring	Clarifying Programming recommendation

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