Medtronic **Clinical Investigation Plan**	
Clinical Investigation Plan/Study Title	Mid-Q Response
Study Product Name	Market released CRT-P and CRT-D devices containing the AdaptivCRT algorithm. Medtronic market released LV lead, and any market released RA and RV leads.
Sponsor/Local Sponsor	Medtronic, Inc. Cardiac Rhythm and Heart Failure Clinical Research 8200 Coral Sea Street NE Mounds View, MN U.S.A. 55112 1-800-328-2518 Medtronic, Bakken Research Center B.V. Cardiac Rhythm and Heart Failure Clinical Research Endepolsdomein 5 6229 GW Maastricht The Netherlands +31-43-35-66-566 Medtronic Japan Co., Ltd. Office: +81-3-6774-4611 1-2-70 Konan, Minato-ku, Tokyo, 108-0075, Japan Medtronic (Shanghai) Management Co., Ltd. Floor 6-17, Building B, The New Bund World Trade Center Phase I , No. 5, Lane 255, Dong Yu Road, Pudong, Shanghai 200126, China Medtronic (Taiwan) Ltd. 2F, No.2, Sec.1, Dunhua S. Rd. Songshan Dist. Taipei City 105, Taiwan (R.O.C.) Medtronic Korea Co. Ltd 17F, Glass Tower, #534 Teneran-ro, Gangnam-gu Seoul, 06181, Korea

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Sponsor Contact Information

Medtronic Inc. and Medtronic Japan Co., Ltd. are sponsoring the Mid-Q Response 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 the centers as needed.

Table 1 Study sponsor contact information

Study contacts	
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Study monitors and contacts	
Monitoring leader Alexander Zielinski, Clinical Research Monitor Phone: [redacted] alexander.zielinski@medtronic.com	

Names, titles, addresses and contact numbers of the investigators responsible for conducting the study:

A complete list of participating investigators and institutions will be distributed under separate cover upon request.

CROs and Core Laboratories

Table 2 CRO and Core Laboratory information

Contact Information	Duties performed
ECG Core Laboratory Centre d'Investigation Clinique – Innovations Technologiques Cardiology Department, Level 0, Pontchaillou Hospital 2, Rue H. Le Guilloux 35033 Rennes Cedex 09 France	• Review of baseline ECGs, determining LBBB presence, measuring P-R interval.

Steering Committee

A Steering Committee (SC) Roster and Charter will be available under separate cover.

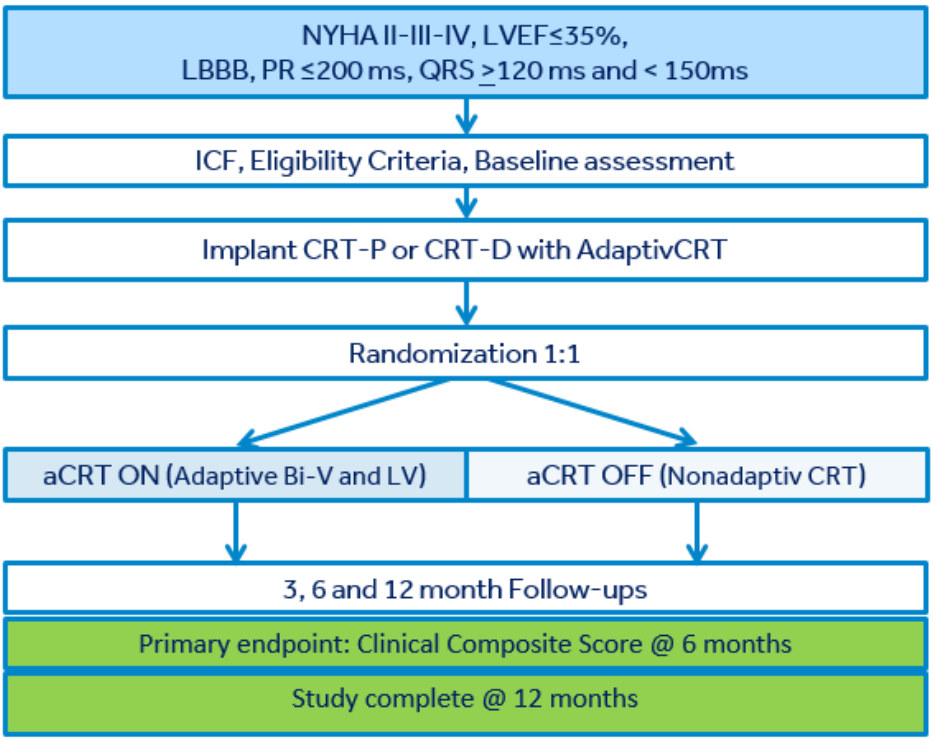
1. Glossary

Term	Definition
ACE-I	Angiotensin Converting Enzyme Inhibitor
aCRT	AdaptivCRT®
AE	Adverse Event
AF	Atrial Fibrillation
ARB	Angiotensin II Receptor Blocker
ARNi	Angiotensin-Receptor/ Neprilysin inhibitor
AV	Atrioventricular
Bi-V, BiV	Biventricular
CABG	Coronary Artery Bypass Graft
CCS	Clinical Composite Score
CIP	Clinical Investigation Plan
CRT	Cardiac Resynchronization Therapy
CRT-D	Cardiac Resynchronization Therapy Defibrillator
CRT-P	Cardiac Resynchronization Therapy Pacemaker
CTA	Clinical Trial Agreement
CV	Cardiovascular
DD	Device Deficiency
DMC	Data Monitoring Committee
EC/MEC/IRB/HREC	Ethics Committee
ECG	Electrocardiogram
FU	Follow-Up
GCP	Good Clinical Practice
HF	Heart Failure
ICF	Informed Consent Form
KCCQ	Kansas City Cardiomyopathy Questionnaire
LBBB	Left Bundle Branch Block
LV	Left Ventricular

Term	Definition
LVEF	Left Ventricular Ejection Fraction
LVESV	Left Ventricular End-Systolic Volume
MI	Myocardial Infarction
MRA	Mineralocorticoid Receptor Antagonist
MSM	Medtronic Secure Messaging
NYHA	New York Heart Association
PGA	Patient Global Assessment
PTCA	Percutaneous Transluminal Coronary Angioplasty
QoL	Quality of Life
RA	Right Atrial
RV	Right Ventricular
S2D	Save-to-Disk (device interrogation, .pdd/.pkg file)
SADE	Serious Adverse Device Effect
SAE	Serious Adverse Event
USADE	Unanticipated Serious Adverse Device Effect

2. Synopsis

Title	Mid-Q Response Study
Clinical Study Type	Post-Market Clinical Study
Product Name	Market released CRT-P and CRT-D devices containing the AdaptivCRT (aCRT) algorithm, Medtronic market released LV leads, and any market released RA and RV leads
Sponsor	Medtronic Inc., Medtronic, Bakken Research Center B.V., and Medtronic Japan Co., Ltd.
Local Sponsor	Medtronic (Shanghai) Management Co., Ltd. Medtronic (Taiwan) Ltd. Medtronic Korea Co. Ltd Medtronic Hong Kong Medical Ltd. Medtronic Malaysia Sdn Bhd Medtronic International Ltd (Singapore Branch) PT Medtronic Indonesia Medtronic Philippines Inc.
Investigation Purpose	The purpose of the Mid-Q Response study is to test the hypothesis that the AdaptivCRT algorithm is superior to standard CRT therapy regarding patient outcomes in CRT indicated patients with moderate QRS duration, preserved atrioventricular (AV) conduction and left bundle branch block (LBBB).
Primary Objective	To test the hypothesis that aCRT ON ("Adaptive Bi-V and LV") increases the proportion of patients that improve on the Clinical Composite Score (CCS) compared to aCRT OFF ("Nonadaptive CRT") at 6 months of follow-up.
Secondary Objectives	• To evaluate the change in NYHA class at 6 and 12 months between the aCRT ON group and the aCRT OFF group. • To characterize the occurrence of hospitalizations for worsening heart failure in the aCRT ON group and the aCRT OFF group at 12 months. • To characterize all-cause and cardiovascular related mortality in the aCRT ON group and the aCRT OFF group at 12 months.

Ancillary Objectives	• To evaluate the change in quality of life at 6 and 12 months, measured by the KCCQ, between the aCRT ON group and the aCRT OFF group. • To assess the combined effects of height, QRS duration, and aCRT on clinical outcomes, as measured by the Clinical Composite Score. • To characterize the incidence of AF in the aCRT ON group and the aCRT OFF group. • To characterize cardiovascular adverse events that occur in the aCRT ON and aCRT OFF groups. • To characterize reverse remodeling as measured via echocardiography, between the aCRT ON group and the aCRT OFF group.
Study Design and Scope	The Mid-Q Response study is a prospective, multi-center, randomized controlled, interventional, single-blinded, post-market study. The study will be executed at approximately 60 centers in Asia including but not limited to centers in Japan, South Korea, Taiwan, Hong Kong, Indonesia, Malaysia, Singapore, Brunei, the Philippines, and China. *Study flow:* 
Randomization	The subjects will be randomly assigned in a 1:1 ratio to the aCRT ON (Adaptiv Bi-V and LV) group or the aCRT OFF (Nonadaptiv CRT) group.

Sample Size	A total of 220 randomized patients followed through 6 months are needed for the study primary analysis. To achieve this, we expect to need 232 enrolled patients. A maximum of 50 randomized patients is allowed at each site.
Inclusion/Exclusion Criteria	Inclusion Criteria: • Subject is willing to sign and date the study Informed Consent Form (ICF). • Subject is indicated for a CRT device according to local guidelines. • Subject has minimally: • Sinus rhythm at time of enrollment. • LBBB as documented on an ECG (preferably within 30 days prior to enrollment but up to 50 days is accepted) with moderately wide QRS: • Intrinsic QRS duration ≥120 ms and <150 ms • QS or rS in leads V1 and V2, and • Mid-QRS notching or slurring in ≥2 of leads V1, V2, V5, V6, I, and aVL. • Intrinsic, normal AV conduction as documented on a recent ECG by a PR interval ≤200 ms (within 30 days prior to enrollment). • Left ventricular ejection fraction ≤35% (documented within 180 days prior to enrollment). • NYHA class II, III or IV (documented within 30 days prior to enrollment) despite optimal medical therapy. Optimal medical therapy is defined as maximal tolerated dose of Beta-blockers and a therapeutic dose of ACE-I, ARB or MRA. Exclusion criteria: • Subject is less than 18 years of age (or has not reached minimum age per local law if that is higher). • Subject is not expected to remain available for at least 1 year of follow-up visits. • Subject has permanent atrial arrhythmias for which pharmacological therapy and/or cardioversion have been unsuccessful or have not been attempted. • Subject is, or previously has been, receiving cardiac resynchronization therapy. • Subject is currently enrolled or planning to participate in a potentially confounding drug or device trial during the course of this study. Co-enrollment in concurrent trials is only allowed when documented pre-approval is obtained from the Medtronic study manager. • Subject has unstable angina, or experienced an acute myocardial infarction (MI) or received coronary artery revascularization (CABG) or coronary angioplasty (PTCA) within 30 days prior to enrollment.

	• Subject has a mechanical tricuspid heart valve or is scheduled to undergo valve repair or valve replacement during the course of the study. • Subject is post heart transplant (subjects on the heart transplant list for the first time are not excluded). • Subject has a limited life expectancy due to non-cardiac causes that would not allow completion of the study. • Subject is pregnant (if required by local law, women of child-bearing potential must undergo a pregnancy test within seven days prior to device implant). • Subject meets any exclusion criteria required by local law.

3. Introduction

3.1. Background

Cardiac Resynchronization Therapy (CRT) is an established therapy for patients with HF symptoms, left ventricular systolic dysfunction, and a wide QRS. [1] [2] However, the magnitude of clinical and hemodynamic benefit of CRT varies significantly among its recipients with no clinical improvement in approximately one third. [1] Patient-specific characteristics, such as severity and type of electrical conduction abnormalities, dyssynchrony and scar burden, have been associated with the degree of CRT benefit. [3] [4]

While CRT is most commonly achieved by using biventricular (BiV) pacing, multiple acute [5] and randomized chronic [6] studies have demonstrated that left-ventricular (LV) pacing can be at least as efficacious as BiV pacing. In patients with sinus rhythm and normal AV conduction, pacing only the LV with appropriate AV delays can result in even superior LV [5] [7] and right-ventricular (RV) [8] [9] function compared to standard BiV pacing.

Optimization of the AV and inter-ventricular (VV) intervals during BiV pacing is another option to maximize the positive effects of CRT. [10] [11] Optimization is usually accomplished by using echocardiography or other modalities. However, these methods can be resource-intensive and only a minority of clinicians routinely optimizes AV and VV delays.

The AdaptivCRT (aCRT) algorithm has been developed to provide RV-synchronized LV pacing when intrinsic AV conduction is normal or BiV pacing otherwise. The algorithm also adjusts AV and VV delays based on periodic automatic evaluation of intrinsic conduction intervals. The algorithm is intended to provide ambulatory CRT optimization and allows more physiologic ventricular activation and greater device longevity in patients with normal AV conduction by reducing unnecessary RV pacing.

The Medtronic Adaptive CRT pre-market approval study has demonstrated that aCRT-optimized CRT is at least as effective as echo-optimized BiV pacing in terms of CCS (73.6% improved in aCRT arm vs. 72.5% in echo optimized arm, with a non-inferiority margin of 12%, p=0.0007) [12].

Additionally, a comparison with a historical echocardiographic AV-optimized CRT cohort indicated that the aCRT algorithm increased the proportion of patients with an improved CCS by 11.9% (95% CI: 2.7% to 19.2%). [13]

A post-hoc sub-analysis of the Adaptive CRT study showed that in patients with sinus rhythm, normal AV conduction and LBBB, more aCRT patients improved in their CCS compared with the echo arm (80.7% vs. 68.4%, p=0.04). In this subgroup the aCRT patients received LV-only pacing 64.0% ± 32.8% of the time. [12] An additional post-hoc analysis of the Adaptive CRT study focused on the patients with moderately wide QRS of 120–150 ms, which comprised 40% of the patients. In

this subgroup, the proportion of patients that had an improved CCS was greater in the aCRT arm than in the echo arm (79% vs. 50%) [14].

Additionally, in an unpublished analysis on extended follow-up duration in patients with normal AV conduction, there was a lower risk of death or HF hospitalization (HR=0.71, 95% CI: 0.40-1.27, p=0.25) with aCRT. Also, a greater proportion of aCRT patients improved in CCS at 6 months (81% vs.69%, p=0.041) and 12 months (77% vs. 66%, p=0.076) than echocardiography-optimized control patients. [15]

Use of the aCRT algorithm is associated with a significant reduction in the probability of a 30-day readmission after both HF and all-cause hospitalizations as demonstrated in another analysis of the Adaptive CRT study. For HF hospitalizations, the 30-day readmission rate was 19.1% (17 of 89) in the aCRT group and 35.7% (15 of 42) in the Echo group (odds ratio: 0.41; 95% confidence interval: 0.19 to 0.86; p = 0.02). For all-cause hospitalization, the 30-day readmission rate was 14.8% (35 of 237) in the aCRT group compared with 24.8% (39 of 157) in the Echo group (odds ratio: 0.54; 95% CI: 0.31 to 0.94; p = 0.03). The risk of readmission after HF or all-cause index hospitalization with aCRT was also significantly reduced beyond 30 days. [16]

Table 3 Adaptive CRT study post-hoc sub-analysis results

CRT Response [12] **Improvement in Packer Clinical Composite Score**	**12% higher response***
HF Hospitalizations or Death [15]	**Reduced risk***
30-day Readmissions [16]	**59% reduction in odds**
Atrial Fibrillation [17] [18] **Time to first 48 consecutive hours or more**	**46% reduced risk of AF**

* in subgroups with prolonged AV conduction at baseline

Furthermore, over the longer-term follow-up (20.2 ± 5.9 months) the aCRT algorithm has been shown to reduce the risk of the incidence of 48 consecutive hours in Atrial Fibrillation (AF) and aCRT patients without history of AF were less likely to develop persistent AF. In a sub-analysis of the Adaptive CRT study, Birnie D. et al compared the long-term effects of aCRT versus conventional CRT pacing on the incidence of AF. During the follow-up period, 8.7% of patients with aCRT and 16.2% of patients with conventional CRT experienced the primary outcome of an AF event of >48

hours, which was a 46% reduced risk with aCRT (hazard ratio 0.54; 95% confidence interval 0.31–0.93; P = 0.03) compared with conventional CRT patients. [17] [18]

Further investigation of clinical outcomes over longer follow-up is needed to support the benefit of aCRT. Therefore, the AdaptResponse study was designed to test the hypothesis that the aCRT algorithm reduces the incidence of total mortality and heart failure decompensation events, increases the proportion of patients with an improved CCS and reduces the incidence of AF in CRT patients with normal AV conduction and LBBB. [19]

The inclusion criteria of AdaptResponse are similar to the Mid-Q Response study except for the QRS duration, which in AdaptResponse is ≥ 130ms for women and ≥ 140ms for men. In the past, a wide QRS was typically defined as a QRS duration ≥120 ms. In recent years new clinical evidence raised doubts about benefit of CRT in women with a QRS duration <130 ms and men with a QRS duration <140 ms. This has led to implementation of stricter QRS criteria in ACCF/AHA/HRS guidelines and ESC guidelines for CRT implantation [20] [21].

The guidelines do not consider any ethnic differences. Ethnic differences have been observed in QRS duration. In the general population, Asian adults were found to have narrower QRS complexes compared to white adults, possibly related to smaller heart sizes in Asians [22]. In addition, association between LVEF and QRS duration have been observed between white and Asian patients with HF [23]. Asian heart failure patients had shorter QRS duration, had smaller body size and had more severely impaired LVEF.

In the Japanese CRT guidelines, the QRS duration for CRT indication for patients with drug resistant heart failure, LBBB, sinus rhythm, EF ≤35% and NYHA III or IV is set to ≥ 120ms [24]. In some other Asian countries, it is also permissible to implant a CRT device in HF patients from a QRS duration of 120 ms.

A recent individual-patient data meta-analysis by Linde et al. of five randomized controlled trials looked at the associations of sex, QRS duration and patient height with benefit of CRT [25]. For all-cause mortality, QRS duration was the only independent predictor of CRT benefit. For the composite of all-cause mortality or first hospitalization for HF, height and QRS duration, but not sex, were independent predictors of CRT benefit. Further analysis suggested increasing benefit with increasing QRS duration amongst shorter patients. Also, this analysis suggests that smaller men might still benefit from CRT even with QRS duration below 140 ms.

In a retrospective analysis, 510 patients from the Japanese multicenter CRT database were divided in five subgroups: LBBB and QRS ≥150 ms (n=200, 39%); LBBB and QRS 120-149 ms (n=60, 16%); non-LBBB with QRS ≥150 ms (n=61, 12%); Non-LBBB with QRS 120-149 ms (n=54, 11%) and narrow QRS complex with QRS <120 ms (n=115, 23%). Echocardiographic response, defined as a relative reduction of left ventricular end-systolic volume (LVESV) ≥15% at 6-12 months after CRT implantation, in the subgroups was 74%, 51%, 38%, 52%, and 50% respectively, with P<0.001. The

incidence of the primary endpoint (composite of all-cause death or hospitalization because of HF) was significantly different between the groups as well, also after adjusting for other baseline characteristics (28.6%, 42.3%, 45.9%, 55.6%, and 55.3% respectively, P<0.001) [26].

From the above studies it was hypothesized that patients in Asia can benefit from CRT in general and from aCRT in particular, even at the lower end of the QRS duration spectrum, because the population is smaller in height compared to the average patient population in the landmark CRT studies, and because aCRT is more effective than standard BiV pacing in the subgroup of patients with a mid-range QRS of 120-150 ms.

Showing the benefit of aCRT therapy in the moderately wide QRS cohort through this study may help to give all heart failure patients who would benefit from CRT access to this therapy. In relation to this, it may provide additional insights for CRT guidelines in Asian countries.

3.2. Purpose

Medtronic Inc. and Medtronic Japan Co., Ltd. are sponsoring the Mid-Q Response study; a prospective, randomized, controlled, interventional, single-blinded, multi-center, post-market Cardiac Resynchronization Therapy in heart failure clinical study.

The purpose of this study is to assess if CRT indicated patients with normal AV conduction, LBBB, and QRS ≥120 and <150 ms treated with aCRT (aCRT ON: Adaptive Bi-V and LV), have a better Clinical Composite Score at 6 months than patients treated with standard BiV pacing (aCRT OFF: Nonadaptive CRT).

To assess the superiority of CRT devices containing the aCRT algorithm, the primary objective of the Mid-Q Response study is to test the hypothesis that aCRT ON increases the proportion of patients that improve on the Clinical Composite Score (CCS) compared to aCRT OFF at 6 months of follow-up.

Eligible subjects will be randomized after baseline assessment and implant of a CRT system containing the aCRT algorithm. Randomization will be done in a 1:1 ratio to either treatment (aCRT ON, Adaptive Bi-V and LV) or control (aCRT OFF, Nonadaptive CRT) groups. All subjects, independent of randomization assignment, will have a CRT system. Study subjects will be followed for 12 months.

3.3. Study scope

The study is expected to be conducted at approximately 60 centers in Asia, including Japan, China, Taiwan, South Korea, Hong Kong, Malaysia, Singapore, Indonesia, Brunei, and the Philippines. Proposed study start is mid-2019.

A total of 220 randomized patients followed through 6 months are needed for the study primary analysis. To achieve this, we expect to need 232 enrolled patients.

To ensure a widespread distribution of data to minimize bias in the study results, the maximum number of patients at a single center is 50 subjects. There is no specific minimum number of randomized subjects required, except where stated in the clinical trial agreement between the sponsor and the individual center.

3.4. Study oversight

The **Steering Committee (SC)** is involved in the scientific content and providing input for the execution of the study. The SC will also approve requests for crossovers and will review accuracy rates of LBBB (as determined by the ECG Core Laboratory).

The **ECG Core Laboratory** will review all baseline ECGs for presence of LBBB with QRS duration ≥120 ms and <150 ms and normal AV conduction. Feedback on accuracy rates will be presented to the Steering Committee and to the sites.

4. Objectives

The listed objectives will test the hypothesis that the aCRT algorithm is superior to standard CRT therapy in regard to patient outcomes.

4.1. Primary Objective(s)

The primary objective of the Mid-Q Response study is to test the hypothesis that aCRT ON increases the proportion of patients that improve on the Clinical Composite Score (CCS) compared to aCRT OFF at 6 months of follow-up.

The analysis will include all randomized patients and will follow the intent-to-treat principle. A secondary analysis will be done including only the patients for whom the ECG Core Laboratory confirmed the presence of LBBB.

4.2. Secondary Objectives

- To evaluate the change in NYHA class at 6 and 12 months between the aCRT ON group and the aCRT OFF group.
- To characterize occurrence of hospitalizations for worsening heart failure in the aCRT ON group and the aCRT OFF group at 12 months.

- To characterize all-cause and cardiovascular related mortality in the aCRT ON group and the aCRT OFF group at 12 months.

4.3. Ancillary objectives:

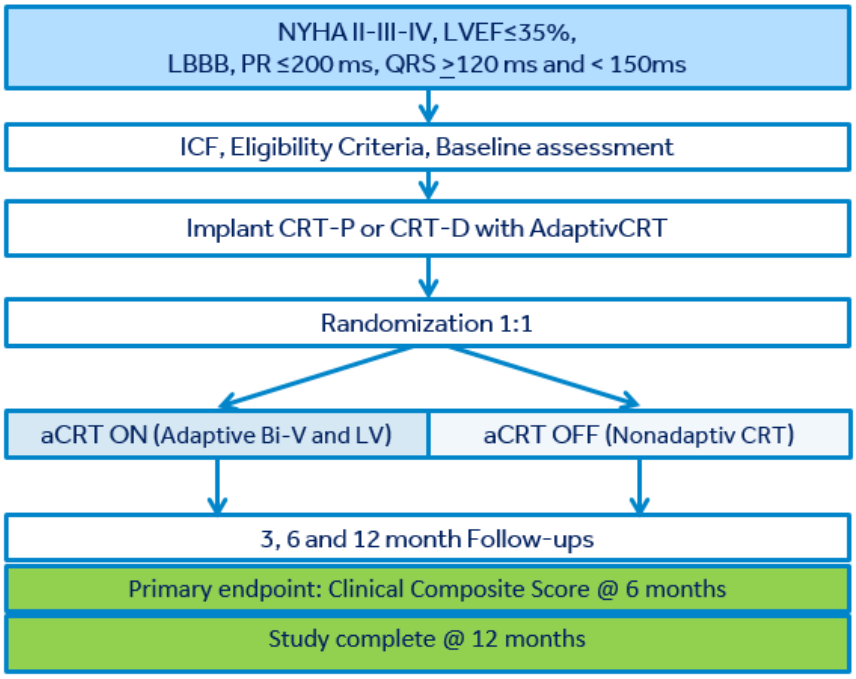
- To evaluate the change in the quality of life, measured by the KCCQ, at 6 and 12 months between the aCRT ON group and the aCRT OFF group.
- To assess the combined effects of height, QRS duration, and aCRT on clinical outcomes, as measured by the Clinical Composite Score.
- To characterize the incidence of AF in the aCRT ON group and the aCRT OFF group.
- To characterize cardiovascular adverse events that occur in the aCRT ON and aCRT OFF groups
- To characterize reverse remodeling as measured via echocardiography, between the aCRT ON group and the aCRT OFF group.

5. Study Design

The Mid-Q Response study is a prospective, randomized controlled, interventional, single-blinded, multi-center, clinical study, performed in Asian countries as described in section 3.3.

CRT indicated patients with moderately wide QRS (≥120 and <150 ms), preserved AV conduction (PR interval ≤200ms) and LBBB will be randomized in a 1:1 ratio to either treatment (aCRT ON: Adaptive Bi-V and LV) or control (aCRT OFF: Nonadaptive CRT) groups. The flow chart for this clinical study is shown in Figure 1.

Figure 1 Study Flow Chart



5.1. Duration

Enrollment is expected to start early 2020 and enrollment completion is estimated to occur 2 to 3 years later. Due to the unknown duration and impact of the COVID-19 pandemic on CRT implants in the participating countries, the enrollment period may be longer than 3 years. Follow up completion (estimated to take place in early 2024) will take place 12 months after enrollment completion.

Details on study duration per the definition of Clinical Trial Act in Japan will be provided under separate cover.

5.2. Rationale

As explained in section 3.1, results from retrospective analyses of the Adaptive CRT study [23] [24] [12] and a meta-analysis by Linde [25] led to the hypothesis that Asian CRT-indicated patients with LBBB and normal AV conduction can benefit from CRT even at the lower end of the QRS duration spectrum because the population is smaller in height and because aCRT is more effective than standard Bi-V pacing in this subgroup.

The Mid-Q Response study is therefore designed as a prospective randomized study in Asian countries, including patients with a moderately wide QRS with LBBB and normal AV conduction. The primary endpoint is the Clinical Composite Score at 6 months post implant.

5.3. Randomization

Subjects will be randomized in a 1:1 ratio to treatment (aCRT ON, with AdaptivCRT programmed to "Adaptive Bi-V and LV") or control (aCRT OFF, with AdaptivCRT programmed to "Nonadaptive CRT") group.

Refer to section 8.8 for further details on randomization and programming requirements and recommendations.

5.4. Crossover

Crossovers significantly increase the sample size needed for the study. Every reasonable effort must be made to keep subjects in their blinded randomization assignment for the duration of the study. Unless required by clinical or technical urgency, the reprogramming of aCRT therapy in any subject must be approved by a member of the study's Steering Committee. The study center must make reasonable effort to contact the study sponsor prior to reprogramming. Failure to gain prior approval for reprogramming of aCRT therapy (even if required urgently) constitutes a deviation and should be reported as such. Every reasonable effort should be made to prevent unblinding of the patient prior to and after reprogramming, unless clinically necessary. In the case of a permanent crossover (i.e. the programming will not be corrected to the original randomization assignment) to the other study arm, a Crossover CRF and Study Deviation CRF must be completed. Full device interrogation data will be collected reflecting the final programming, and a copy of the interrogation files must be sent to Medtronic with a copy being maintained at the center in the subject's file. Subjects will be analyzed per their randomly assigned treatment in accordance with the intention-to-treat principle.

5.5. Blinding

The study will be single-blinded (i.e. subjects are blinded to randomization assignment) to reduce the effect of bias. Every effort must be made to ensure the randomization assignment is not revealed to the subject.

After all study tests and procedures have been completed just prior to subject exit from the study, the subject may be informed (verbally or in written form) of their randomization assignment.

5.6. 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):

- Patients will be evaluated to confirm eligibility for enrollment with defined inclusion/exclusion criteria prior to randomization.

- An ECG Core Laboratory will be used to confirm presence of LBBB and normal AV conduction.
- Subjects will be randomized to ensure comparable treatment groups.
- Subjects will be blinded to their treatment group.
- To ensure a widespread distribution of data between centers, the maximum number of randomized subjects allowed per center is no more than 50.
- Data collection requirements and study procedures will be standardized across all centers and geographies.
- All study center personnel and Medtronic personnel will be trained on their respective aspects of the study using standardized training materials. All study clinicians will be trained on and required to follow the CIP.
- Monitoring visits will be conducted for adherence to the CIP and to verify the CRF data against the source data.
- The Steering Committee members will not have influence on the HF treatment decisions by center investigators during the trial, except for approval for crossover, as described in Section 5.4.The analysis will be intent-to-treat, following pre-defined statistical methods specified in this Clinical Investigation Plan and the Statistical Analysis Plan.
- Registration of the trial on clinicaltrials.gov (and other local required registry databases e.g. Japan Registry of Clinical Trials) and the publication plan will ensure that study results will be reported.

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

6. Product Description

6.1. General

The study will be using market released CRT-P and CRT-D devices containing the aCRT algorithm, Medtronic market released LV leads, and any market released RA and RV leads. All system components will be implanted per intended use as specified in the respective manuals. Medtronic may incorporate additional Medtronic CRT-P and/or CRT-D devices containing the aCRT algorithm, or devices containing an update of the aCRT algorithm, LV leads, programmers and software into this clinical study as they become commercially available, provided the scientific soundness is not adversely affected as assessed by the Steering Committee. Additional commercially available devices should not be used until notification from Medtronic is received. Instructions for use of the devices used in this study are provided in their respective manuals. The device accountability for this study purpose is not required.

6.2. Medtronic CRT-D and CRT-P devices

Medtronic commercially available CRT-D and CRT-P devices containing the aCRT algorithm are required.

6.3. Medtronic left ventricular leads

Medtronic commercially available LV transvenous pacing leads that are compatible with the CRT devices containing the aCRT algorithm are required. Epicardial leads can only be used if a transvenous lead cannot be placed. If investigators wish to use a non-Medtronic epicardial lead, it is recommended that they confirm device compatibility with a Medtronic representative.

6.4. Market released right ventricular (defibrillation) lead

Commercially available RV (defibrillation) leads that are compatible with the CRT devices containing the aCRT algorithm are required. Medtronic commercially available RV (defibrillation) leads are recommended.

6.5. Market released right atrial lead

Commercially available RA lead models that are compatible with the CRT devices containing the aCRT algorithm are required. Medtronic commercially available RA leads are recommended.

6.6. Medtronic CareLink programmer

The Medtronic CareLink Model 2090 Programmer (with associated software) and/or CareLink SmartSync™ Device Manager are used to program the CRT device. Programmers from other manufacturers are not compatible with Medtronic devices.

6.7. Medtronic CareLink home monitors and Network

The transfer of patient and device data from implanted Medtronic devices can be executed by using any of the compatible Medtronic CareLink home monitors: CareLink Monitor Model 2490C, MyCareLink Relay™ Home Communicator, and MyCareLink Heart™ mobile app (used with smartphones). The CareLink home monitor interrogates implanted devices and temporarily stores these data. It collaborates with the appropriate Medtronic server to confirm the establishment of an Internet connection with server and performs any required file translation functions necessary for data transfer. It executes data file transfer and collaborates with the appropriate Medtronic server to confirm data file transfer through the Internet connection with the server. The CareLink home monitors are not programmers and cannot be used to program implanted device parameters. CareLink home monitors are not a substitute for appropriate medical attention in the event of an emergency and should only be used as directed by medical staff.

Medtronic CRT devices used in this study qualify for use with the Medtronic CareLink home monitors and Medtronic CareLink Network; however, the use of CareLink in this clinical study is optional and does not replace the need for in-person follow-up visits.

Medtronic may incorporate additional home monitors as they receive regulatory approval.

6.8. Market-released Pacing System Analyzer

The system supports the use of the Medtronic CareLink Model 2290 Analyzer, an accessory of the Medtronic CareLink programmer. The system allows having a device session and an analyzer session running at the same time, to quickly switch from one to the other without having to end or restart sessions, and to send data from the analyzer to the programmer.

7. Selection of Subjects

7.1. Study Population

The Mid-Q Response study will include heart failure patients in Asian countries indicated for CRT per local guidelines with moderately wide QRS (duration ≥120ms and <150ms), preserved AV conduction (PR interval ≤ 200 ms) and LBBB.

7.2. Subject Enrollment

Patients will be screened to ensure they meet all the Mid-Q Response inclusion- and none of the exclusion criteria prior to study enrollment.

No study-specific procedures may be performed prior to obtaining the signed patient Informed Consent Form (ICF). Refer to section 8.5 for details on enrollment.

7.3. Inclusion Criteria

Patients must meet the following inclusion criteria to be eligible to participate in the study:

- Subject is willing to sign and date the study Informed Consent Form (ICF).
- Subject is indicated for a CRT device according to local guidelines.
- Subject has minimally:
  - Sinus rhythm at time of enrollment.
  - Left Bundle Branch Block (LBBB) as documented on an ECG (preferably within 30 days prior to enrollment but up to 50 days is accepted) with moderately wide QRS:
    - Intrinsic QRS duration ≥120 ms and <150 ms

- QS or rS in leads V1 and V2, and
- Mid-QRS notching or slurring in ≥2 of leads V1, V2, V5, V6, I, and aVL.

- Intrinsic, normal AV conduction as documented on an ECG by a PR interval ≤200ms (preferably within 30 days prior to enrollment but up to 50 days is accepted).
- Left ventricular ejection fraction ≤35% (documented within 180 days prior to enrollment).
- NYHA class II, III or IV (documented within 30 days prior to enrollment) despite optimal medical therapy. Optimal medical therapy is defined as maximal tolerated dose of Beta-blockers and a therapeutic dose of ACE-I, ARB or MRA.

7.4. Exclusion Criteria

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

- Subject is less than 18 years of age (or has not reached minimum age per local law if that is higher).
- Subject is not expected to remain available for at least 1 year of follow-up visits.
- Subject has permanent atrial arrhythmias for which pharmacological therapy and/or cardioversion have been unsuccessful or have not been attempted.
- Subject is, or previously has been, receiving cardiac resynchronization therapy.
- Subject is currently enrolled or planning to participate in a potentially confounding drug or device trial during the course of this study. Co-enrollment in concurrent trials is only allowed when documented pre-approval is obtained from the Medtronic study manager.
- Subject has unstable angina, or experienced an acute myocardial infarction (MI) or received coronary artery revascularization (CABG) or coronary angioplasty (PTCA) within 30 days prior to enrollment.
- Subject has a mechanical tricuspid heart valve or is scheduled to undergo valve repair or valve replacement during the course of the study.
- Subject is post heart transplant (subjects on the heart transplant list for the first time are not excluded).
- Subject has a limited life expectancy due to non-cardiac causes that would not allow completion of the study.
- Subject is pregnant (if required by local law, women of child-bearing potential must undergo a pregnancy test within seven days prior to device implant).
- Subject meets any exclusion criteria required by local law.

8. Study Procedures

All clinical investigators managing the subject's heart failure must be qualified practitioners and experienced in the diagnosis and treatment of subjects with heart failure. All implanting physicians must be experienced and/or trained in the handling of CRT devices. Center personnel training and delegation will be completed prior to participation in this clinical study.

Medtronic personnel or their representatives may perform the following activities at the study sites during the study, under supervision of site personnel:

- Technical support at all visits (e.g. programming of the CRT device according to study requirements, performing device interrogations)
- Monitoring activities

8.1. Site activation

During the activation process (prior to enrollment of subjects in the study), Medtronic will provide clinical study materials (e.g. Investigator Site File, database access codes etc.) and train site personnel on the CIP, relevant standards and regulations, informed consent process and on data collection and reporting tools. If new members join the study center team, they will receive training on the applicable clinical study requirements relevant to their role before contributing to the clinical study.

A CTA shall be entered into effect by Medtronic, the participating investigation site and/or the principal clinical investigator at each investigation site as per the 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 investigator indicates approval of the CIP and subsequent amendments.

Prior to performing study related activities, all centers must have Ethics Committee approval, as applicable for that geography.

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

- Ethics Committee approval (and voting list, as required by local law) of the current version of the CIP and ICF
- Regulatory authority approval or notification (as required per local law)
- Signed/dated CTA on file with sponsor

- Current, signed and dated Curriculum Vitae (CV) of investigators and other key members of investigation site team CV (as required by local law)
- Documentation of delegated tasks
- Signed/dated documentation of training of required study personnel

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

In addition, all participating site staff must be trained on the current version of the CIP pertinent to their role in the study and must be delegated by the principal investigator to perform study related activities, which must be documented on the Delegated Task List. Site personnel performing only standard of care procedures and no study related activities throughout the study (including but not limited to CRT implant, physical exam, device interrogations) do not need to be trained on the CIP.

8.2. Equipment requirements

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

- Computer with high speed internet access using Microsoft Internet Explorer (version 11 or higher), Google Chrome, and/or Safari for data entry
- Market-released Medtronic programmer (Model 2090 or future equivalent)
- 12-lead ECG equipment

The maintenance and calibration of the programmers used for this study will be assessed outside of this clinical study. Centers are responsible for maintaining and calibrating non-programmer equipment used in the course of this study in accordance with established center practice. Clinical Monitors will not monitor maintenance or calibration schedules.

8.3. Schedule of Events

Subjects enrolled in the Mid-Q Response study will be followed through 12 months. A high-level overview of events is provided in Table 4.

Table 4 Data collection and study procedure requirements at subject visits

Study Procedure	Enrollment#	Baseline	Implant#	Randomization	3, 6 and 12 Months Visit	Study Exit*****
Subject Informed Consent	X					
Inclusion/exclusion	X	X				
12- lead Electrocardiogram (ECG)*		X				
Left Ventricular Ejection Fraction (LVEF) measurement**	X					
Demographics		X				
Physical examination		X			X	
Blood***		X			X	
Echocardiographic data***		X From within 6 months prior to enrollment			X	
Cardiovascular (CV) medications****		X				X
Medical history		X				
Current heart failure symptoms status		X			X	X
Final implanted system configuration and LV lead placement			X			
Device interrogation (and CareLink data if available)			X	X	X	X
Device programming per randomization assignment				X		
Device optimization*** (Control Group only)				As it occurs		
Quality of life and Health Outcome measures (KCCQ)		X			X	

Study Procedure	Enrollment#	Baseline	Implant#	Randomization	3, 6 and 12 Months Visit		Study Exit*****
NYHA assessment		X*			X		
Patient global assessment					X		
Vital status							X
Crossover				As it occurs			
System modifications			As they occur				
Adverse events (AEs)	As they occur						
Study Deviations	As they occur						
Death******	As it occurs						

* Unless done within 30 days prior to enrollment

** Unless done within 180 days prior to enrollment

*** Data only collected if procedure is standard of care and if allowed per local regulations. In China, this data will not be collected.

****Including daily dose at baseline and study exit of guideline recommended medication, including but not limited to the following medications: diuretics, ß-blockers, ACE inhibitors, ARBs, MRAs, ARNi, I_f-channel blockers, cardiac glycosides. See also section 8.6.

***** Study Exit: To be completed at/after 12 months visit is completed. A separate exit CRF is required, a separate exit visit is not needed.

****** Death: In case of death complete only a Death CRF and corresponding AE CRF, no Exit CRF should be completed.

Enrollment and Implant: although it is strongly recommended to perform the implant after enrollment, it is allowed to enroll subjects within 3 days after implant as implant is not a study related procedure. Please make sure all study related procedures are done after enrollment, and the baseline KCCQ is performed within 5 days after implant.

8.4. Subject Consent

Patient informed consent is defined as a legally effective, documented confirmation of a subject's (or their legally authorized representative or guardian, per local requirements) 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 a signed Informed Consent Form and an Authorization to Use and Disclose Personal Health Information /Research Authorization/ other privacy language ("Data Protection Authorization") ,as required by local law, that has been approved by the applicable Ethics Committee and signed and personally dated by the subject (or their legally authorized representative or guardian, per local requirements) and by the person who conducted the informed consent discussion, as applicable to local requirements. A subject may only consent after information has been given to the subject on all aspects of the clinical investigation that are relevant to the subject's decision to participate. Informed consent may be given by the legally authorized representative in accordance with local law.

Prior to enrolling subjects, each applicable Ethics Committee will be required to approve the Informed Consent Form and Data Protection Authorization where applicable, as required by law. The document(s) must be controlled (i.e. versioned and dated) to ensure it is clear which version(s) were approved by the Ethics Committee. Any adaptation of the sample ICF must be reviewed and approved by Medtronic and the Ethics Committee reviewing the application prior to enrolling subjects. Geography specific Informed Consent Form templates will be provided under separate cover.

Prior to initiation of any study-specific procedures, a signed ICF must be obtained from the subject (or their legally authorized representative or guardian, per local requirements) and by the person who conducted the informed consent discussion, as applicable to local requirements. Likewise, privacy or health information protection regulation may require subjects to sign additional forms to authorize centers to submit subject information to the study sponsor. The informed consent process must be conducted by the principal investigator or an authorized designee, and the ICF and Data Protection Authorization where applicable, as required by law must be given to the subject (or their legally authorized representative or guardian, per local requirements) in a language he/she is able to read and understand. The process of patient informed consent must be conducted without using coercion or undue improper influence on or inducement of the subject to participate by the investigator or other center personnel.

The process of obtaining patient informed consent shall:

- Ensure that the principal investigator or his/her authorized designee conducts the informed consent process
- Include all aspects of the clinical investigation that are relevant to the subject's decision to participate throughout the clinical investigation
- Avoid any coercion or undue improper influence on, or inducement of, the subject to participate
- Not waive or appear to waive subject's legal rights
- Use language that is non-technical and understandable to the subject
- Provide ample time for the subject to read and understand the ICF and to ask questions, receive answers and consider participation
- Include a personally dated signature of the subject (or legally authorized representative or guardian, per local requirements) acknowledging that their participation in the study is voluntary
- Include a personally dated signature by the principal investigator or authorized designee responsible for conducting the informed consent process
- Include any other locally required signatories, such as witnesses, as indicated by country specific legislations

- Provide the subject with a copy of the consent form and Data Protection Authorization where applicable, signed and dated if required by local law
- Ensure important new information is provided to new and existing subjects throughout the clinical investigation

If the ICF is obtained on the same day the subject begins participating in study-related procedures, it must be documented in the subject's case history that consent was obtained prior to participation in any study-related procedures. It is best practice for the informed consent process 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) patient informed consent will be allowed, provided detailed documentation of the process is recorded in the subject's case history and the witness signs and dates the ICF The ICF shall be obtained through a supervised oral process. An independent witness must be present throughout the process. The ICF and any other information must be read aloud and explained to the prospective subject (or his/her legally authorized representative, per local requirements). The witness signs and personally dates the ICF 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 ICF as well. The ICF 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 ICF must be filed in the hospital/clinical chart and/or with the subject's study documents.

The ICF (in Japan, the signature page only) and Data Protection Authorization where applicable, as required by law, must be available for monitoring and auditing. Any Medtronic Field personnel who support the implant must be able to review the subject's signed and dated ICF and verify its completeness prior to proceeding with the implant. In the event that Medtronic Field personnel identify patient informed consent as being incomplete, study procedures will not be allowed to occur until the consent of the subject can be adequately and appropriately obtained. In Japan, only the monitor assigned to this study may be able to review the signed informed consent prior to the implant procedure.

Any changes to a previously approved ICF throughout the course of the study must be approved by Medtronic and the Ethics Committee reviewing the application before being used to consent a prospective 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 Ethics Committee. 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.

8.5. Enrollment

A subject is considered enrolled in the Mid-Q Response when the Mid-Q Response consent process has been finalized. Enrollment can be a stand-alone visit or can occur on the same day as the baseline visit. If enrollment occurs on the same date as any study specific procedures, time of enrollment and study specific procedures should be clearly indicated in patient medical record.

Each study center must document participation of each enrolled subject in subject's source documentation and maintain a log of all subjects enrolled in the study, assigning an identification code linked to their names, alternative subject identification or contact information.

8.6. Baseline

The baseline visit must occur within 14 days after subject enrollment. Baseline testing will occur after the consent process has been finalized. The baseline visit can be a stand-alone visit or can be performed on the same day of, but prior to the implant procedure. When a subject is enrolled after implant, the baseline data should reflect the patient status pre-implant and the baseline visit must be completed within 5 days after implant.

The following data are required to be collected at the baseline visit:

- Subject demographics
- Verification of all inclusion and exclusion criteria
- Physical exam (including height, weight, heart rate and blood pressure)
- Medical history, including comorbidities and cardiovascular, arrhythmia, and surgical history
- Cardiovascular medications
- Current heart failure symptoms status
- NYHA HF assessment (unless documented within 30 days prior to enrollment)
- 12-lead ECG recording (unless documented within 30 days prior to enrollment)
- Quality of Life and Health outcome Measures
  - Kansas City Cardiomyopathy Questionnaire (KCCQ)
- Blood measurements (only collected when standard of care)
- Echocardiography data (only collected when standard of care and originating from up to 6 months prior to enrollment)
- Report AEs and Study Deviations (as they occur)

CV medications include ACE inhibitors, ARBs, MRAs, ARNi, antiarrhythmics, anti-coagulants and antiplatelets, antihypertensives, antilipidemics (incl. statins), ß-blockers, If-channel blockers, calcium channel blockers, diuretics, digitalis, inotropes, nitrates, digoxin, SGLT2 inhibitors and vasodilators.

For CV medications, daily dose is collected at baseline. Apart from CV medications, the use of insulin is collected. There are no medication restrictions in this study unless they are investigational and may confound the study results.

8.6.1. Baseline ECG

LBBB with moderate QRS duration has to be diagnosed (per investigator assessment) per the following criteria: QRS duration ≥120 ms and <150 ms, QS or rS in leads V1 and V2, and mid-QRS notching or slurring in ≥2 of leads V1, V2, V5, V6, I, and aVL. The Baseline ECG (12 lead ECG, original size, auto saved PDF format) must be sent to the ECG Core Laboratory for review of these criteria. Details on the review process will be provided under separate cover.

8.7. Implant

It is strongly recommended to perform the implant after enrollment, however, it is allowed to enroll subjects within 3 days after implant. All study related procedures should be done after enrollment.

When implant is performed after enrollment, implant must occur after the baseline visit and within 30 days after subject enrollment.

The implant will be performed according to the hospital's standard implant practice and is not considered a study related procedure. Implant guidelines can also be found in the device manuals. The following data are required to be collected at the implant visit:

- Final system configuration (CRT-P or CRT-D device and lead models, serial numbers and locations)
- LV lead placement optimization method
- Adverse Events, and Study Deviations (as they occur)
- Final device interrogation

At implant, it is recommended that the device is programmed to CRT OFF until the subject is randomized. Full device interrogation (Interrogate ALL) data collection following the implant procedure is required when the subject is enrolled pre-implant and recommended when the subject is enrolled post-implant. When collected, a copy of the interrogation files must be sent to Medtronic with a copy being maintained at the center in the subject's file.

Note: An unsuccessful implant [i] is not considered an adverse event. Events occurring during an unsuccessful implant (e.g. dissection, perforation) are adverse events and will be recorded and

[i] An implant procedure that results in one or more of the leads not placed, or where all leads are placed but not all are completely connected to the device, or where electrical measurements are unsatisfactory, and an invasive intervention is planned for mitigation.

classified. Subjects experiencing unsuccessful implant procedures must be followed for 30 days post implant attempt or until all implant and procedure-related AE's are resolved, whichever comes last. A second attempt may be made, but is not required, after inclusion and exclusion criteria have been re-verified. Randomization may only be done after a successful implant.

8.7.1. Implant Requirements and Recommendations

It is recommended that the LV lead placement is targeted for an LV lateral, anterolateral or posterolateral position. Data on LV lead placement decision and method will be collected.

8.7.2. CRT Optimization

Optimization of the AV-VV intervals may be completed and documented. Additional features to optimize CRT may be used upon market commercialization.

8.8. Randomization and Treatment Assignment

Subjects who meet all inclusion and none of the exclusion criteria, and have a successfully implanted CRT device, will be assigned to a treatment at random during the randomization visit, which must occur within 7 days after a successful implant. Subjects will be randomized using the randomization schedule determined by a Medtronic statistician. Centers will receive this assignment electronically in the study database from Medtronic upon completion of the randomization case report form.

At the time of the randomization device programming, a device check will be conducted, and the default settings will be verified. If subjects are assigned to the aCRT ON group, "Adaptive Bi-V and LV" will be programmed. If subjects are assigned to the aCRT OFF group, the delegated person will ensure that "Nonadaptive CRT" is programmed. Control group subjects will be optimized per physician's discretion. The method of AV and VV optimization in the control group will be collected. Full device interrogation (Interrogate ALL) data will be collected reflecting the final programming, and a copy of the interrogation files must be sent to Medtronic with a copy being maintained at the center in the subject's file.

The following procedures will be completed / data will be collected at the randomization visit:

- Device programming according to assignment
- AV/VV optimization method (control group only, if optimization occurs per standard of care)
- Final device interrogation (Interrogate All)
- Report AEs, System Modifications, Study Deviations and Crossovers (as they occur)

When implant is performed after enrollment, randomization should occur within 37 days after enrollment. When randomization is done later, verification of all inclusion and all exclusion criteria must be repeated.

Once a subject is assigned to a study group (treatment or control), he/she will remain in that arm and all efforts will be made to provide the optimal therapy specified for that treatment assignment. In the circumstance this is clinically or technically not feasible, the subject will remain in the assigned treatment arm for statistical analysis based on the intention-to-treat principle, as it represents a normal medical situation of success and failure of delivering the planned medical therapy.

8.8.1. Programming Requirements and Recommendations

The following programming requirements and recommendations are applicable to study subjects, according to their respective randomization assignment. Any deviation from the programming requirements will constitute a study deviation, whereas deviations from programming recommendations are not considered study deviations.

Table 5 Programming Requirements and Recommendations

Parameter	Treatment Group	Control Group
Adaptive CRT	**Adaptive Bi-V and LV**	**Nonadaptive CRT**
Mode	[redacted]	[redacted]
V. Blank Post VP	[redacted]	[redacted]
SAV	[redacted]	[redacted]
PAV	[redacted]	[redacted]
VV Delay	[redacted] *	[redacted]
V. Pacing	[redacted]	[redacted]
Left Ventricular Capture Management (LVCM)	[redacted]	[redacted]
Lower Rate	[redacted]	[redacted]
Upper Tracking Rate	[redacted]	[redacted]
Upper Sensor Rate	[redacted]	[redacted]

Ventricular Sense Response	[redacted]	[redacted]
Conducted AF response	[redacted]	[redacted]
Lead polarity for quadripolar LV leads	[redacted]	[redacted]
Multiple Point Pacing (MPP)	[redacted]	[redacted]
EffectivCRT During AF	[redacted]	[redacted]

* For CRT devices with programmable VV Delay in Adaptive mode: Program to Auto

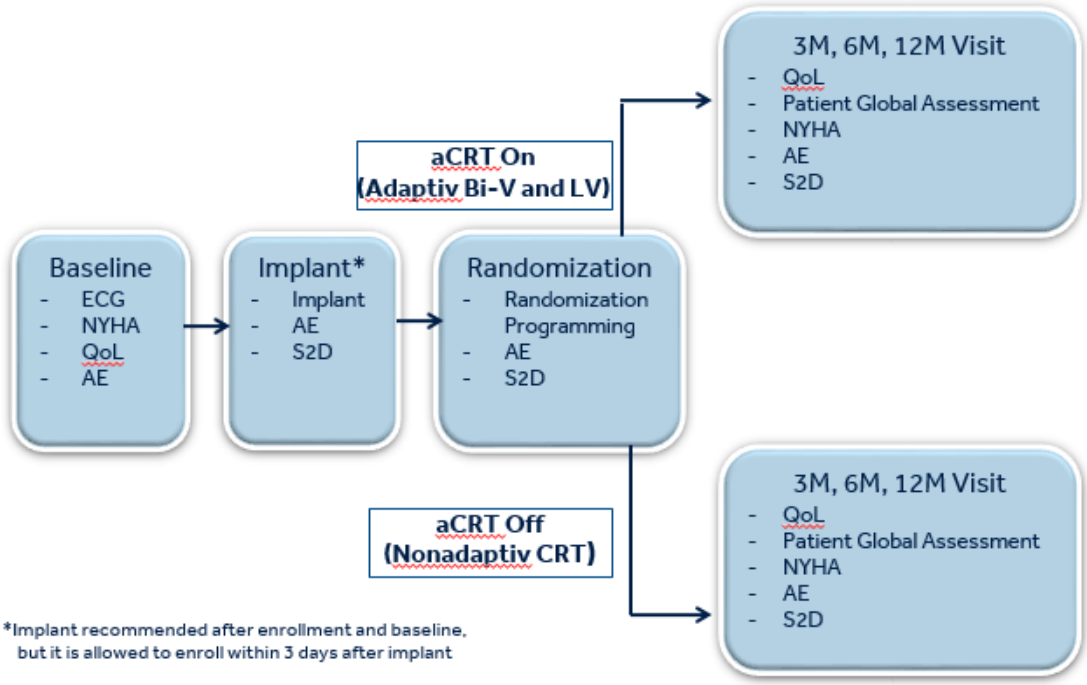
8.9. Scheduled follow-up visits

After receiving randomization notice via the randomization CRF, Medtronic will provide the target dates and windows for each follow-up visit to the implanting center via the randomization CRF. Follow-up visit windows open on the Window Start date and remain open as defined below. It is recommended that subjects are scheduled as close as possible to the target date for a given follow-up visit.

Should a subject visit fall outside the pre-specified window, a Study Deviation must be reported, and the original follow-up schedule maintained for subsequent visits. Data analyses include follow-up visits, regardless of whether the visit occurs within the window. Therefore, an early or late visit is preferred over a missed visit, but still must be accompanied by a deviation. Follow-up visit windows are listed in Table 3 and are based on days post-randomization.

Required visits post-randomization include follow-up visits at 3 months, 6 months, and 12 months as shown inFigure 2. During these visits information will be collected about adverse events (AE), Cardiovascular (CV) medications, and Heart Failure (HF) assessment, as well as additional information and procedures which vary by visit (see Table 4). Quality of Life (QoL) and Health outcome will be addressed using the KCCQ questionnaire, which subjects will complete during applicable study visits. Full device interrogation (interrogate ALL) data will be collected for subjects at the end of the visit (final interrogation) and a copy of the interrogation files (Save-to-Disk, S2D) must be sent to Medtronic, with a copy also being maintained at the center in the subject's file.

Figure 2: Visit Timelines



The post-randomization follow-up windows are provided in Table 6.

Table 6 post-randomization follow-up windows

Study Follow-up Visit	**Window (Calculated days post-randomization)**		
	Window Start (days post-randomization)	Target (days post-randomization)	Window End (days post-randomization)
3 Month follow-up	77	91	105
6 Month follow-up	183	183	211
12 Month follow-up*	365	365	393

*12 Month follow-up visit in the second half of the window is preferred but not required

8.9.1. 3, 6 and 12 month Follow-up visits

- NYHA HF assessment
- Physical examination
- Blood measurements (only collected when standard of care)
- Echocardiography data (only collected when standard of care)
- Current heart failure symptoms status
- Final device interrogation (Interrogate All)
- AV/VV optimization method (control group only, if optimization occurs per standard of care)
- Quality of Life and Health Outcome Measures:
  - Kansas City Cardiomyopathy Questionnaire (KCCQ)
- Patient Global Assessment
- Report AEs and hospitalizations, System Modifications, Study Deviations, and Crossovers (as they occur)

8.10. Device Interrogation (Interrogate All)

For the implant (if performed after enrollment), randomization and follow-up visits, a final full "Interrogate ALL" device interrogation file (.pdd or .pkg) must be obtained and saved in a digital format (e.g., USB). Store one copy at the site and send a copy to Medtronic. It is recommended that data are not cleared during any interrogation.

8.11. Adverse Events

All serious and all system, procedure, and/or cardiovascular related Adverse Events (AEs) will be collected throughout the study duration. These are reported upon center awareness and assessed at scheduled follow-up visits to ensure all applicable AEs have been reported.

Refer to section 10 for adverse event details.

8.12. System Modification

A system modification will be reported in the event the device and/or leads require invasive modification (e.g., device or lead explant, device or lead replacement, lead repositioning). In the event of a system modification, the follow-up schedule for the subject will remain unchanged. The following information is required to be collected for a system modification:

- Report reason for modification
- Report the details of the system modification procedure
- Device programming according to randomization assignment (aCRT ON for treatment group and aCRT OFF for control group)

- Device interrogation (initial and final "interrogate ALL"; a copy of the interrogation files must be sent to Medtronic with a copy also being maintained at the center)
- Report the associated AE

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

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

8.13. Study Exit

Subjects should be exited from the study when the 12 months visit is completed.

Prior to exiting a subject from the study, it is recommended to follow the subject until all ongoing system- and procedure-related AEs are resolved or are unresolved with no further actions planned. After all study tests and procedures have been completed just prior to subject exit from the study, the subject may be informed of their randomization assignment. Following exit, subjects will continue to receive standard medical care. There will be no further required study-related follow-up visits for these subjects. All data available through the time of the subject's exit will be used for the study analyses. The following procedures are required to be collected at the exit visit*:

- Report the reason for exit
- Vital status check
- Current CV medications
- Current heart failure symptoms status
- Initial and Final device interrogation, if available (Interrogate ALL)
- Report AEs and Study Deviations (as they occur)

*Note: this does not need to be collected separately when exit occurs on same date as the 12 month visit.

Subjects will not be replaced with newly enrolled subjects upon exit. As described in Section 12.4.2 0, the sample size accounts for attrition.

8.13.1. Subject Withdrawal or Discontinuation

A subject can withdraw from the study at any time. If a subject is withdrawn from the clinical study, the reason for withdrawal will be recorded in the Exit CRF and in the subject's hospital record. In addition, centers should follow the regulations set forth by their Ethics Board.

Possible reasons for premature withdrawal or exit from the study are:

- Study completed

- Subject chooses to withdraw (i.e. consent withdrawal)
- Subject did not meet eligibility criteria after consent but prior to randomization (once randomized, subjects should stay in the study)
- Investigator withdrew subject from the study for medical reasons
- Subject did not have a successful CRT implant and no attempt at re-implant is made. If randomization is completed prior to successful implant by error, the subject should not be exited.
- Subject lost to follow-up (not expected to occur due to the short study duration for individual subjects)
- Subject death
- Subject did not provide consent or data protection authorization

Exits after randomization should be avoided as much as possible. Prior to exiting a subject from the study, pre-approval should be obtained from the Medtronic study manager, unless subject chooses to withdraw.

8.13.2. Study completed

Upon study closure, subjects will be exited from the study. After all study tests and procedures have been completed just prior to subject exit from the study, the subject may be informed (verbally or in written form) of their randomization assignment. Subjects in the control group may have aCRT turned ON. For subjects within a visit window upon study closure, the exit visit and scheduled visit may be combined. For other patients a separate exit visit must be planned. For all subjects, a Study Exit CRF including Vital Status information will be completed.

The study will continue until the predetermined number of randomized patients has completed the 12-month visit, unless Medtronic determines to stop earlier. The study may be stopped early due to lack of enrollment, e.g. if the average enrollment rate is less than 0.15 subjects enrolled per active center per month over any 6 consecutive months during the study.

8.13.3. 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. In addition, regulations set forth by the governing Ethics Committee must be followed.

8.14. Assessment of Safety

Aggregate safety data will be reviewed internally at a minimum annually following first subject enrollment. The Safety Representative, Medical Advisor, Clinical Study Manager, and other

appropriate functional groups (e.g., Regulatory Affairs, Quality) as needed will participate in the Internal Safety Data Review/Trending meetings.

The following are the key safety events identified a priori that will be reviewed for this study:

- (Worsening) Heart Failure events
- Events with outcome death

The type of data for aggregate review is as follows:

- Aggregate presentation of all AEs filtered by relatedness, seriousness, etc.
- Aggregate presentation of all Deaths filtered by death classification through last data collection/modification.

Important safety findings or signals identified will be reported per local requirements.

8.15. Recording Data

Clinical data is collected at designated time points throughout the study. Data will be collected using an electronic data management system for clinical studies. Data will be stored in a secure, password-protected database which will be backed up nightly. Data will be reviewed using programmed and manual data checks. Data queries will be made available to study sites for resolution. Study management reports may be generated by Medtronic to monitor data quality and study progress. At the end of the study, the data will be frozen and retained by Medtronic. Data collection requirements are summarized in Table 4.

8.16. 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. Crossover is considered a deviation, but additional requirements apply, see section 5.4.

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).

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 endpoint analysis). However, prior approval from Medtronic is required for such situations.

All study deviations must be reported to Medtronic regardless of whether medically justifiable, pre-approved by Medtronic, an inadvertent occurrence, or taken to protect the subject in an emergency. In the occurrence of a corrupted device interrogation file, Medtronic may request a deviation to document that a readable interrogation file is unavailable.

In the event the deviation involves a failure to obtain a subject's consent, or is made to protect the life or physical well-being of a subject in an emergency, the deviation must be reported to the Ethics Committee as well as Medtronic within five (5) working days, or according to local requirements. Reporting of all other study deviations should comply with Ethic Committee policies and/or local laws and deviations must be reported to Medtronic as soon as possible upon the center becoming aware of the deviation. Refer to section 15.2 and 15.3 for deviation reporting requirements and timeframes for reporting to Medtronic and/or regulatory bodies.

Medtronic is responsible for analyzing deviations, assessing their significance, and identifying any additional corrective and/or preventive actions (e.g. amend the Clinical Investigation Plan, conduct additional training, terminate the 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 will provide center-specific reports to investigators summarizing information on deviations that occurred at the investigational site on a periodic basis.

9. Risks and Benefits

9.1. Potential Risks

The safety and clinical performance of the Medtronic market-released CRT systems have been demonstrated through previous pre-clinical testing and previous clinical studies. Specifically, safety of the AdaptivCRT® algorithm was demonstrated in the Adaptive CRT study. All products used within this study are market-released. Therefore, it is not anticipated that subjects enrolled in this study will be exposed to any risks beyond those normally associated with CRT systems, transvenous and subcutaneous lead systems, or their implant procedure.

With the exception of the risks associated with the device and implant procedure, there are no risks associated with study-related procedures (e.g. quality of life questionnaires), since these are not incremental to standard of care treatment and monitoring of patients with symptomatic heart failure. Therefore, the risk analysis in this section is specific to the implantation, management and therapy from the implanted CRT-P/D system.

The potential risks to subjects implanted with CRT-P or CRT-D system include, but are not limited to, the following:

- Air embolism
- Cardiac dissection or perforation
- Cardiac tamponade
- Coronary sinus dissection
- Death
- Endocarditis or pericarditis
- Erosion through the skin
- Exit block
- Extracardiac muscle or nerve stimulation
- Fibrillation or other arrhythmias
- Heart block
- Heart wall or vein wall rupture
- Hematoma/seroma
- Infection
- Lead dislodgement
- Lead conductor fracture or insulation failure
- Loss of capture
- Myocardial irritability
- Myopotential sensing
- Pericardial effusion or rub
- Pneumothorax
- Rejection phenomena
- Threshold elevation
- Thrombosis
- Thrombotic embolism
- Valve damage

Subjects who are pregnant may be at increased risk (e.g., radiation exposure, and other unforeseen risk to the fetus), and are excluded from participation in the study. If a subject becomes pregnant during the study, she must notify the physician immediately. The subject will remain in the study for intention to treat analysis, but the investigator will avoid any procedures that may be determined harmful.

There may be other discomforts and risks related to the CRT device and/or this study that are not foreseen at this time.

9.2. Risk minimization

There is no additional risk for the patient by participating in this clinical study as compared to a standard CRT implant. The potential risks associated with the commercially available CRT implant

were identified and have been successfully mitigated. Any potential risks associated with this study are further minimized by selecting qualified investigators and training study personnel on the Clinical Investigation Plan.

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

Risks will be minimized by careful assessment of each subject prior to, during, and after implant of the CRT system.

Medtronic has further minimized the possibility of risks by product testing applicable to all commercially available devices prior to their use in this clinical study, implementing quality control measures into production processes, providing guidelines for subject selection and evaluation, and providing adequate instructions and labeling.

After implantation, subjects in this clinical study will be followed at regular intervals to monitor the condition of the implanted system and the battery. At each protocol required follow-up, in all subjects, the investigator must interrogate the CRT device to verify appropriate CRT function and to evaluate pacing and sensing characteristics and to assess any adverse events.

9.3. Potential Benefits

There is no direct benefit for the subjects participating in the study as the devices are already commercially available. The information gained from this study could result in the improved management of heart failure. Additionally, information collected from this study may assist in the design of new products, therapies and/or instructions for use.

9.4. Risk-Benefit Rationale

There is no incremental risk or benefit for subjects participating in the study.

10. Adverse Events

All serious and all system, procedure, and/or cardiovascular related adverse events (AEs) will be collected throughout the study duration, starting at the time of signing the ICF. These AEs should be reported timely, accurately and completely. Reporting and review of safety information for clinical studies are crucial for the protection of subjects. The products used in the clinical trial are market approved and used within the current indications for use as indicated in the product labeling. Sections below define the clinical event reporting requirements for the study.

10.1. Adverse Event Definitions

10.1.1. Adverse Events

Adverse Event (AE) definitions are provided in Table 7. All serious and all system, procedure, and/or cardiovascular related AEs will be collected throughout the study duration, starting at the time of signing the ICF. Reporting of these events to Medtronic will occur on an AE Form, including a description of the AE, date of onset of the AE, date of site awareness, signs and symptoms, treatment, resolution, and investigator assessment of both the seriousness and the relatedness to heart failure, the implant or system modification procedure, and to the system. Each AE must be recorded on a separate AE Form.

Subject deaths are also required to be reported. Refer to section 10.3 for Subject Death collection and reporting requirements.

Documented pre-existing conditions are not considered AEs unless the nature or severity of the condition has worsened. However, episodes of symptomatic AF need to be reported. In all geographies, Unavoidable Adverse Events, listed in Table 7 need not be reported unless the adverse event worsens or is present outside the stated timeframe post-implant. For AEs that require immediate reporting, initial reporting may be done by phone, fax, or on the CRF completing as much information as possible, with missing or follow-up information provided as soon as it becomes available. The AE CRF must be completed as soon as possible.

10.1.2. 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 form. All adverse events must be followed until the adverse event has been resolved, is unresolved with no further actions planned, the subject exits the study or until study closure, whichever occurs first.

In the event that a subject is exited from the study prior to the 12 month visit or study closure, all efforts should be made to continue following the subject until all unresolved system or procedure related adverse events, as classified by the investigator, are resolved or they are unresolved with no further actions planned.

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

10.2. Definitions, Classification and Reporting of Adverse Events

10.2.1. Adverse Event Definitions

The clinical study will collect all serious and all system, procedure, and/or cardiovascular related adverse events. Where the definition indicates "device", it refers to any market released device used in the study to provide CRT. This might be any market released component of the system and includes but is not restricted to: the CRT-P or CRT-D device, the RA, RV or LV leads, the programmer, and implant tools.

Table 7 Adverse Event definitions

General	
Adverse Event (AE)	Any untoward medical occurrence, unintended disease or injury, or untoward clinical signs (including abnormal laboratory findings) in subjects, whether or not related to the medical device. *NOTE 1: This definition includes events related to the medical device or the comparator.* *NOTE 2: This definition includes events related to the procedures involved* (ISO 14155:2011, 3.2)
Relatedness	
Procedure related	An Adverse Event that occurs due to any procedure related to the implantation or surgical modification of the system.
System related (includes all implantable components and features, associated introduction tools and programmers as defined in the Clinical Investigation Plan)	Device-related: An adverse event that results from the presence or performance (intended or otherwise) of the CRT 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. LV lead-related: An adverse event that results from the presence or performance (intended or otherwise) of the LV lead. Implant tool-related: An adverse event that results from the presence or performance (intended or otherwise) of the implant tool. Programmer-related: An adverse event that results from the presence or performance (intended or otherwise) of the programmer.
Cardiovascular related	An Adverse Event relating to the heart and the blood vessels or the circulation, including but not limited to Atrial Fibrillation, Myocardial Infarction, stroke, perivascular problems.
Heart Failure related	An adverse event related to worsening heart failure signs and symptoms such as hypervolemic and hypovolemic status requiring the administration, alteration, adjustment or augmentation of HF therapy (diuretics, inotropes

	and/or vasodilators etc.) or the utilization of ultrafiltration devices.
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)
Adverse Device Effect (ADE)	Adverse event related to the use of the 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 medical device.* *NOTE 2: This definition includes any event resulting from use error or from intentional misuse of the medical device.* (ISO 14155:2011, 3.1)
Serious Adverse Device Effect (SADE)	Adverse device effect that has resulted in any of the consequences characteristic of a serious adverse event. (ISO 14155:2011, 3.36)
Unanticipated Serious Adverse Device Effect (USADE)	Serious adverse device effect which by its nature, incidence, severity or outcome has not been identified in the current version of the risk analysis report

	NOTE 1: Anticipated serious adverse device effect (ASADE) is an effect which by its nature, incidence, severity or outcome has been identified in the risk analysis report. (ISO 14155:2011, 3.42)
Other	
Unavoidable Adverse Event	An Adverse Event inherent to a surgical procedure that is expected to occur in all subjects for a projected duration according to the Investigator's opinion, including, but not limited to:

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

For hospitalizations associated with applicable adverse events, investigators should classify whether a hospitalization is a heart failure hospitalization, according to the following definition: Intervention for heart failure decompensation is defined as an event that (i) occurred primarily because of new or worsening signs and symptoms of HF, or biomarker or imaging evidence of HF, and (ii) received additional or increased pharmacological or mechanical intervention to treat HF. In case the patient is not hospitalized, the treatment is required to be intravenous or invasive.

More details on the classification of heart failure related hospitalization and outpatient invasive intervention for heart failure decompensation are provided in Table 8 and documented on the AE CRF.

Table 8 Classification definition of heart failure hospitalization

Term	Definition

Heart Failure related hospitalization	Hospitalization due to heart failure will be defined as a therapeutic admission lasting >24hrs that occurred primarily because of the documented presence of:
	• Use of additional or increased pharmacologic or mechanical interventions directed at the treatment of heart failure, and at least 1 of the following 2 criteria:
	  • Clinical manifestations of heart failure
	  • Biomarker or radiographic evidence consistent with heart failure
	
	Clinical manifestations of heart failure include the following signs and symptoms: New or worsening
	• Dyspnea
	• Orthopnea
	• Paroxysmal nocturnal dyspnea
	• Edema
	• Pulmonary rales
	• Jugular venous distension
	• Third heart sound or gallop rhythm
	• Hypotension or cardiogenic shock not occurring in the context of an acute myocardial infarction or as the consequence of an arrhythmia, or
	• Other clinical evidence of new or worsening heart failure, e.g., weight gain, or confinement to bed predominantly due to heart failure symptoms
	
	Biomarker results consistent with heart failure include documented increased or increasing levels of a natriuretic peptide (BNP or NTproBNP).
	Radiographic evidence consistent with heart failure includes documented worsening pulmonary congestion or pulmonary edema on chest X-ray or other generally recognized imaging pattern.
	The use of additional or increased pharmacologic or mechanical interventions directed at the treatment of heart failure includes:
	• Initiation of intravenous diuretic, inotropic, or vasodilator therapy
	• Significant addition or increase in oral heart failure therapy
	• Up-titration of intravenous therapy, if already on therapy
	• Initiation of mechanical or surgical intervention (mechanical circulatory or ventilatory support, heart transplantation or ventricular pacing to improve cardiac function), or the use of ultrafiltration,

	hemofiltration, or dialysis that is specifically directed at treatment of heart failure.
Invasive intervention for HF decompensation	This category will be defined as a clinical event where invasive treatment provided in an ambulatory setting for signs and/or symptoms of heart failure decompensation but where the patient is not hospitalized. The definition of signs and symptoms will be the same as the heart failure definition for hospitalization (see above). Invasive treatments will include any intravenous or invasive therapy directed at the management of heart failure (e.g., IV diuretics, IV vasodilators, IV inotropes, ultrafiltration, etc).

10.2.2. Adverse Events Classification and Reporting

All study reportable adverse events will be reported on case report forms and will be reviewed by a Medtronic specialist. AEs will be classified according to the definitions provided.

Upon receipt of adverse events at Medtronic, a Medtronic representative will review the adverse event 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 will be completed according to local regulatory requirements. It is the responsibility of the investigator to abide by any additional AE reporting requirements stipulated by the Ethics Committee responsible for oversight of the study.

Foreseeable Adverse Events are listed in Appendix A: Foreseeable Adverse Event List (FAL), which is a list of adverse events related to the system or procedure that have been observed in previous studies and may be experienced by subjects. This list may help to assess if an adverse event is unexpected in nature.

For emergency contact regarding an SAE, contact a clinical study representative immediately (refer to the study contact list provided in the center's study documents binder/investigator site file or refer to the contact information provided on the title page).

Adverse Events and Deaths will be classified according to the standard definitions as outlined in Table **9**.

Table 9 Adverse Event classification responsibilities

What is classified?	Who classifies?	Classification Parameters
Relatedness	Investigator	System, procedure, or heart failure related
	Sponsor	System, procedure, heart failure related, cardiovascular related
Seriousness	Investigator	SAE
	Sponsor	SAE, SADE, USADE
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
	Sponsor	Sudden Cardiac, Non-sudden Cardiac, Non-Cardiac, Unknown

10.3. Subject Death

10.3.1. Death data collection

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

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

System Interrogation Data Recommendations:

- After the subject has died but prior to explant, the system shall be interrogated and a full summary interrogation (Interrogate All) performed when possible.

- Make the interrogation file before any programming to prevent overwriting information in the CRT device's memory and/or distinguishing between events detected during versus before the explant procedure.

If the system is not interrogated, an explanation must be entered on the Subject Death form. For CRT-D systems, the VT and VF detection capabilities must be disabled to avoid inadvertent shocks. If any system component is returned to Medtronic, internal returned product reporting systems may be used to gather additional information about the returned device/component.

The following data will be collected:

- Adverse Event leading to death
- Date of death
- Detailed description of death
- Cause of death
- Relatedness to system and/or procedure
- Device interrogation (Interrogate ALL) (if available)

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

Regulatory reporting of Subject Deaths will be completed according to local regulatory requirements. Refer to section 10.4 for investigator and sponsor reporting requirements.

10.4. Adverse Event Records and Reporting Requirements

Adverse Events should 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 center's Ethics Committee.

Investigator will submit to sponsor:

- SAEs: Report to the sponsor, without unjustified delay, all serious adverse events
- SADEs: Immediately after the investigator learns of the event or of new information in relation to an already reported event.
- USADEs: Immediately after the investigator learns of the event or of new information in relation to an already reported event.

All SAEs, SADEs and USADEs will be submitted by investigator and/or sponsor to Regulatory Authority, Head of Medical Institution, EC per local reporting requirement.

10.5. Product Complaint Reporting

All devices used in this study are market released. Therefore, vigilance and Medical Device Reporting (MDR) 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. In case the adverse event is related to a non-Medtronic market released device used during the study, post-market surveillance is also applicable, and the investigator is responsible for immediate reporting of the product complaint via the regular channels for market released products.

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

It is the responsibility of the investigator to report all product complaint(s) associated with a medical device distributed by Medtronic, regardless whether they are related to intended use, misuse or abuse of the product. Reporting must be done immediately and via the regular channels for market-released products according to local Product Complaint Handling SOPs.

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

- Any malfunction or deterioration in the characteristics and/or performance of a device, as well as any inadequacy in the labeling or instructions for use which led or might have led to the death or serious deterioration in the state of health of a patient, user, or other person (device deficiency).

- Any technical or medical reason resulting in withdrawal of a device from the market by the manufacturer.

A serious deterioration in the state of health includes:

- Life-threatening illness or injury
- Permanent impairment of a body function or permanent damage to a body structure
- A condition necessitating medical or surgical intervention to prevent permanent impairment to a body structure or a body function

11. Data Review Committees

The Mid-Q Response ECG Core Laboratory will review all baseline ECGs from patients enrolled in the Mid-Q Response study for presence of LBBB and normal AV conduction. Feedback on accuracy will be reported to Medtronic and the sites.

No other committees will review data during the course of the study. Adverse Events will be reviewed and classified by Investigators and Medtronic. A Data Monitoring Committee (DMC) is not considered needed for Mid-Q Response, due to the well-understood risk profile of CRT therapy, short follow up duration and no interim analyses are planned.

12. Statistical Design and Methods

Medtronic employed statisticians will perform the statistical analyses described in this section. No interim analyses will be performed for the Mid-Q Response study and there are no criteria defined for termination of the study on statistical grounds. An Intention-to-Treat analysis will be performed and will serve as the primary analysis for all objectives in this study. The Intention-to-Treat cohort will include all randomized subjects. A Mid-Q Response Statistical Analysis Plan (SAP) will be created to specify analyses in further detail. In case the SAP deviates from this Clinical Investigation Plan (CIP), or the actual analysis deviates from CIP and/or SAP, this will be explained in the Final Report.

12.1. Rationale for Study Design

The CCS is selected as the primary endpoint because it is an established endpoint in the research of CRT that can be assessed in all patients with 6 months of follow up. The study is randomized to ensure comparable groups between aCRT On and aCRT Off. Patients are blinded to exclude bias. However, investigators are not blinded to recognize that blinding would involve a prohibitive burden to clinical practice.

The secondary and ancillary endpoints are NYHA class, hospitalizations for worsening heart failure, all-cause and cardiovascular death, KCCQ, AF and cardiovascular adverse events. Death and HF hospitalizations are components of the CCS and frequently used as endpoint in pivotal trials in heart failure [27]. The NYHA class measures severity of heart failure symptoms and is also a component of the CCS. KCCQ is a measure of Quality of Life specific to heart failure. AF is common in HF patients and there is preliminary evidence that aCRT reduces the incidence of AF worsening [18]. Finally, cardiovascular adverse events are collected to allow for reporting and review of safety information.

12.2. General Aspects of Analysis

The final report will include descriptive summaries of patient characteristics at baseline, follow-up experience, attrition, adverse events, and study deviations.

Statistical methods used for analysis of objectives will include Chi-square test, mixed-effects logistic regression, ordinal proportional odds logistic regression, and competing-risk survival analysis using Cumulative Incidence Functions.

Subgroups may be considered, which will include age, gender, body height, heart failure etiology, LVEF, NYHA class, and QRS duration. Note that race and ethnicity are not collected in this study.

All data will be reported. Data that is not used for the analysis of objectives, such as data from subjects that were not randomized, will be summarized separately. Missing data will be identified and the number of patients with missing data will be reported. No imputation of missing data will be done for the main analyses. However, multiple imputation may be used for sensitivity analyses. Note that the CCS is defined for all subjects, also if there is contributing data missing. The algorithm determining CCS (see below) uses last observation carried forward (LOCF) for the NYHA class. Data management procedures will be used to detect and correct spurious data.

12.3. Primary Objective

The primary objective of the study is to test the hypothesis that aCRT ON increases the proportion of patients with moderately wide QRS, LBBB and intact AV conduction that improve on the Clinical Composite Score (CCS) compared to aCRT OFF at 6 months of follow-up.

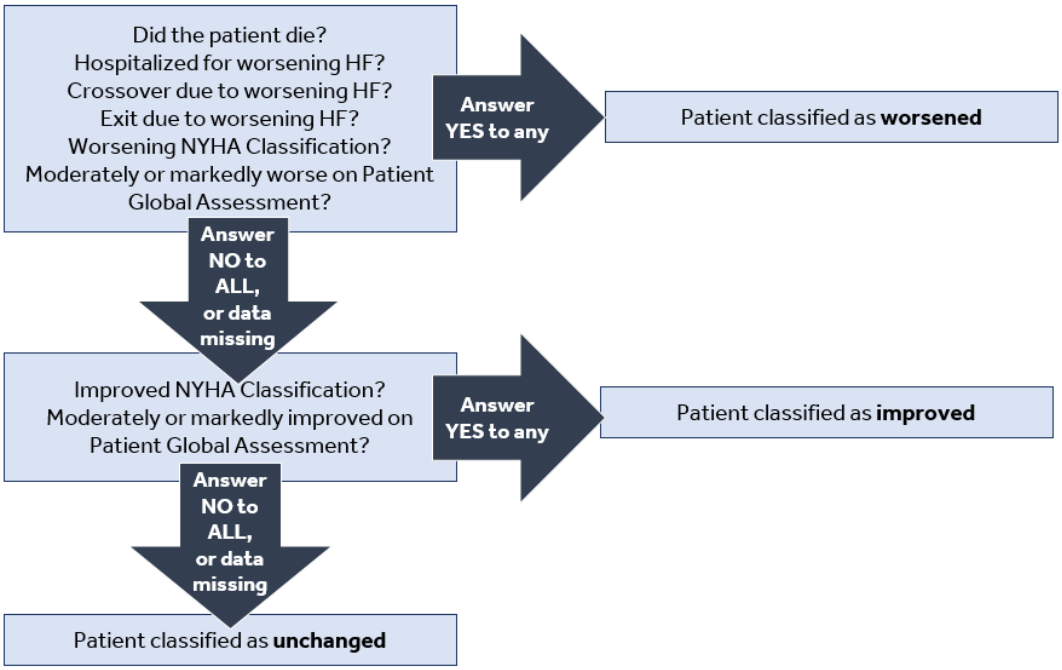
12.3.1. Primary Endpoint

The primary endpoint for the study will be the Clinical Composite Score (CCS) at 6 months. The CCS classifies patients according their clinical status at 6 months post-randomization into categories Improved, Unchanged, and Worsened. A patient is classified Worsened in case of death, hospitalization for worsening heart failure, worsened NYHA class (using last observation carried forward), or worsened status on the Global Assessment Score. Also, patients that exit

the study or cross over because of worsening heart failure are classified Worsened. A patient is classified Improved when not Worsened and there is an improvement in NYHA class or Global Assessment Score. Patients that are not Worsened or Improved are Unchanged including all patients that miss NYHA class and Global Assessment Score data and are not classified Worsened because of death, HF hospitalization, exit or crossover (see flowchart in Figure 3).

The main analysis will look at the percentage of patients with Improved CCS.

Figure 3 Clinical Composite Score Flowchart



12.3.2. Hypothesis and Analysis Methods

The null-hypothesis that will be tested is that the proportion of patients with Improved CCS is not different between the randomized arms:

H_0 : $p_{aCRT} = p_{control}$

H_A : $p_{aCRT} \neq p_{control}$

The analysis will use a Chi-square test comparing the proportion Improved between randomized arms. The null-hypothesis will be rejected when the p-value is < 0.05. It will be concluded that aCRT is associated with a higher proportion Improved in case the null-hypothesis is rejected and the proportion Improved is higher in the aCRT ON arm.

A sensitivity analysis may be done using a logistic regression model with randomized arm, gender and NYHA class as fixed effects and site as random effect. Sites with a low number of enrollments will be grouped into clusters.

12.3.3. Analysis Set

All randomized patients will be included in the analysis. Patients will be analyzed in the arm that the patient was randomized to irrespective of the actual treatment that the patient received (intent-to-treat principle).

The primary analysis will include all randomized patients and will follow the intent-to-treat principle. A secondary analysis will be done including only the patients for whom the ECG Core Laboratory confirmed the presence of LBBB.

12.4. Sample Size rationale

12.4.1. Historical Data

The MIRACLE trial was a randomized trial in NYHA class III patients, comparing CRT vs control. CCS was Improved in 67% of the CRT patients and 39% of the control patients [1].

The REVERSE trial was a randomized trial in mostly NYHA class II patients, comparing CRT vs control. CCS at 6 months was Improved in 55% of the CRT patients and 42% of the control patients [28]. (Note that the primary analysis of REVERSE was at 12 months.)

The Adaptive CRT trial was a randomized trial in NYHA class III patients comparing AdaptivCRT vs echo-optimized CRT. In the subgroup of patients with QRS ≤ 150ms, CCS was Improved in 79% of the AdaptivCRT patients and 50% of the echo-optimized CRT patients, with Odds Ratio (OR) = 3.76.

12.4.2. Sample Size Assumptions

- The CRT arms from MIRACLE and REVERSE have CCS Improved in 67% and 55% of the patients. It is assumed that this represents the difference between NYHA classes II and III, and that the corresponding OR = 1.66 will be the same for both arms of the Mid-Q Response study.
- Based on the Adaptive CRT trial results, it is conservatively assumed that CCS would be Improved for 59% of the NYHA III patients in the regular CRT control arm. Applying the OR =

1.66 for NYHA III vs II would give a CCS Improved rate of 46% for NYHA class II patients with regular CRT.

- Similarly, the percentage improved for NYHA II patients in the AdaptivCRT arm would be 69%, compared to 79% for the NYHA III patients.
- The expected enrollment in the Mid-Q Response study is 55% NYHA class III and 45% NYHA class II, so that the overall CCS Improved rate will be 53% in the regular CRT arm and 75% in the AdaptivCRT arm. To add conservatism, for sample size calculation, the rate in the regular CRT arm is raised to 55%.
- Assuming CCS is improved in 75% of patients in the AdaptivCRT arm and in 55% of patients in the regular CRT arm, a minimum of 220 patients must be randomized to achieve a power of 80% to demonstrate a significant difference in presence of 3% crossover in both arms. Pre-randomization attrition is expected to be at most 5%, so that approximately 232 patients will be enrolled to fulfil the sample size requirements for the primary analysis. Up to 3% post-randomization drop out is expected; however, subjects who drop out post randomization contribute to primary objective because, by definition, CCS is not impacted by missing data.

12.5. Secondary Objectives

12.5.1. Evaluate Change in NYHA Class

NYHA class will be collected at baseline and at the 3, 6, and 12-month follow-up visits. The follow-up assessments will be analyzed with an ordinal proportional odds logistic regression model that will account for the correlation of subsequent assessments within each patient. The treatment arm allocation will be included as a main effect. The baseline NYHA class will also be included in the model as fixed effect. Analysis will be corrected for time trends if needed.

12.5.2. Characterize Occurrence of HF Hospitalization

Hospitalizations will be classified as heart failure-related by the investigators. The incidence of HF hospitalizations will be estimated with Cumulative Incidence Functions for both randomized arms separately, treating death as a competing risk. Incidence will be reported with a figure and with estimates with 95% confidence interval at 12 months post randomization.

12.5.3. Characterize All-Cause and Cardiovascular Mortality

All-cause mortality will be estimated by the Kaplan-Meier method for both randomized arms separately and reported with a figure and with estimates with 95% confidence interval at 12 months post randomization.

Death will be classified as cardiovascular or non-cardiovascular by the investigators. Cardiovascular mortality will be estimated with Cumulative Incidence Functions, treating non-cardiovascular death as a competing risk.

12.5.4. Ancillary Objectives

Analysis methods for ancillary objectives will be defined in the Statistical Analysis Plan.

13. Ethics

13.1. Statement(s) of Compliance

The Mid-Q Response clinical study is required to be in compliance to the CIP, Clinical Trial Agreement (CTA) and local laws/regulations within the respective geography where the study is being conducted.

The Mid-Q Response clinical study is designed with good clinical practice (GCP) principles as guidance. These include the protection of the rights, safety and well-being of human subjects, controls to ensure the scientific conduct and credibility of the clinical investigation, and the definition of responsibilities of the sponsor and investigators.

The study will be conducted according to federal, national and local laws, regulations, standards, and requirements of the countries/geographies where the study is being conducted. The study will also be conducted in accordance with the Declaration of Helsinki. The principles of the Declaration of Helsinki are implemented in this study by means of the patient informed consent process, EC/MEC/IRB/HREC (all henceforth referred to as an" Ethics Committee") approval, study training, clinical trial registration, risk benefit assessment, and publication policy.

In all participating countries, local laws and regulations (including Declaration of Helsinki 2013) will be followed. In Japan, the study will be conducted in compliance with Clinical Trials Act.

The study will be publicly registered prior to first enrollment in accordance with the 2007 Food and Drug Administration Amendments Act (FDAA) and Declaration of Helsinki on http://clinicaltrials.gov.

In addition, the study may be registered in local regulatory databases where required by local law, including but not limited to Japan Registry of Clinical Trials (jRCT) for Japan.

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

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

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

Any additional requirements imposed by the EC/IRB or regulatory authority shall be followed.

14. Study Administration

14.1. 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 center in order to ensure that the study is conducted in accordance with the CIP, the Clinical Trial Agreement, and applicable regulatory and local requirements. Trained Medtronic personnel, 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 Subject Informed Consent, Research Authorization (where applicable) and Clinical Trial Agreement. The principal investigator should also be available during monitoring visits.

14.1.1. Monitoring visits

The frequency of monitoring visits will be based upon subject enrollment, duration of the study, study compliance, number of adverse events, number of deviations from previous monitoring visits, remote monitoring findings, and any suspected inconsistency in data that requires investigation. Monitoring for the study, including but not limited to interim monitoring visits, and closeout visits will be done in accordance to the study-specific monitoring plan.

The Principal Investigator and site personnel will provide the Medtronic monitor(s) with complete access to primary source data (e.g., paper and electronic hospital/clinical charts, laboratory records etc.) that support the data on the eCRFs as well as other documentation supporting the conduct of the study. The monitor will perform source data verification and routine reviews of study related regulatory documents during scheduled monitoring visits, and work to secure compliance. Planned extent of source data verification will be performed in accordance to the study- specific monitoring plan.

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

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

14.2. Data Management

Data will be collected using an electronic data management system for clinical studies. Case Report Form (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 centers 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 by Medtronic.

The investigator must ensure accuracy, completeness and timeliness of the data reported in the e-CRFs. Only authorized persons can complete and sign e-CRFs, as specified on the Delegated Tasks List included in the Investigator Site File.

The data reported on the CRFs shall be derived from source documents and be consistent with these source documents, and any discrepancies shall be explained in writing. Source documents, such as Baseline ECGs, device interrogation files, worksheets, and lab results, must be created and maintained by the investigational site team.

Device data from CareLink transmissions will be uploaded to secure servers and made accessible to the study team. Device interrogation files collected via electronic media at office visits will be sent to Medtronic. Upon receipt via transmission or electronic media, device data will be maintained within secure databases and retrieved for analysis and reporting.

The sponsor or a regulatory authority may audit or inspect the study center to evaluate the conduct of the study. The clinical investigator(s)/institution(s) shall allow study related monitoring, audits, Ethics Committee review, and regulatory inspection(s) by providing direct access to source data/documents. If study site's documents are electronic, these must be made available in their original form (or print outs signed and dated with the statement that this is complete and true reproduction of the original source document) if requested by the sponsor and/or regulatory authority. For Japan, audit related procedures and plans will be provided under separate cover. Study sites should inform Medtronic upon notification of an audit by a regulatory body immediately.

14.3. Confidentiality

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 (Cognizant Technology Solutions, ECG Core Laboratory) in a key coded form, unless it's impossible to make it anonymous, for instance, where the patient's name cannot be removed from the data carrier.

Confidentiality of data will be observed by all parties involved at all times throughout the clinical study. All data shall be secured against unauthorized access. The privacy of each subject and confidentiality of his/her information shall be preserved in reports and when publishing any data. The Informed Consent Form and the process for conducting this study will be in compliance with any applicable local law. To maintain confidentiality, the subject's name or any other identifying data should not be recorded on any study document other than the ICF. This scenario will be covered in the ICF. In the event a subject's name or other identifying data is included for any reason, it will be blinded as applicable. In the event of inability to blind the identification (e.g. digital media), it will be handled in a confidential manner by the authorized personnel. Data relating to the study might be made available to third parties (for example in case of an audit performed by regulatory authorities), provided the data are treated as confidential and that the subject's privacy is guaranteed. No identifiable subject information will be published.

14.4. Liability

Warranty information is provided in the product packaging for the commercially released CRT-P or CRT-D devices and leads, and additional copies are available upon request.

Insurance (Japan)
Information regarding warranty and compensation will be provided under separate cover per the local regulation.

Insurance (South Korea)
Medtronic Korea Co., Ltd. is a wholly owned subsidiary of Medtronic Inc., which as the parent company of such entity maintains appropriate clinical trial liability insurance coverage as required under applicable laws and regulations and will comply with applicable local law and custom concerning specific insurance coverage. If required, a Clinical Trial insurance statement/certificate will be provided to the Ethics Committee.

Insurance (China)
Medtronic (Shanghai) Management Co., Ltd. is a wholly owned subsidiary of Medtronic Inc., which as the parent company of such entity maintains appropriate clinical trial liability insurance coverage as required under applicable laws and regulations and will comply with applicable local law and custom concerning specific insurance coverage. If required, a Clinical Trial insurance statement/certificate will be provided to the Ethics Committee.

Insurance (Taiwan)
Medtronic Taiwan Ltd. is a wholly owned subsidiary of Medtronic Inc., which as the parent company of such entity maintains appropriate clinical trial liability insurance coverage as required under applicable laws and regulations and will comply with applicable local law and

custom concerning specific insurance coverage. If required, a Clinical Trial insurance statement/certificate will be provided to the Ethics Committee.

Insurance (Hong Kong)
Medtronic Hong Kong Medical Ltd. is a wholly owned subsidiary of Medtronic Inc., which as the parent company of such entity maintains appropriate clinical trial liability insurance coverage as required under applicable laws and regulations and will comply with applicable local law and custom concerning specific insurance coverage. If required, a Clinical Trial insurance statement/certificate will be provided to the Ethics Committee.

Insurance (Malaysia)
Medtronic Malaysia Sdn Bhd. is a wholly owned subsidiary of Medtronic Inc., which as the parent company of such entity maintains appropriate clinical trial liability insurance coverage as required under applicable laws and regulations and will comply with applicable local law and custom concerning specific insurance coverage. If required, a Clinical Trial insurance statement/certificate will be provided to the Ethics Committee.

Insurance (Indonesia)
PT Medtronic Indonesia is a wholly owned subsidiary of Medtronic Inc., which as the parent company of such entity maintains appropriate clinical trial liability insurance coverage as required under applicable laws and regulations and will comply with applicable local law and

Insurance (Singapore & Brunei)
Medtronic International Ltd Singapore. is a wholly owned subsidiary of Medtronic Inc., which as the parent company of such entity maintains appropriate clinical trial liability insurance coverage as required under applicable laws and regulations and will comply with applicable local law and custom concerning specific insurance coverage. If required, a Clinical Trial insurance statement/certificate will be provided to the Ethics Committee.

custom concerning specific insurance coverage. If required, a Clinical Trial insurance statement/certificate will be provided to the Ethics Committee.

Insurance (Philippines)
Medtronic Philippines Inc. is a wholly owned subsidiary of Medtronic, which as the parent company of such entity maintains appropriate clinical trial liability insurance coverage as required under applicable laws and regulations and will comply with applicable local law and custom concerning specific insurance coverage. If required, a Clinical Trial insurance statement/certificate will be provided to the Ethics Committee.

14.5. CIP Amendments

Medtronic will submit any significant amendment to the CIP, including a justification for this amendment, to the appropriate regulatory authorities and to the investigators to obtain approval from their Ethics Board, if applicable. Administrative amendments to the Clinical Investigation Plan will be submitted to the Ethics Board and appropriate regulatory authorities for notification, if applicable. Any revisions or amendments to the CIP or ICF, along with a statement of justification for the changes, will be submitted to all affected Regulatory Authorities and governing Ethics Boards, according to applicable regulations. All amendments to the CIP shall be agreed between Medtronic and the principal investigator(s). Approval by regulatory agencies and Ethics Board (where applicable) must be obtained prior to implementing a CIP revision at the site.

In case the investigator will propose any appropriate modification(s) of the CIP or investigational software or investigational software use, Medtronic will review this proposal and decide whether the modification(s) will be implemented.

14.6. Record Retention

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

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

Medtronic will retain the study records according to Medtronic policy.

14.7. Publication and Use of Information

Results may be submitted for publication. If results from the Mid-Q Response study will be published, they will be handled according to Medtronic Standard Operating Procedures and as indicated in the Clinical Trial Agreement.

Refer to the Mid-Q Response publication plan for additional details, including general statements regarding publication committee, publication management, authorship and transparency.

14.8. Suspension or Early Termination

14.8.1. 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 Clinical Investigation Plan requirements have been satisfied and/or by a decision by Medtronic or regulatory authority, whichever occurs first. In all geographies, except Japan, the study closure process is complete upon distribution of the Final Report or after final payments, whichever occurs last. In Japan, the study closure process is completed when the local Lead PI submits the summary of the Final Report which was reviewed by the authorized EC in advance, to the Minister of Health, Labor and Welfare for posting the study results in the local registry database (jRCT), the local Lead PI informs this to the other PIs in Japan, and subsequently each PI reports this to the HOMI and Medtronic thereof in writing. In all geographies, ongoing Ethics Committee oversight is required until the overall study closure process is complete.

14.8.2. Early termination or suspension

Early Termination is the closure of a clinical study that occurs prior to meeting CIP-defined endpoints. This is possible for the whole study or a single center. Suspension is a temporary postponement of study enrollment. This is possible for the whole study or a single center.

14.8.2.1. 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 or regulatory body (where the study is operating under regulatory body authority)
- (Temporary) unavailability of the study devices
- Medtronic may stop the study due to lack of enrollment, e.g. if the average enrollment rate is less than 0.15 subjects enrolled per active center per month over any 6 consecutive months during the study.

14.8.2.2. Investigator/center termination or suspension

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

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

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

14.8.3. Procedures for termination or suspension

14.8.3.1. Medtronic-initiated and regulatory authority-initiated

- Medtronic will promptly inform the clinical investigators of the termination or suspension and the reasons and inform the regulatory authority(ies) where required
- In the case of study termination or suspension for reasons other than a temporary Ethics Committee approval lapse, the investigator, or in Japan the local Lead PI, will promptly inform the applicable Ethics Committee.
- In the case of study termination, the investigator must inform the subjects/legally authorized representatives and may inform the personal physician of the subjects to ensure appropriate care and follow-up is provided
- In the case of study termination, subjects may be informed of their randomization assignment
- 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
- In the case of study suspension, enrolled subjects should stay on their randomized programming, if possible
- CRT device therapy may be managed and reprogrammed as deemed appropriate at the discretion of the investigator upon study termination.
- In case the suspension is lifted, the investigator should assess whether or not to continue the study at the respective site

14.8.3.2. Investigator-initiated

- The investigator will inform Medtronic and provide a detailed written explanation of the termination or suspension.

- The investigator (or in Japan the local Lead PI), will promptly inform the institution, or in Japan the HOMI (where required per regulatory requirements)
- The investigator or the local Lead PI will promptly inform the Ethics Committee
- The investigator or the local Lead PI will promptly inform the regulatory authorities (where required)
- The investigator will promptly inform the subjects, or legally-authorized representative or guardians and 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
- CRT device therapy may be managed and reprogrammed as deemed appropriate at the discretion of the investigator upon study termination.

14.8.3.3. Ethics committee-initiated

- The investigator (or in Japan the local Lead PI) 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 Ethics Committee policy or its determination that an overriding safety concern or ethical issue is involved
- The investigator will inform his/her institution, or in Japan the HOMI (where required per local requirements)
- The investigator will promptly inform the subjects, or legally-authorized representative or guardians and the personal physician of the subjects, with the rationale for the study termination or suspension
- CRT device therapy may be managed and reprogrammed as deemed appropriate at the discretion of the investigator upon study termination.

15. Required Records and Reports

15.1. Investigator records

The investigator is responsible for the preparation and retention of the records cited below. All of the below records, with the exception of case history records and case report forms, should be kept in the Investigator Site File (i.e., the study binder provided to the investigator) or Subject Study Binder. CRFs must be maintained and signed electronically within the electronic data capture system during the study. The following records are subject to inspection and must be retained for a period of two years (or longer as local law or hospital administration requires) after the date on

which the investigation is terminated. Measures will be taken to avoid loss or premature destruction.

- All correspondence between the Ethics Committee, 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 signed by subject and investigator.
  - Observations of adverse events/adverse device effects/device deficiencies
  - Medical history, including comorbidities and cardiovascular, arrhythmia, and surgical history
  - Baseline, implant and follow-up data (if applicable)
  - Documentation of the dates and rationale for any deviation from the protocol
- Electronically signed and dated CRFs and blank set of CRFs where required by local law
- All approved versions of the CIP and ICF
- Signed and dated Clinical Trial Agreement (CTA)
- Current curriculum vitae of principal investigators and key members of investigation site team (as required by local law, signed and dated if required by local law)
- Documentation of delegated tasks
- Ethic Committee approval documentation. Written information that the investigator or other study staff, when member of the Ethics Committee, did not participate in the approval process. Approval documentation must include the Ethics Board composition, where required per local law.
- Regulatory authority notification, correspondence and approval, where required per local law
- Study training records for site staff
- Insurance certificates, where required per local law
- Final Study Report including the statistical analysis
- Any other records that local regulatory agencies require to be maintained

15.2. Investigator reports

The investigator is responsible for the preparation (review and signature) and submission to the sponsor of all case report forms, adverse events and adverse device effects (reported per the country-specific collection requirements), deaths, and any deviations from the clinical investigation plan. If any action is taken by an Ethics Committee with respect to this clinical study, copies of all pertinent documentation must be forwarded to Medtronic immediately. Reports are subject to inspection and to the retention requirements as described above for investigator records.

Safety data investigator reporting requirements are listed in the Adverse Events section 10.

Table 10 Investigator reports applicable for all countries per Medtronic requirements

Report	Submit to	Description/Constraints
Withdrawal of Ethics Committee approval	Sponsor and relevant authorities	The investigator must report a withdrawal of approval by the reviewing Ethics Committee of the investigator's part of the investigation within 5 working days.
Study Deviations	Sponsor and Ethics Committee	Any deviation from the clinical investigational plan shall be recorded together with the explanation of the deviation. Notice of deviations from the CIP to protect the life or physical well-being of a subject in an emergency shall be given as soon as possible, but no later than 5 working days after the emergency occurred. Except in such emergency, prior approval is required for changes in the plan or deviations.
Final Report	Ethics Committee and relevant Authorities	This report must be submitted within 3 months of study completion or termination.

15.3. Sponsor records

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

- All correspondence which pertains to the investigation
- Signed Clinical Trial Agreements (CTA)
- Current signed and dated curriculum vitae of principal investigator and key members of the investigation site team (as required by local law)
- Documentation of delegated tasks
- All signed and dated case report forms submitted by investigator
- Approved templates of informed consents, and other information provided to the subjects and advertisements, including translations
- Copies of all IRB/MEC approval letters and relevant Ethics Committee correspondence and Ethic Committee voting list/roster/letter of assurance
- Names of the institutions in which the clinical study will be conducted
- Regulatory authorities' correspondence, notifications and approvals as required by national legislation
- Insurance certificates, where required per local law
- Names/contact addresses of monitors
- Statistical analyses and underlying supporting data
- Final report of the clinical study
- The Clinical Investigation Plan, Informed Consent Form, and revisions
- 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

15.4. Sponsor reports

Medtronic shall prepare and submit the following complete, accurate, and timely reports listed in the tables below, as required by local laws and Ethics Committees. In addition to the reports listed below, Medtronic shall, upon request of reviewing Ethics Committee or regulatory agency, provide accurate, complete and current information about any aspect of the study. Safety data Medtronic reporting requirements are listed in the Adverse Event section.

Table 11 Sponsor reports

Report	Submit to	Description/Constraints
(Premature) termination or suspension of the clinical investigation	Investigators, Ethics Committee, Relevant authorities and Head of the Institution	Provide prompt notification of termination or suspension and reason(s).
Withdrawal of Ethics Committee approval	Investigators, Ethics Committee, Relevant authorities and Head of the Institution	Investigators, Ethics Committees will be notified only if required by local laws or by the Ethics Committee.
Withdrawal of CA approval	Investigators, Ethics Committee, Relevant authorities and Head of the Institution	Investigators, Ethics Committees will be notified only if required by local laws or by the Ethics Committee.
Progress Reports	Ethics Committee and relevant authorities	This will be submitted to the Ethics Committee only if required by the Ethics Committee.
Final report	Investigators, Ethics Committee and Regulatory authorities upon request	N/A
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.

Electronic versions of the Medtronic records and reports will be kept on a password-protected document management system. After closure of the study, all records and reports will be archived indefinitely. Measures will be taken to avoid loss or premature destruction.

16. References

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17. Appendices

APPENDIX A. FORESEEABLE ADVERSE EVENT LIST

The information provided in this section pertains to foreseeable adverse events that may be observed in Mid-Q Response subjects and may assist in identifying those events for a given device or therapy that are unexpected in nature. The implantation of the CRT devices involves surgery, therefore, standard adverse events associated with a surgical procedure may be experienced (e.g. anesthesia complications, injury, infections, bleeding, exacerbation of pre-existing conditions, healing complications, etc.). However, the focus of this section is to specifically address in more detail, those events that are foreseeable due to the implantation, use, performance, and/or presence of the CRT system.

Potential risks associated with the implantation of the CRT devices as well as risk minimization are discussed in section 9. Treatment required for procedure and/or system related adverse events that are experienced may include medication, device reprogramming, device modification (e.g. repositioning, surgical abandonment, surgical removal), or other surgical and medical remedies. The adverse events associated with the use of CRT systems include, but are not limited to, the following:

Foreseeable Adverse Events and Adverse Device Effects

Acceleration of tachyarrhythmias

Air embolism

Angina pectoris

Anxiety

Atrial arrhythmia

Bleeding/hemorrhage

Cardiac (heart wall or vein wall) rupture

Cardiac dissection

Cardiac perforation

Cardiac tamponade

Cardiac vein dissection

Cardiac vein perforation

Cerebrovascular accident

Coronary sinus dissection

Coronary sinus perforation

Deep vein thrombosis

Depression

Device battery issue

Device connection issue

Device electrical impedance issue

Device lead damage

Device lead fracture

Device migration

Device protrusion/extrusion

Device rejection

Dysplasia

Electrical conduction disorders

Electromagnetic interference

Elevated pacing threshold

Emotional distress

Endocarditis

Erosion

Exit block

Failure to capture

Far-field R-wave sensing

Fibrotic tissue growth

Fluid accumulation

Heart block

Heart failure worsening

Hemothorax

Impedance increased

Implant delivery tool problem

Implant site bruising

Implant site cellulitis

Implant site discharge

Implant site erythema

Implant site fibrosis

Implant site hematoma
Implant site infection
Implant site necrosis
Implant site pain
Implant site seroma
Implant site swelling
Inappropriate device signal detection
Inappropriate device therapy
Inappropriate extra-cardiac device stimulation
Incision site hematoma
Infection
Keloid scar
Lead abrasion and discontinuity
Lead conductor failure
Lead connector failure
Lead dislodgement
Lead insulation failure
Loss of capture
Myocardial damage
Myocardial infarction
Myocardial irritability
Myopotential sensing
Nerve damage
Oversensing
Pacemaker syndrome
Pericardial effusion
Pericardial hemorrhage
Pericardial rub
Pericarditis
Phrenic nerve stimulation
Pneumothorax
Pocket erosion
Pulmonary/pleural effusion
Sepsis
Septic shock
Subcutaneous emphysema
Syncope
Thromboembolism
Thrombosis
Tissue necrosis
Transient ischemic attack
Twiddler's syndrome
Undersensing
Valve damage
Vasovagal reaction
Venous occlusion
Venous stenosis
Ventricular arrhythmia

Previous Clinical Data

The listing below provides an example of reported system and procedure related adverse events associated with the use of CRT systems reported in the Adaptive CRT clinical study. It summarizes more commonly occurring adverse events (≥1% prevalence) by MedDRA preferred term. The adverse event relatedness adjudications are not mutually exclusive. Adverse events can be adjudicated as being related to multiple causes (e.g. an event can be related to both a lead and an implant procedure).

Table 12 provides a summary of adverse events by preferred term, by highest incidence of event rate. Cardiac failure was the most frequently occurring event (218 events in 129 subjects).

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

Due to limitations in the included patient population, this data may be used in combination with current event reporting information and published literature to assess for an unexpected increase in occurrence.

Table 12 Observed Adverse Events in Adaptive CRT clinical study

Adverse Event Preferred Term	Number of Events (Number, % of Subjects)					
	Adaptive CRT (n=318) Total years of follow-up = 534.6		Control (n=160) Total years of follow-up = 272.7		Total Subjects (n=478) Total years of follow-up = 807.3	
	Events	Complications[1]	Events	Complications	Events	Complications
Cardiac failure	145 (84, 26.4%)	117 (66, 20.8%)	73 (45, 28.1%)	56 (36, 22.5%)	218 (129, 27.0%)	173 (102, 21.3%)
Atrial fibrillation	15 (13, 4.1%)	5 (3, 0.9%)	23 (17, 10.6%)	10 (8, 5.0%)	38 (30, 6.3%)	15 (11, 2.3%)
Pneumonia	24 (19, 6.0%)	19 (15, 4.7%)	12 (9, 5.6%)	11 (9, 5.6%)	36 (28, 5.9%)	30 (24, 5.0%)
Device stimulation issue	19 (16, 5.0%)	4 (4, 1.3%)	16 (12, 7.5%)	2 (2, 1.3%)	35 (28, 5.9%)	6 (6, 1.3%)
Ventricular tachycardia	20 (17, 5.3%)	4 (4, 1.3%)	11 (9, 5.6%)	5 (3, 1.9%)	31 (26, 5.4%)	9 (7, 1.5%)
Chest pain	18 (16, 5.0%)	7 (7, 2.2%)	10 (9, 5.6%)	6 (6, 3.8%)	28 (25, 5.2%)	13 (13, 2.7%)
Device dislocation	11 (11, 3.5%)	11 (11, 3.5%)	11 (8, 5.0%)	10 (7, 4.4%)	22 (19, 4.0%)	21 (18, 3.8%)
Bronchitis	14 (14, 4.4%)	6 (6, 1.9%)	8 (7, 4.4%)	3 (2, 1.3%)	22 (21, 4.4%)	9 (8, 1.7%)
Chronic obstructive pulmonary disease	8 (6, 1.9%)	7 (5, 1.6%)	13 (8, 5.0%)	7 (4, 2.5%)	21 (14, 2.9%)	14 (9, 1.9%)
Urinary tract infection	11 (10, 3.1%)	6 (6, 1.9%)	10 (9, 5.6%)	4 (4, 2.5%)	21 (19, 4.0%)	10 (10, 2.1%)
Renal failure acute	12 (10, 3.1%)	9 (7, 2.2%)	7 (7, 4.4%)	5 (5, 3.1%)	19 (17, 3.6%)	14 (12, 2.5%)
Dyspnoea	8 (8, 2.5%)	1 (1, 0.3%)	9 (8, 5.0%)	1 (1, 0.6%)	17 (16, 3.3%)	2 (2, 0.4%)
Hypotension	11 (11, 3.5%)	1 (1, 0.3%)	5 (5, 3.1%)	1 (1, 0.6%)	16 (16, 3.3%)	2 (2, 0.4%)
Anaemia	8 (8, 2.5%)	6 (6, 1.9%)	6 (6, 3.8%)	5 (5, 3.1%)	14 (14, 2.9%)	11 (11, 2.3%)
Renal failure	9 (8, 2.5%)	6 (5, 1.6%)	3 (3, 1.9%)	2 (2, 1.3%)	12 (11, 2.3%)	8 (7, 1.5%)
Atrial flutter	9 (8, 2.5%)	5 (5, 1.6%)	3 (3, 1.9%)	1 (1, 0.6%)	12 (11, 2.3%)	6 (6, 1.3%)
Gastrointestinal haemorrhage	5 (5, 1.6%)	5 (5, 1.6%)	6 (4, 2.5%)	6 (4, 2.5%)	11 (9, 1.9%)	11 (9, 1.9%)
Sepsis	9 (7, 2.2%)	9 (7, 2.2%)	2 (2, 1.3%)	2 (2, 1.3%)	11 (9, 1.9%)	11 (9, 1.9%)
Dehydration	6 (6, 1.9%)	5 (5, 1.6%)	4 (4, 2.5%)	2 (2, 1.3%)	10 (10, 2.1%)	7 (7, 1.5%)
Ventricular fibrillation	5 (5, 1.6%)	1 (1, 0.3%)	5 (5, 3.1%)	1 (1, 0.6%)	10 (10, 2.1%)	2 (2, 0.4%)
Upper respiratory tract infection	4 (2, 0.6%)	0 (0, 0.0%)	6 (4, 2.5%)	0 (0, 0.0%)	10 (6, 1.3%)	0 (0, 0.0%)
Diarrhea	5 (5, 1.6%)	2 (2, 0.6%)	4 (2, 1.3%)	1 (1, 0.6%)	9 (7, 1.5%)	3 (3, 0.6%)
Hyperglycaemia	4 (4, 1.3%)	4 (4, 1.3%)	4 (4, 2.5%)	4 (4, 2.5%)	8 (8, 1.7%)	8 (8, 1.7%)
Angina pectoris	6 (6, 1.9%)	3 (3, 0.9%)	2 (2, 1.3%)	2 (2, 1.3%)	8 (8, 1.7%)	5 (5, 1.0%)
Implant site infection	3 (3, 0.9%)	1 (1, 0.3%)	5 (5, 3.1%)	4 (4, 2.5%)	8 (8, 1.7%)	5 (5, 1.0%)
Intracardiac thrombus	4 (4, 1.3%)	1 (1, 0.3%)	4 (4, 2.5%)	3 (3, 1.9%)	8 (8, 1.7%)	4 (4, 0.8%)
Non-cardiac chest pain	6 (6, 1.9%)	2 (2, 0.6%)	2 (2, 1.3%)	1 (1, 0.6%)	8 (8, 1.7%)	3 (3, 0.6%)

	Events	Complications[1]	Events	Complications	Events	Complications
Coronary artery disease	7 (7, 2.2%)	7 (7, 2.2%)	0 (0, 0.0%)	0 (0, 0.0%)	7 (7, 1.5%)	7 (7, 1.5%)
Hyperkalaemia	4 (4, 1.3%)	2 (2, 0.6%)	3 (3, 1.9%)	1 (1, 0.6%)	7 (7, 1.5%)	3 (3, 0.6%)
Implant site haematoma	3 (3, 0.9%)	2 (2, 0.6%)	4 (4, 2.5%)	1 (1, 0.6%)	7 (7, 1.5%)	3 (3, 0.6%)
Device pacing issue	4 (4, 1.3%)	0 (0, 0.0%)	3 (3, 1.9%)	1 (1, 0.6%)	7 (7, 1.5%)	1 (1, 0.2%)
Syncope	3 (3, 0.9%)	0 (0, 0.0%)	4 (3, 1.9%)	1 (1, 0.6%)	7 (6, 1.3%)	1 (1, 0.2%)
Oversensing	4 (4, 1.3%)	0 (0, 0.0%)	3 (3, 1.9%)	0 (0, 0.0%)	7 (7, 1.5%)	0 (0, 0.0%)
Acute myocardial infarction	4 (4, 1.3%)	4 (4, 1.3%)	2 (2, 1.3%)	2 (2, 1.3%)	6 (6, 1.3%)	6 (6, 1.3%)
Cellulitis	3 (3, 0.9%)	3 (3, 0.9%)	3 (3, 1.9%)	3 (3, 1.9%)	6 (6, 1.3%)	6 (6, 1.3%)
Gastritis	3 (3, 0.9%)	2 (2, 0.6%)	3 (3, 1.9%)	2 (2, 1.3%)	6 (6, 1.3%)	4 (4, 0.8%)
Abdominal pain	3 (3, 0.9%)	1 (1, 0.3%)	3 (3, 1.9%)	2 (2, 1.3%)	6 (6, 1.3%)	3 (3, 0.6%)
Back pain	2 (2, 0.6%)	1 (1, 0.3%)	4 (4, 2.5%)	1 (1, 0.6%)	6 (6, 1.3%)	2 (2, 0.4%)
Supraventricular tachycardia	6 (6, 1.9%)	2 (2, 0.6%)	0 (0, 0.0%)	0 (0, 0.0%)	6 (6, 1.3%)	2 (2, 0.4%)
Dizziness	5 (5, 1.6%)	0 (0, 0.0%)	1 (1, 0.6%)	0 (0, 0.0%)	6 (6, 1.3%)	0 (0, 0.0%)
Sinusitis	4 (4, 1.3%)	0 (0, 0.0%)	2 (2, 1.3%)	0 (0, 0.0%)	6 (6, 1.3%)	0 (0, 0.0%)
Cardiac arrest	4 (4, 1.3%)	4 (4, 1.3%)	1 (1, 0.6%)	1 (1, 0.6%)	5 (5, 1.0%)	5 (5, 1.0%)
Transient ischaemic attack	3 (3, 0.9%)	2 (2, 0.6%)	2 (2, 1.3%)	2 (2, 1.3%)	5 (5, 1.0%)	4 (4, 0.8%)
Deep vein thrombosis	3 (3, 0.9%)	2 (2, 0.6%)	2 (2, 1.3%)	1 (1, 0.6%)	5 (5, 1.0%)	3 (3, 0.6%)
Implant site pain	4 (4, 1.3%)	3 (3, 0.9%)	1 (1, 0.6%)	0 (0, 0.0%)	5 (5, 1.0%)	3 (3, 0.6%)
Diabetes mellitus	3 (3, 0.9%)	2 (2, 0.6%)	2 (2, 1.3%)	0 (0, 0.0%)	5 (5, 1.0%)	2 (2, 0.4%)
Hypertension	2 (2, 0.6%)	1 (1, 0.3%)	3 (3, 1.9%)	1 (1, 0.6%)	5 (5, 1.0%)	2 (2, 0.4%)
Orthostatic hypotension	4 (4, 1.3%)	2 (2, 0.6%)	1 (1, 0.6%)	0 (0, 0.0%)	5 (5, 1.0%)	2 (2, 0.4%)
Chest discomfort	4 (4, 1.3%)	1 (1, 0.3%)	1 (1, 0.6%)	0 (0, 0.0%)	5 (5, 1.0%)	1 (1, 0.2%)
Nasopharyngitis	3 (3, 0.9%)	0 (0, 0.0%)	2 (2, 1.3%)	0 (0, 0.0%)	5 (5, 1.0%)	0 (0, 0.0%)

[1] An adverse event is considered a complication when it a) results in death, b) involves any termination of significant device function, or c) required an invasive intervention

Adverse events in literature

Potential adverse events and patient complications associated with the implantation of CRT systems have been documented in various literature articles.

1. Ahsan, Syed, et al., Early and Late Complications of Cardiac Resynchronization Therapy: A Single Centre Experience Over 8 Years of 402 Patients; Circulation. 2009; 120:S787

Retrospective data were analyzed for all acute and chronic complications occurring over 490 consecutive CRT device procedures in 402 patients, from 2000 through 2008. Associated complications were reported by timeframe.

Complication Type	Early (<90 days) n	Late (>90 days) n	Mean time to late complication in months
Pneumothorax	2	0	-
Phrenic Nerve stimulation requiring revision	3	4	11.4 (±8)
Infection	7	7	14.9 (±11)
Noise on RV/RA lead	1	3	17.0 (±22)
Box Migration	2	1	15.0
RV/RA Lead Fracture	1	1	33.1
LV Lead Fracture	0	3	12.4 (±2)
Death	1		-
Lead Erosion	3	0	-
RV/RA Lead Displacement	5	6	4.9 (±2)
LV Lead Displacement	5	5	6.8 (±4)
Inability to implant LV lead	20	0	-
TOTAL	46 (9.4%)	32 (6.5%)	

2. Dickstein, Kenneth, et al. The European Cardiac Resynchronization Therapy Survey; European Heart Journal (2009) 30, 2450–2460

The primary aim of this survey is to describe current European practice associated with CRT implantations. A total of 140 centers from 13 European countries contributed data from consecutive patients successfully implanted with a CRT device with or without an ICD between November 2008 and June 2009. The total number of patients enrolled was 2438.

Event	**%**
Peri-procedural complications	10
Bleeding	1
Pocket haematoma	3
Pneumothorax	1
Pericardial tamponade	0.3
Coronary sinus dissection	1
Phrenic nerve pacing	2
Lead dislocation	3
Post –implantation device related complications	4
Lead displacement	2
Lead malfunction	0
Phrenic nerve stimulation	2

3. Romeyer-Bouchard, Cecile, et al. Prevalence and risk factors related to infections of cardiac resynchronization therapy devices; European Heart Journal (2010) 31, 203–210

This study included an evaluation of the prevalence of CRT device-related infections (DRI). Between January 2001 and May 2007, the study included CRT implantations performed in 303

patients (247 men, 82%). Thirteen patients developed a DRI: endocarditis in four, pocket erosion in three, pocket abscess in five and septicemia in one. The prevalence of DRI was 4.3 at 2.6 years (1.7% per year incidence). The study results showed the risk of CRT infection is twice that of a standard pacemaker implant risk.

4. Lee DS, Krahn AD, Healey JS, et al. Evaluation of early complications related to de novo cardioverter defibrillator implantation. J Am Coll Cardiol 2010;55:774-82.

The Ontario ICD Database was a prospective, multi-center registry of 3,340 new ICD implants and major complications were reported in 4.1% of procedures. The events most frequently experienced are displayed in Table 13.

Table 13 Frequent Major and Minor Complications

	Number of Occurrences	Number of Patients Affected	% Patients With Complications
Major complications*			
Lead replacement	94	90	2.7
Lead repositioning	67	67	2.0
Pocket infection requiring debridement	40	32	1.0
Electrical storm	33	29	0.9
Lead dislodgement with repositioning	29	28	0.8
Lead extraction	23	23	0.7
Pulmonary edema	24	21	0.6
Myocardial perforation	15	14	0.4
Pneumothorax/hemothorax	13	13	0.4
Post-implant myocardial infarction	8	8	0.2
Sepsis	8	7	0.2
Cardiogenic shock	7	6	0.2
Minor complications*			
Incisional infection	38	35	1.1
Pocket hematoma	41	33	1.0
Lead dislodgement not repositioned†	28	27	0.8
Subclavian vein thrombosis	8	8	0.2

*Only complications with frequency >5 are shown.

†Lead dislodgement without replacement or repositioning.

5. American College of Cardiology (ACC) National Cardiovascular Data Registry ICD Report 1st Quarter 2010 (30Aug2010)

The American College of Cardiology (ACC) National Cardiovascular Data Registry (ACC-NCDR™) contains a suite of several hospital-based cardiovascular data registries including the ICD Registry™. The ICD Registry allows tracking of implantable cardioverter defibrillator procedures within the United States including associated adverse events.

Table 14 Bi-V ICD Adverse Events – ACC-NCDR ICD Quarterly Report

Registry Variables for Bi-V Systems	Primary Prevention Cumulative To Date (N = 183259) n (%)	Secondary Prevention Cumulative To Date (N = 29815) n (%)	Total Cumulative To Date (N = 213074) n (%)
AV Fistula	9 (<0.005)		9 (<0.005)
CVA/Stroke	111 (0.06)	25 (0.08)	136 (0.06)
Cardiac Arrest	573 (0.31)	184 (0.62)	757 (0.36)
Cardiac Perforation	142 (0.08)	24 (0.08)	166 (0.08)
Cardiac Valve Injury	2 (<0.005)		2 (<0.005)
Conduction Block	73 (0.04)	5 (0.02)	78 (0.04)
Coronary Venous Dissection	363 (0.2)	51 (0.17)	414 (0.19)
Drug Reaction	167 (0.09)	24 (0.08)	191 (0.09)
Hematoma	1907 (1.04)	245 (0.82)	2152 (1.01)
Hemothorax	192 (0.1)	21 (0.07)	213 (0.1)
Infection Related to Device	52 (0.03)	15 (0.05)	67 (0.03)
Lead Dislodgement	2338 (1.28)	317 (1.06)	2655 (1.25)
MI	48 (0.03)	7 (0.02)	55 (0.03)
Pericardial Tamponade	183 (0.1)	21 (0.07)	204 (0.1)
Peripheral Embolus	57 (0.03)	15 (0.05)	72 (0.03)
Peripheral Nerve Injury	7 (<0.005)	2 (0.01)	9 (<0.005)
Phlebitis - Deep	56 (0.03)	12 (0.04)	68 (0.03)
Phlebitis - Superficial	48 (0.03)	18 (0.06)	66 (0.03)
Pneumothorax	795 (0.43)	113 (0.38)	908 (0.43)

Registry Variables for Bi-V Systems	Primary Prevention Cumulative To Date (N = 183259) n (%)	Secondary Prevention Cumulative To Date (N = 29815) n (%)	Total Cumulative To Date (N = 213074) n (%)
TIA	47 (0.03)	5 (0.02)	52 (0.02)

Additional Adverse Events

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

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

APPENDIX B. CLINICAL INVESTIGATION PLAN SIGNATURE PAGE (IF APPLICABLE)

Mid-Q Response Study

The Mid-Q Response study is a prospective, randomized, controlled, interventional, single-blinded, multi-center, post-market, Cardiac Resynchronization Therapy (CRT) in heart failure (HF) clinical study performed in Asian countries. The study is being conducted to test the hypothesis that market released CRT devices which contain the AdaptivCRT® (aCRT) algorithm have a superior outcome compared to standard CRT devices in CRT indicated patients with normal AV conduction and left bundle branch block (LBBB).

Clinical Investigation Plan Version 2.0, 29-DEC-2020.

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

Hospital		
Title, First and Last Name	**Signature**	**Date**

18. Version History

Version	Summary of Changes	Author(s)/Title
1.0 28-MAR-2019	• Not Applicable, New Document	Loes Schoenmakers, Clinical Research Specialist Lidwien Vainer, Principal Clinical Research Specialist Mireille van Ginneken, Principal Clinical Research Specialist Bart Gerritse, Senior Principal Statistician
2.0 29-DEC-2020	• CIP template transitioned from v A to v B; • Minor editorial updates; • Updated Lead Principal Investigator address; • Updated Table 1: Study sponsor contact information; • Removed "Cognizant Technology Solutions" as CRO from Table 2: CRO and Core Laboratory information; • Updated synopsis to reflect updates to the CIP; • Approximate number of centers increased from 55 to 60 in section 3.3; • Section 4.3 updated to include an additional ancillary objective to characterize reverse remodeling measured via echocardiography; • Section 5.1 language updated to accurately capture enrollment start and to extend study duration as necessary due to the unforeseen impact of COVID-19;	Methee Schreuder, Clinical Research Specialist Lidwien Vainer, Clinical Research Manager Bart Gerritse, Sr. Principal Statistician Kazuhiro Hidaka, Sr. Clinical Research Specialist

	• Section 6.6 updated to include CareLink SmartSync™ Device Manager as a Medtronic CareLink programmer; • Section 6.7 updated to include MyCareLink Relay™ Home Communicator and MyCareLink Heart™ mobile app as suitable Medtronic CareLink home monitors; • Section 7.3 updated to accept ECGs up to 50 days prior to enrollment; • Section 8.2 updated to clarify that a Google Chrome and/or Safari are also suitable for data entry; • Table 4 (Section 8.3) updated to include Echocardiography data collection; • Sections 8.6 and 8.7 updated to clarify that baseline data should reflect pre-implant data when a patient is enrolled post-implant; • Echocardiography data collection (only if standard of care) added to sections 8.6 (Baseline) and 8.9.1 (3, 6, and 12 month Follow-up visits); • Section 8.8.1 updated to clarify that deviations from programming recommendations are not considered study deviations; • Section 8.10 updated to include .pkg files as an acceptable device interrogation file; • Row added to Table 9: Adverse Event classification responsibilities to capture sponsor responsibilities for death classifications; • Section 13.1 updated to remove reference to ISO 14155:2011; • Since a Mid-Q Response Publication Plan has been finalized, Appendix A was removed.	