Medtronic

AdaptResponse

Clinical Investigation Plan

Version 2.0

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Regional Sponsors and Contacts		
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SPONSOR CONTACT INFORMATION

Medtronic, Inc. is sponsoring the AdaptResponse trial. 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	
Worldwide clinical study leader Lidwien Vainer, Sr. Clinical Research Specialist Phone: [redacted] Fax: [redacted] lidwien.vainer@medtronic.com	US / Canada [redacted] Phone: [redacted] Fax: [redacted] scott.a.sarazin@medtronic.com
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Taiwan [redacted]	*India* [redacted]
Latin America [redacted]	*Korea* [redacted]
Study monitors and contacts	
Worldwide monitoring leader [redacted]	US/Canada monitoring leader [redacted]

Name and title of persons authorized to sign protocol and amendments for the sponsor:
This information may be subject to change during the course of the clinical study. Updates will be sent to the centers as needed.

Dan Schaber, Vice President Heart Failure Clinical Research

Jeff Stein, Clinical Biostatistics Director responsible for oversight of the statistical aspects of the study

Helma van den Berg, Sr Regulatory Affairs Specialist

Name, title, address and contact number of the sponsor's medical expert for the study:
This information may be subject to change during the course of the clinical study. Updates will be sent to the centers as needed.

David Steinhaus, M.D., VP & GM Heart Failure
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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
Cognizant Technology Solutions 500 Frank W. Burr Blvd. Teaneck, NJ 07666 United States Direct Phone: (201) 801-0233 Direct Fax: (201) 801-0243	• Development of study electronic case report forms, edit checks, and study management reports. • Review of electronic case report forms, management of discrepancies, and coding of medications and deviations.
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

Table 3 Steering Committee contact information

Committee Member	Contact information
Bruce Wilkoff, MD Chair, Steering Committee	Address: The Cleveland Clinic Foundation, 9500 Euclid Avenue, Desk F15, Cleveland, Ohio, 44195 Telephone: [redacted] Fax: [redacted] Email: wilkofb@ccfr.org Professional Position: Director of Cardiac Pacing and Tachyarrhythmia Devices
Gerasimos Filippatos, MD Co-chair, Steering Committee	Address: University of Athens, Department of Cardiology, Heart Failure Unit 28 Doukissis Plakentias, 11523 Athens, Greece Telephone: [redacted] Email: geros@otenet.gr Professional Position: Head of Heart Failure Unit, Department of Cardiology, Athens University Hospital
David Birnie, MD	Address: University of Ottawa Heart Institute, 40 Ruskin Street, Ottawa, Ontario K1Y 4W7 Telephone: [redacted] Fax: +[redacted] Email: dbirnie@ottawaheart.ca Professional Position: Staff Cardiac Electrophysiologist Director, Arrhythmia Service, University of Ottawa Heart Institute
Michael Gold, MD	Address: Medical University of South Carolina, 25 Courtenay Drive Suite 7031, Charleston, SC 29425-8911 Telephone: [redacted] Fax: [redacted] Email: goldmr@musc.edu Professional Position: Director, Division of Cardiology, Medical University of South Carolina
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Kengo Kusano, MD	Address: National Cerebral and Cardiovascular Center 5-7-1 Fujishiro-dai, Suita, Osaka 565-8565, Japan. Telephone: [redacted] Fax: [redacted] Email: kusanokengo@hotmail.com Professional Position: Director, Division of Arrhythmia and Electrophysiology, Department of Cardiovascular Medicine,
Christophe Leclercq, MD	Address: University of Rennes, CHU Pontchaillou, Rue Henri le Guilloux 2, 35033, Rennes, Cédex 09, France Telephone [redacted] Fax: [redacted] Email: christophe.leclercq@chu-rennes.fr Professional Position: Professor of Cardiology

Wilfried Mullens, MD	Address: Ziekenhuis Oost-Limburg, Schiepse Bos 6, 3600, Genk, Belgium Telephone: [redacted] Fax: [redacted] Email: wilfried.mullens@gmail.com Professional Position: Professor Cardiologist Heart Failure

1. INTRODUCTION

1.1 Study purpose and description

Medtronic, Inc. is sponsoring the AdaptResponse study; a prospective, randomized, controlled, interventional, single-blinded, multi-center, post-market, global Cardiac Resynchronization Therapy (CRT) in heart failure (HF) clinical study. The purpose of this clinical study is 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 atrio-ventricular (AV) conduction and left bundle branch block (LBBB).

To assess the superiority of CRT devices containing the aCRT algorithm, the primary objective of the AdaptResponse study is to test the hypothesis that AdaptivCRT® reduces the incidence of the combined endpoint of all-cause mortality and intervention for heart failure decompensation, compared to standard CRT therapy, in patients with a CRT indication, LBBB and normal AV conduction. The secondary endpoints will include the components of the primary endpoint, Clinical Composite Score (CCS) and time to atrial fibrillation (AF).

Intervention for heart failure decompensation (HF event) is defined as an event requiring *invasive intervention (i.e. IV diuretics, ultrafiltration, or equivalent) or inpatient hospitalization.*

Following enrollment and baseline assessment, eligible subjects will be implanted with a CRT system containing the aCRT algorithm and randomized in a 1:1 fashion to either treatment (aCRT ON, Adaptive Bi-V and LV) or control (aCRT OFF, Nonadaptive CRT) groups. All subjects, independent of randomization assignment, will receive a CRT system. Study subjects will be followed until the minimally required number of endpoint events is reached or until study closure, whichever occurs first.

1.2 Study scope

The study is expected to be conducted at approximately 250 centers including Australia, Canada, Europe, Russia, India, Japan, Korea, Latin America, Middle East, Taiwan and the US. Approximately 3500 subjects will be randomized in the study. Proposed study start date is 01 June 2014.

To ensure a widespread distribution of data to minimize bias in the study results, the maximum number of subjects randomized at a single center is 200 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.

The study utilizes an “event-driven” study design. Enrollment will end when approximately 3500 patients are randomized or there is reasonable certainty that the required number of events will be reached, as determined by the Data Monitoring Committee (DMC), whichever occurs first. The study may be stopped early if the average enrollment rate is less than 0.25 subjects enrolled per active center per month over any 6 consecutive months during the study. The study may also be stopped on recommendation of the DMC, see stopping guidelines in section 10.2. Study subjects will be followed until official study closure defined as when requirements have

been satisfied per the Clinical Investigation Plan (CIP) and/or a decision by Medtronic, Ethics Committee, or regulatory authority, whichever occurs first.

Accordingly, the expected total study duration is approximately 8 years, representing approximately 4 years of enrollment and approximately 4 years of subject follow-up. The actual duration of the study will depend on the accrual of 1100 primary endpoint events. The duration of individual subject participation will vary based on timing of their enrollment; however, at a minimum, participation of an individual subject is expected to be 30 months unless early study exit occurs.

1.3 Study oversight

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

The **Data Monitoring Committee** (DMC) provides oversight for the overall conduct of the study, and specifically for subject safety and scientific validity. The DMC will review interim results of the study.

The **Endpoint Adjudication Committee** (EAC) will adjudicate the HF- and AF related endpoints.

The **ECG Core Laboratory** will review all baseline ECGs for presence of LBBB and normal AV conduction. Feedback on accuracy rates will be presented to the Steering Committee and to the sites.

2. BACKGROUND AND JUSTIFICATION

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 allow 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]

Additionally, in an unpublished analysis on extended follow-up duration in patients with normal AV conduction, [redacted]. 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.[14]

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.[23]

Table 4 Adaptive CRT study post-hoc sub-analysis results

CRT Response[12] **Improvement in Packer Clinical Composite Score**	**12% higher response***
HF Hospitalizations or Death[14]	**Reduced risk***
30-day Readmissions[23]	**59% reduction in odds**
Atrial Fibrillation[15,24] **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 AF (HR=0.54 [95% CI 0.31-0.93]; p=0.03) and aCRT patients without history of AF were less likely to develop persistent AF (HR=0.44 [95% CI 0.19-1.03]; p=0.05).[15]

Birnie D. et al compared in a sub-analysis of the Adaptive CRT study, 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. [24]

Further investigation of clinical outcomes over longer follow-up is needed to support the benefit of aCRT. Therefore the AdaptResponse study is 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.[25]

3. SYSTEM DESCRIPTION AND INTENDED USE

The study will be conducted 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.

3.1 Medtronic CRT-D and CRT-P devices

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

3.2 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.

3.3 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.

3.4 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.

3.5 Medtronic CareLink programmer

The Medtronic CareLink Model 2090 Programmer and software are used to program the CRT device. The programming head will be needed for communications with this device. Programmers from other manufacturers are not compatible with Medtronic devices.

3.6 Medtronic CareLink Home Monitor 2490C and Network

The CareLink Monitor Model 2490C is an external monitor that is indicated for use in the transfer of patient and device data from implanted Medtronic devices. The CareLink Monitor Model 2490C 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 Monitor 2490C is not a programmer and cannot be used to program implanted device parameters. CareLink 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 Monitor 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.

3.7 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.

4. REGULATORY COMPLIANCE

The AdaptResponse clinical study is a prospective, randomized, controlled, interventional single-blinded, multi-center, post-market global study. This 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 AdaptResponse clinical study is designed with the good clinical practice (GCP) principles outlined in ISO 14155:2011 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 (PIC) process, MEC/IRB/HREC (all henceforth referred to as an ”Ethics Committee”) approval, study training, clinical trial registration, risk benefit assessment, and publication policy.

In Europe, local laws and regulations (including Declaration of Helsinki 2013) will be followed

In Russia, local laws and regulations will be followed.

In the US, the study will be conducted in compliance with 21 CFR Parts 11, 50 and 56.

In Australia, applicable local regulations will be followed.

In Japan, the study will be conducted in compliance with the Ethical Guidelines for Medical and Health Research Involving Human Subjects and the Clinical Study Act.

In India, applicable India laws and regulations will be followed.

In Latin America, local laws will be complied with.

In Taiwan and Korea, applicable laws and regulations will be followed.

In Canada, the Canadian Medical Devices Regulations, 1998 (SOR/98-282), and the Canadian Regulatory Guidelines for Mandatory Problem Reporting of Medical Devices, 2011 (H164-145/2011E) will be followed.

The study has been publicly registered in accordance with the 2007 Food and Drug Administration Amendments Act (FDAA) and Declaration of Helsinki on http://clinicaltrials.gov (PL 110-85, Section 810(a)).

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

- Medtronic
- Steering Committee
- 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.

5. METHODOLOGY

5.1 Study objectives

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

5.1.1 Primary objective

The primary objective of the AdaptResponse Study is to test the hypothesis that AdaptivCRT® reduces the incidence of the combined endpoint of all-cause mortality and intervention for heart failure decompensation, compared to standard CRT therapy, in patients with a CRT indication, LBBB and normal AV conduction. Intervention for heart failure decompensation (HF event) is defined as an event requiring "*invasive intervention (i.e. IV diuretics, ultrafiltration, or equivalent) or inpatient hospitalization".*

The study will be event driven, comparing the rate of first events. The study will continue until a predetermined number of events has been observed, unless the DMC advises to stop earlier.

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.

5.1.2 Secondary objectives

- To test the hypothesis that aCRT ON reduces all-cause mortality compared to aCRT OFF.
- To test the hypothesis that aCRT ON reduces the rate of intervention for heart failure decompensation compared to aCRT OFF.
- 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.
- To test the hypothesis that aCRT ON reduces the incidence of AF compared to aCRT OFF.
- To test the hypothesis that the change in quality of life, measured by the KCCQ, in the aCRT ON group is better than the change in the aCRT OFF group.
- To test the hypothesis that the change in health outcome, measured by the EQ-5D, in the aCRT ON group is better than the change in the aCRT OFF group.
- To test the hypothesis that aCRT reduces the incidence of all-cause re-admissions after a heart failure (HF) admission within 30-days of the index event.
- To assess cost-effectiveness of CRT devices with the aCRT algorithm relative to traditional CRT devices.

5.1.3 Ancillary objectives

- To test the hypothesis that the change in NYHA class in the aCRT ON group is better than the change in the aCRT OFF group.
- To test the hypothesis that the change in BNP/NT-proBNP in the aCRT ON group is better than the change in the aCRT OFF group.
- To characterize cardiovascular adverse events that occur in the aCRT ON and aCRT OFF groups.
- To test the hypothesis that aCRT reduces the incidence of all-cause re-admissions after an all-cause admission within 30-days of the index event.
- To characterize occurrence of spontaneous VT/VF episodes and compare between the aCRT ON and aCRT OFF groups.

5.2 Primary endpoint

5.2.1 Primary endpoint definition

Intervention for heart failure decompensation (HF event) is defined as an event requiring "invasive intervention (i.e. IV diuretics, ultrafiltration, or equivalent) or inpatient hospitalization".

The primary endpoint is the composite of all-cause death and any intervention for heart failure decompensation as adjudicated by the EAC. The date of the endpoint will be the date of death or the date of initiation of treatment for decompensation as determined by the EAC.

The EAC will determine if an endpoint has been met. Sites may adhere to their standard practice diagnosing heart failure, but are required to report all diagnostic assessments, tests and procedures done with supporting material as appropriate to allow the EAC to adjudicate.

5.2.2 Endpoint Adjudication Committee

All potential endpoints will be reviewed by the Endpoint Adjudication Committee (EAC). Please refer to Appendix D for an overview of the EAC's tasks.

5.3 Subject selection criteria

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

No study-specific procedures may be performed prior to obtaining written patient informed consent.

5.3.1 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 Patient Informed Consent (PIC) Form.
- 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 (within 30 days prior to enrollment). Criteria[16] for complete LBBB must include:
        - Intrinsic QRS duration ≥140 ms (men) or ≥130 ms (women),
        - 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 less than or equal to 200ms (within 30 days prior to enrollment).
    - Left ventricular ejection fraction less than or equal to 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 Aldosterone Antagonist.

5.3.2 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).
- Subject is not expected to remain available for at least 2 years 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.

5.4 Randomization

Subjects will undergo a CRT implant procedure after completion of the baseline assessment if all inclusion and none of the exclusion criteria are met. Subjects who have a successful CRT implant will be randomized within 7 days of completing the implant procedure. Subjects will be randomized in a 1:1 fashion to treatment (aCRT ON, with AdaptivCRT programmed to “Adaptive Bi-V and LV”) or control (aCRT OFF, with AdaptivCRT programmed to “Nonadaptive CRT”) group. Subjects will be randomized using the randomization schedule determined by a Medtronic statistician. The randomization schedule will be stratified by center and by NYHA class. Centers will receive this assignment electronically in the study database from Medtronic upon completion of the randomization case report form.

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.

5.5 Crossover

Crossovers significantly increase the required number of events and therefore 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.

5.6 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.

The Data Monitoring Committee (DMC) will regularly review summarized adverse event data to address potential safety issues. The DMC will be unblinded to subject treatment assignments. However; the EAC will be blinded to the treatment designation when reviewing case files, wherever reasonably achievable.

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.

5.7 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 at baseline to confirm eligibility for enrollment with defined inclusion/exclusion criteria prior to implant and 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.
- Subject demographics will be collected at baseline and differences that may affect primary endpoints will be identified.
- To ensure a widespread distribution of data between centers, the maximum number of randomized subjects allowed per center is no more than 200.
- All implanters in the study will be experienced in the implant of CRT devices.
- 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.
- HF events and deaths will be adjudicated by an independent and blinded EAC.
- An independent DMC will review endpoint and other data to monitor the overall integrity of the study.

- 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 5.5.
- 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 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. 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

6.1 Site activation

During the activation process (prior to enrollment of subjects in the study), Medtronic will train site personnel on the CIP, relevant standards and regulations, informed consent process, written Clinical Trial Agreements (CTAs) 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 PIC Form
- 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 coordinator 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
- Site initiation visit, where required

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.

6.2 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 for data entry (version 9 or higher)
- 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.

6.3 Data collection

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 5.

Table 5 Data collection and study procedure requirements at subject visits

Study Procedure	Enrollment	Baseline	Implant	Randomization	3 and 6 Months	12, 18, 24 Months	Every 6 Months	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	x	x	
Blood***		x			x	x	x	
Cardiovascular (CV) medications****		x			x	x	x	x
Medical history		x						
Current heart failure symptoms status		x			x	x	x	x
Final implanted system configuration and LV lead placement optimization method			x					
Device interrogation (and CareLink data if available)			x	x	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 (EQ-5D and KCCQ)		x			x	x		
NYHA assessment		x*			x	x	x	
Patient global assessment					x			
Vital status								x
Crossover				As it occurs				
System modifications			As they occur					
Adverse events (AEs)	As they occur							
Healthcare utilizations	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

****Including daily dose at baseline of guideline recommended medication, including but not limited to the following medications: diuretics, ß-blockers, ACE inhibitors, ARBs, MRAs, ARNi, If-channel blockers, cardiac glycosides

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

6.4 Patient informed consent process

Patient informed consent (PIC) 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 Patient Consent and a/an Authorization to Use and Disclose Personal Health Information/Research Authorization/HIPAA/other privacy language as required by local law that has been approved by the study center's Ethics Committee and signed and personally dated by the subject (or their legally authorized representative or guardian, per 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 study center's applicable Ethics Committee will be required to approve the PIC Form, and Authorization to Use and Disclose Personal Health Information/Research Authorization/HIPAA/other privacy language 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 PIC Form 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, patient informed consent must be obtained from the subject (or their legally authorized representative or guardian, per 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 PIC Form and Authorization to Use and Disclose Personal Health Information/Research Authorization/HIPAA/other privacy language 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 informed consent form 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 (not applicable in US and Canada)
- 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, the Authorization to Use and Disclose Personal Health Information/Research Authorization/HIPAA/other privacy language and any other written information, 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 PIC Form 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 patient informed consent. The PIC shall be obtained through a supervised oral process. An independent witness must be present throughout the process. The PIC 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 PIC 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 PIC Form as well. The PIC Form should document the method used for communication with the prospective subject and the specific means by which the prospective subject communicated agreement to participate in the study.

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

The PIC Form (in Japan, the signature page only) and Authorization to Use and Disclose Personal Health Information/Research Authorization/HIPAA/other privacy language 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 PIC Form 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 PIC Form 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.

6.5 Enrollment

A subject is considered enrolled when the consent process has been finalized. Enrollment can be a stand-alone visit or can occur on the same day as the baseline visit.

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.

6.6 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. 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)
- LVEF (unless documented within 180 days prior to enrollment)
- Quality of Life and Utility Measures
    - Kansas City Cardiomyopathy Questionnaire (KCCQ)

    - EQ-5D
- Blood measurements (only collected when standard of care)
- Report AEs, Study Deviations and Healthcare Utilizations (as they occur)

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

6.6.1 Baseline ECG

LBBB needs to be diagnosed using the Strauss criteria[16]. Criteria for complete LBBB should include QRS duration ≥140 ms (men) or ≥130 ms (women), 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 must be sent to the ECG Core Laboratory for review. Details on the review process will be provided under separate cover.

6.7 Implant

The implant visit 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. 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, Health Care Utilizations, 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 will be collected following the implant procedure, 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.

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 classified. Subjects experiencing unsuccessful implant procedures must be followed for 30 days

[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.

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.

6.7.1 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.

6.7.2 CRT Optimization

Optimization of the AV-VV intervals may be completed and documented. Additional features to optimize CRT may be used upon market commercialization. Any deviation from the programming requirements outlined in section 6.9.1 will constitute a study deviation.

6.8 Randomization

Subjects will be assigned to a treatment at random during the randomization visit, which must occur within 7 days after a successful implant. 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, Crossovers, and Healthcare Utilizations (as they occur)

If randomization does not occur within 37 days after enrollment, verification of all inclusion and all exclusion criteria must be repeated before randomization.

6.8.1 Programming Requirements and Recommendations

The following programming requirements and recommendations are applicable to study subjects, according to their respective randomization assignment.

Table 6 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]	No requirement
SAV	[redacted]	Per preferred in-office /physician method
PAV	[redacted]	Per preferred in-office /physician method
VV Delay	[redacted]	Per preferred in-office /physician method
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]

[ii] For CRT devices with programmable VV Delay in Adaptive mode: Program to Auto recommended

6.9 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 7 and are based on days post-randomization.

Required visits post-randomization include follow-up visits at 3 months, 6 months, and every 6 months thereafter until study closure. During these visits information will be collected about adverse events (AE), health care utilization (HCU), Cardiovascular (CV) medications, and Heart Failure (HF) assessment, as well as additional information and procedures which vary by visit (see Table 5). Quality of Life (QoL) and Health outcome will be addressed using the KCCQ and the EQ-5D questionnaires, 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 1: Visit Timeline

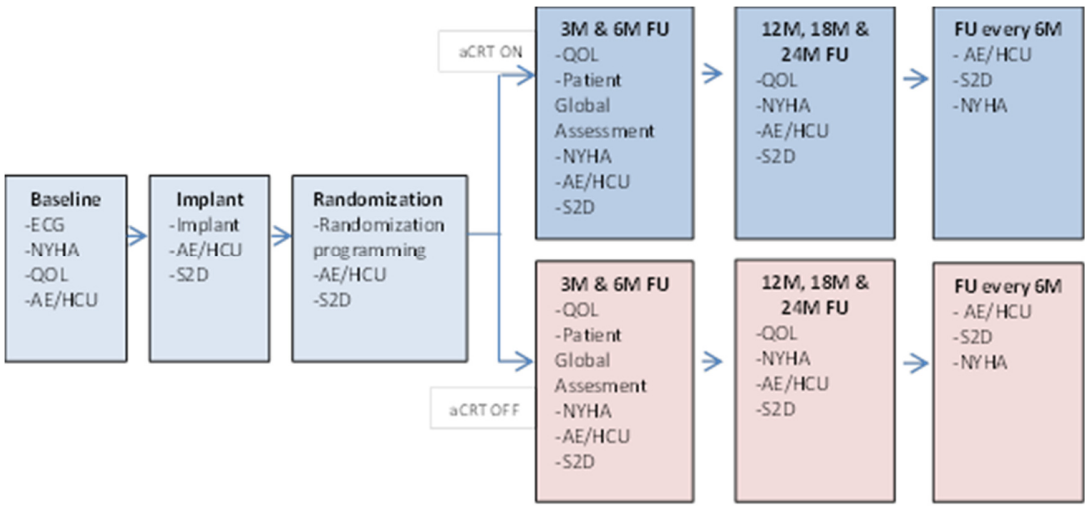


Table 7 Post-randomization follow-up windows

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	56	91	105
6 Month follow-up	153	183	213
12 Month follow-up	335	365	395
18 Month follow-up	518	548	578
24 Month follow-up	700	730	760
30 Month follow-up	883	913	943
36 Month follow-up	1066	1096	1126
42 Month follow-up	1249	1279	1309
48 Month follow-up	1431	1461	1491
54 Month follow-up	1614	1644	1674
60 Month follow-up	1796	1826	1856
66 Month follow-up	1979	2009	2039
72 Month follow-up	2162	2192	2222
78 Month follow-up	2344	2374	2404
84 Month follow-up	2527	2557	2587
90 Month follow-up	2709	2739	2769

6.9.1 3 and 6 month Follow-up visits

- NYHA HF assessment
- Physical examination
- Blood measurements (if collected per standard of care)
- Current CV medications
- 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)
    - EQ-5D
- Patient Global Assessment
- Report AEs, System Modifications, Study Deviations, Crossovers, and Healthcare Utilizations (as they occur)

6.9.2 12, 18, 24 month Follow-up visits

- NYHA HF assessment
- Physical examination
- Blood measurements (if collected per standard of care)
- Current CV medications
- 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)
    - EQ-5D
- Report AEs, System Modifications, Study Deviations, Crossovers, and Healthcare Utilizations (as they occur)

6.9.3 Follow-up visit every 6 months until study closure

- NYHA HF assessment
- Physical examination
- Blood measurements (if collected per standard of care)
- Current CV medications
- Current heart failure symptoms status
- Final device interrogation (Interrogate All)

- AV/VV optimization method (control group only, if optimization occurs per standard of care)
- Report AEs, System Modifications, Study Deviations, Crossovers, and Healthcare Utilizations (as they occur)

6.10 Device Interrogation (Interrogate All)

For the implant, randomization and follow-up visits, a final full “Interrogate ALL” device interrogation file (.pdd) 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.

6.11 Adverse Events

The primary objective depends on complete reporting of HF events, including interventions for heart failure decompensation and cardiovascular adverse events (AEs). These are reported upon center awareness and assessed at scheduled follow-up visits to ensure all applicable hospitalizations and AE’s have been reported. Refer to section 8 for adverse events details.

6.12 Healthcare Utilization

Healthcare Utilization (HCU) information should be reported upon center awareness and assessed at all follow-up visits to ensure all applicable Healthcare Utilizations have been reported. All hospitalizations, emergency department visits, outpatient treatment involving overnight stay, cardiovascular-related urgent care and cardiovascular-related clinic visits will be considered reportable Healthcare Utilizations for this study. Any visit where changes occur to protocol-required programming parameters will be considered cardiovascular-related. For HCU’s involving changes to protocol-required programming parameters, both an initial and final device interrogation will be required, and a copy of the interrogation files must be sent to Medtronic with a copy also being maintained at the center in the subject’s file. Additionally, collection of current cardiovascular medications will be required for all HCU’s. Any remote transmissions via the Medtronic CareLink® system will also be collected.

Healthcare Utilization information will be included in the review of potential HF related events and hospitalizations by the blinded Endpoint Adjudication Committee (EAC). Supporting source documentation may be requested if needed for study or endpoint evaluation. Relevant documentation may include but is not limited to: a copy of the hospital discharge summary report, and medical records such as chest x-ray reports, echocardiogram reports, medication documentation, lab results related to the event and consultation reports (e.g., Heart Failure, Renal, Cardiology, Pulmonary, etc.).

6.13 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.

6.14 Conditional Disengagement

After a patient is randomized every effort should be made to keep the subject in the study. However, it is recognized that there are circumstances where limited data may be collected, or study exit will need to occur. In these cases we will consider either modified data collection requirements where subjects may conditionally disengage in study procedures but data from the subject can still be collected because the subject has not revoked consent, or exit when study participation is completely ended. In randomized subjects, modified data collection is always preferred over exit.

Subjects may be conditionally disengaged from study procedures for any of the following reasons:

- Subject chooses to disengage (e.g., follow-up schedule cannot be adhered to, study burden too large, relocation to another geographic location but telephone follow-up still acceptable)
- Investigator deems conditional disengagement necessary (e.g. medically justified)

If the subject wishes to disengage from the study, or the investigator deems it necessary, the center is required to document the reason. Prior approval from the study team is required and a Limited Data Collection CRF needs to be completed. Data collection requirements no longer apply, but sites are encouraged to collect as much data as possible on the regular CRFs.

6.15 Study Exit

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

- Study completed
- Subject lost to follow-up
- Subject death
- Subject did not meet eligibility criteria and was not randomized
- Subject did not have a successful implant and no attempt at re-implant is made
- Subject did not provide consent or data protection authorization

- Subject chooses to exit (i.e. revokes consent)

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, Study Deviations and Healthcare utilization (as they occur)

Subjects will not be replaced with newly enrolled subjects upon exit. As described in Section 11.3.4, the sample size accounts for attrition.

6.15.1 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.

6.15.2 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.

6.15.3 Subject chooses to exit (i.e. revokes consent)

If the subject wishes to exit from the study (i.e. the subject revokes consent), the center is required to document the reason for exit.

In addition, study centers shall follow the regulations set forth by the governing Ethics Committee. Adverse events, healthcare utilizations and study deviations should be assessed at the time of exit and recorded on the appropriate case report forms. In addition,

whenever possible, an initial and final full device interrogation (Interrogate ALL) should be collected prior to subject exit, and a copy of the interrogation files should be sent to Medtronic with a copy also being maintained at the center in the subject's file.

7. STUDY DEVIATIONS

A study deviation is defined as an event within a study that did not occur according to the Clinical Investigation Plan or the Clinical Trial Agreement. Crossover is considered a deviation, but additional requirements apply, see section 5.5.

Prior approval by Medtronic is expected in situations where the investigator anticipates, contemplates, or makes a conscious decision to deviate. In all geographies, 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 end point 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 Table 11 through 18 for geography-specific deviation reporting requirements and timeframes for reporting to Medtronic and/or regulatory bodies.

Medtronic is responsible for analyzing deviations, assessing their significance, and identifying any additional corrective and/or preventive actions (e.g. amend the Clinical Investigation Plan, conduct additional training, terminate the 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.

8. ADVERSE EVENTS

Timely, accurate, and complete reporting of clinical events is of crucial importance for success of the study. To assess the superiority of CRT devices containing the aCRT algorithm, it is important that all information related to heart failure decompensation events, atrial fibrillation status, and other cardiovascular adverse events are reported. Additionally, reporting and review of safety information for clinical studies are crucial for the protection of subjects. Sections below define the clinical event reporting requirements for the study, and the geography specific safety reporting requirements.

8.1 Adverse Event definitions

8.1.1 Adverse Events

Adverse Event (AE) definitions are provided in Table 8. 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 PIC form. Reporting of these events to Medtronic will occur on an AE Form, including a description of AE, date of onset of AE, date of site awareness, signs and symptoms, treatment, resolution, and investigator assessment of both the seriousness and the relatedness to heart failure, the procedure, and to the system. Each AE must be recorded on a separate AE Form.

Health Care Utilization will be reported on the Health Care Utilization Form.

Subject deaths are also required to be reported. Refer to section 8.3 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. Episodes of symptomatic AF need to be reported. In all geographies, Unavoidable Adverse Events, listed in Table 8 need not be reported unless the adverse event worsens or is present outside the stated timeframe post-implant. For AEs that require immediate reporting (see Table 10), 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.

8.1.2 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 has conditionally disengaged or is exited from the study prior to 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".

8.2 Definitions, Classification and Reporting

8.2.1 Adverse Event Definitions

The clinical study will collect all serious and all system, procedure, and/or cardiovascular related adverse events.

Table 8 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
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, operational and download software and programmers necessary for conducting study-related procedures as defined in the Clinical Investigation Plan)	Device-related: An adverse event that results from the presence or performance (intended or otherwise) of the device. RA lead-related: An adverse event that results from the presence or performance (intended or otherwise) of the RA lead. RV lead-related: An adverse event that results from the presence or performance (intended or otherwise) of the RV lead. 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, e.g. 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 foetal distress, foetal 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.
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.
Serious Adverse Device Effect (SADE)	Adverse device effect that has resulted in any of the consequences characteristic of a serious adverse event.
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

<table>
<tr><td></td><td>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.</td></tr>
<tr><td colspan="2">Other</td></tr>
<tr><td>Unavoidable Adverse Event</td><td>An Adverse Event inherent to a surgical procedure that is expected to occur in all subjects for a projected duration according to the Investigator’s opinion, including, but not limited to:
<table>
<tr><th>Event Description</th><th>Timeframe (hours) from the Surgical Procedure</th></tr>
<tr><td>Anesthesia related nausea / vomiting</td><td>24</td></tr>
<tr><td>Low-grade fever (<100°F or 37.8°C)</td><td>48</td></tr>
<tr><td>Pocket site / Incisional pain</td><td>72</td></tr>
<tr><td>Mild to moderate bruising / ecchymosis</td><td>168</td></tr>
<tr><td>Sleep problems (insomnia)</td><td>72</td></tr>
<tr><td>Back pain related to laying on table</td><td>72</td></tr>
<tr><td>Shoulder pain/discomfort/stiffness related to shoulder immobilization during procedure</td><td>72</td></tr>
</table></td></tr>
<tr><td>Intervention for heart failure decompensation</td><td>An event requiring inpatient hospitalization for heart failure, or requiring invasive intervention for heart failure (i.e. IV diuretics, ultrafiltration, or equivalent).</td></tr>
<tr><td>Hospitalization</td><td>A therapeutic admission lasting >24hrs.</td></tr>
</table>

8.2.2 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. Refer to Table 10 for a list of required investigator and Medtronic reporting requirements and timeframes. It is the responsibility of the investigator to abide by any additional AE reporting requirements stipulated by the Ethics Committee responsible for oversight of the study.

Foreseeable Adverse Events are listed in Appendix G: the 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 below:

Table 9 Adverse Event classification responsibilities

What is classified?	Who classifies?	Classification Parameters
Relatedness	Investigator	System, procedure, or heart failure related
	Sponsor	System, procedure, or heart failure 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

The DMC will monitor adverse event rates and evaluate risk-benefit.

The EAC will review all applicable Healthcare Utilizations and all study reportable events during the study, assessing outpatient treatment and hospitalizations, to determine HF relatedness and AF relatedness for the study objectives.

8.3 Subject Death

8.3.1 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 return product reporting systems may be used to gather additional information about the returned device/component.

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

8.3.2 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 Table 10 for a list of required investigator and sponsor reporting requirements and timeframes.

8.4 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.

Relevant (adverse event related) and available copies of hospital records should be sent to Medtronic, when allowed by local law/regulations

Table 10 Adverse event reporting requirements

Serious Adverse Events (**SAEs**)	
Investigator submit to:	
Medtronic	**Canada:** Investigators are required to report to the sponsor immediately except for those SAEs that the protocol or other document (e.g. Investigator's Brochure) identifies as not needing immediate reporting. The immediate reports should be followed promptly by detailed, written reports. Medical Devices Regulations, sections 59-61. *A guidance for "immediately" is within 72 hours of the investigator becoming aware of the event; Report to sponsor, without unjustified delay (ISO 14155:2011, sec 9.8.b).*

	India: All serious adverse events shall be reported to the sponsor. (*Indian GCP section 3.3.4.3*). It is recommended to report all serious adverse events to the sponsor within 24h. For reported deaths the investigator shall supply any additional information e.g. autopsy report and terminal medical reports. (*Indian GCP section 3.3.4.5*). **Taiwan:** All SAEs should be reported to the sponsor immediately and a detailed written report should be provided to the sponsor as soon as possible. It is recommended for investigator to report all SAEs to the sponsor within 48 hours (Medical Device GCP Guidance (2016-01-01) Article 106). All SAEs should be reported to TFDA and ADR center (Regulatory authorities) within 7 days of first knowledge *(Procedure for Reporting Severe Adverse Reactions to Medicines (2004-8-31) Article 5).* **Korea**: The PI shall quickly report all SAEs (excluding what classified in the protocol or the IB as ones not requiring immediate report) as expedited reports of ADE under Attached Form No. 35 to the sponsor within the period provided in the protocol (KGCP Article 8 item 18). It is recommended for the investigator to report safety events within 48 hours from become aware date. **All geographies:** Report to the sponsor, without unjustified delay, all serious adverse events.
Regulatory Authority	**All geographies:** Submit to regulatory authority per local reporting requirement
Head of Medical Institution	**Japan**: The principal investigator shall report to the Head of Medical Institution, with respect to the progress of the research and status of any adverse event which occurs in implementing of the research, in accordance with specifications prescribed in this CIP. (*The Ethical Guidelines for Medical and Health Research Involving Human Subjects*) When a principal investigator becomes aware of any serious adverse event while carrying out the research which involves any invasiveness, the principal investigator shall promptly report to the Head of Medical Institution and take appropriate measures following the operating procedures including this CIP and any direction from the Head of Medical Institution (*The Ethical Guidelines for Medical and Health Research Involving Human Subjects*). Reporting requirements of this study: Since this study is implemented with the market-approved devices and under the approved indications, ONLY an unanticipated serious adverse event for which causal relationship with the device/system/procedure/Heart Failure cannot be ruled out shall be reported. In the case when the study site has any additional reporting requirements, the principal investigator shall follow them. The principal investigator shall report the status of any adverse event periodically which occurs in implementing of this study per the site procedure.
EC	**All geographies:** Submit to EC per local reporting requirement.
Sponsor submit to:	
Investigators	**Japan:** The sponsor as the study leader shall share information on the occurrence of an unanticipated serious adverse event for which causal relationship with the

	device/system/procedure/Heart Failure cannot be ruled out with the other principal investigators in Japan when such information has been reported by a principal investigator. **All geographies:** Submit to investigator per local reporting requirement.
Regulatory authorities	**Taiwan:** All SAEs should be reported to TFDA and ADR center (Regulatory authorities) within 15 days of first knowledge *(Procedure for Reporting Severe Adverse Reactions to Medicines (2004-8-31) Article 6).* **Canada:** Preliminary and final reporting to the Canadian Ministry of Health of events occurring inside (always) or outside Canada (in case of corrective actions) that is related to a failure of the device or a deterioration in its effectiveness, or any inadequacy in its labeling or its directions for use and has led to the death or a serious deterioration in the state of health of a patient, user or other person or could do so were it to recur. Report a) within 10 days after awareness, if incident has led to death or a serious deterioration in the state of health of a patient, user or other person b) within 30 days, if incident has not led to led to death or a serious deterioration in the state of health of a patient, user or other person, but could do so were it to recur c) as soon as possible, if incident occurred outside of Canada and is related to a corrective action. (Canada Medical Device Regulations, SOR/98-282; Mandatory Problem Reporting 59(1), 59(2), 60 (1)) **All geographies:** Submit to regulatory authority per local reporting requirement.
EC	**Japan**: The sponsor shall report information on the occurrence of an unanticipated serious adverse event for which causal relationship with the device/system/procedure/Heart Failure cannot be ruled out to the applicable EC when such information has been reported by a principal investigator. **All geographies:** Submit to EC per local reporting requirement.

Serious Adverse Device Effects (SADEs)	
Investigator submit to:	
Medtronic	**Canada:** Investigators are required, to submit as soon as possible and per local requirements. **India:** All serious adverse device effects shall be reported to the sponsor. (*Indian GCP section 3.3.4.3*). It is recommended to report all serious adverse events to the sponsor within 24h. **Taiwan:** All SADEs should be reported to the sponsor, TFDA and ADR center (Regulatory authorities) within 7 days of first knowledge *(Procedure for Reporting Severe Adverse Reactions to Medicines (2004-8-31) Article 5).* **Korea:** SADEs which have caused death or life threatening should be reported within 7 calendar days from the date when the investigator had relevant effects reported or informed. A detailed report should be submitted within 8 calendar days from the initial report. SADEs excluding death or life threatening should be reported within 15 calendar days from the date when the investigator had relevant effects reported or informed *(KGCP Article 8 item 18).* **All geographies:** Immediately after the investigator learns of the event or of new information in relation to an already reported event.
Regulatory Authority	**All geographies:** Submit to regulatory authority per local reporting requirement.
Head of Medical Institution	**Japan:** Since this study is implemented with market-approved devices and under the approved indications, ONLY an unanticipated serious adverse event for which causal relationship with the device/system/procedure/Heart Failure cannot be ruled out shall be reported. In the case when the study site has any additional reporting requirements, the principal investigator shall follow them. The principal investigator shall report the status of any adverse event periodically which occurs in implementing of this study per the site procedure.
EC	**All geographies:** Submit to EC per local reporting requirement.
Sponsor submit to:	
Investigator	**Japan:** The sponsor as the study leader shall share information on the occurrence of an unanticipated serious adverse event for which causal relationship with the device/system/procedure/Heart Failure cannot be ruled out with the other principal investigators in Japan when such information has been reported by a principal investigator. **Korea:** SADEs which have caused death or life threatening should be reported within 7 calendar days from the date when the investigator had relevant effects reported or informed. A detailed report should be submitted within 8 calendar days from the initial report. SADEs excluding death or life threatening should be reported within 15 calendar days from the date when the investigator had relevant effects reported or informed *(KGCP Article 8 item 18).* **All geographies:** Submit to investigator per local reporting requirement.
Regulatory authorities	**Canada:** Preliminary and final reporting to the Canadian Ministry of Health of events occurring inside (always) or outside Canada (in case of corrective actions) that is related to a failure of the device or a deterioration in its effectiveness, or any inadequacy in its labeling or its directions for use and has led to the death or a serious deterioration in the state of health of a patient, user or other person or could do so were it to recur. Report a) within 10 days after

	awareness, if incident has led to death or a serious deterioration in the state of health of a patient, user or other person b) within 30 days, if incident has not led to led to death or a serious deterioration in the state of health of a patient, user or other person, but could do so were it to recur c) as soon as possible, if incident occurred outside of Canada and is related to a corrective action. (Medical Devices Regulation Mandatory Problem Reporting 59 (1), 59 (2), 60 (1)) **Taiwan:** All SADEs should be reported to TFDA and ADR center (Regulatory authorities) within 15 days of first knowledge *(Procedure for Reporting Severe Adverse Reactions to Medicines (2004-8-31) Article 6).* **Korea:** SADEs which have caused death or life threatening should be reported within 7 calendar days from the date when the investigator had relevant effects reported or informed. A detailed report should be submitted within 8 calendar days from the initial report. SADEs excluding death or life threatening should be reported within 15 calendar days from the date when the investigator had relevant effects reported or informed *(KGCP Article 8 item 18).* **All geographies:** Submit to regulatory authority per local reporting requirement.
EC	**Japan:** The sponsor shall report information on the occurrence of an unanticipated serious adverse event for which causal relationship with the device/system/procedure/Heart Failure cannot be ruled out to the applicable EC when such information has been reported by a principal investigator. **All geographies:** Submit to EC per local reporting requirement.
Unanticipated Serious Adverse Device Effects (USADEs)	
Investigator submit to:	
Medtronic	**Canada:** Investigators are required to submit as soon as possible and per their local requirements. **India:** All USADEs shall be reported to the sponsor. (*Indian GCP section 3.3.4.3*). It is recommended to report all serious adverse events to the sponsor within 24h. **Taiwan:** All USADEs should be reported to the sponsor, TFDA and ADR center (Regulatory authorities) within 7 days of first knowledge *(Procedure for Reporting Severe Adverse Reactions to Medicines (2004-8-31) Article 5).* **Korea:** USADEs which have caused death or life threatening should be reported within 7 calendar days from the date when the investigator had relevant effects reported or informed. A detailed report should be submitted within 8 calendar days from the initial report. USADEs excluding death or life threatening should be reported within 15 calendar days from the date when the investigator had relevant effects reported or informed *(KGCP Article 8 item 18).* **All geographies:** Immediately after the investigator learns of the event or of new information in relation to an already reported event.
Regulatory Authority	**Taiwan:** All USADEs should be reported to the sponsor, TFDA and ADR center (Regulatory authorities) within 7 days of first knowledge *(Procedure for Reporting Severe Adverse Reactions to Medicines (2004-8-31) Article 5).*

	All geographies: Submit to regulatory authority per local reporting requirement.
Head of Medical Institution	**Japan:** Since this study is implemented with market-approved devices and under the approved indications, ONLY an unanticipated serious adverse event for which causal relationship with the device/system/procedure/Heart Failure cannot be ruled out shall be reported. In the case when the study site has any additional reporting requirements, the principal investigator shall follow them. The principal investigator shall report the status of any adverse event periodically which occurs in implementing of this study per the site procedure.
EC	**All geographies:** Submit to EC per local reporting requirement.
Sponsor submit to:	
Investigator	**Japan:** The sponsor as the study leader shall share information on the occurrence of an unanticipated serious adverse event for which causal relationship with the device/system/procedure/Heart Failure cannot be ruled out with the other principal investigators in Japan when such information has been reported by a principal investigator. **Korea:** USADEs which have caused death or life threatening should be reported within 7 calendar days from the date when the investigator had relevant effects reported or informed. A detailed report should be submitted within 8 calendar days from the initial report. USADEs excluding death or life threatening should be reported within 15 calendar days from the date when the investigator had relevant effects reported or informed *(KGCP Article 8 item 18).* **All geographies:** Submit to investigator per local reporting requirement.
Regulatory authorities	**Canada:** Preliminary and final reporting to the Canadian Ministry of Health of events occurring inside (always) or outside Canada (in case of corrective actions) that is related to a failure of the device or a deterioration in its effectiveness, or any inadequacy in its labeling or its directions for use and has led to the death or a serious deterioration in the state of health of a patient, user or other person or could do so were it to recur. Report a) within 10 days after awareness, if incident has led to death or a serious deterioration in the state of health of a patient, user or other person b) within 30 days, if incident has not led to led to death or a serious deterioration in the state of health of a patient, user or other person, but could do so were it to recur c) as soon as possible, if incident occurred outside of Canada and is related to a corrective action. (Canada Medical Device Regulations, SOR/98-282; Mandatory Problem Reporting 59 (1), 59 (2), 60 (1)). **Taiwan:** All USADEs should be reported to TFDA and ADR center (Regulatory authorities) within 15 days of first knowledge *(Procedure for Reporting Severe Adverse Reactions to Medicines (2004-8-31) Article 6).* **Korea:** SADEs which have caused death or life threatening should be reported within 7 calendar days from the date when the investigator had relevant effects reported or informed. A detailed report should be submitted within 8 calendar days from the initial report. SADEs excluding death or life threatening should be reported within 15 calendar days from the date when the investigator had relevant effects reported or informed *(KGCP Article 8 item 18).* **All geographies:** Submit to regulatory authority per local reporting requirement.
Head of Study Implementing Entity	**Japan:** Information on the occurrence of an unanticipated serious adverse event for which causal relationship with the device/system/procedure/Heart Failure cannot be ruled out shall be reported when such information has been reported by a principal investigator.

EC	**Japan:** The sponsor shall report information on the occurrence of an unanticipated serious adverse event for which causal relationship with the device/system/procedure/Heart Failure cannot be ruled out to the applicable EC when such information has been reported by a principal investigator. **For US**: Notification as soon as possible, but not later than 10 working days after the sponsor first learns of the effect. (21 CFR 812.150(b)(1)) **All geographies**: Submit to EC per local reporting requirement.

All other study **reportable** Adverse Events (system, procedure and cardiovascular-related)	
Investigator submit to:	
Medtronic	**All geographies:** Submit in a timely manner after the investigator first learns of the event.
Regulatory authorities	**All geographies:** Submit to regulatory authority per local reporting requirement.
Head of Medical Institution	**Japan:** Since this study is implemented with market-approved devices and under the approved indications, ONLY an unanticipated serious adverse event for which causal relationship with the device/system/procedure/Heart Failure cannot be ruled out shall be reported. In the case when the study site has any additional reporting requirements, the principal investigator shall follow them. The principal investigator shall report the status of any adverse event periodically which occurs in implementing of this study per the site procedure.
EC	**All geographies:** Submit to EC per local reporting requirement.
New information that may **adversely** affect safety of the subjects or the conduct of the study	
Investigator submit to:	
Medtronic	**India:** Investigator shall promptly report to sponsor and monitor new information that may adversely affect safety of the subject or the conduct of the study. *(Indian GCP section 3.3.4.4*) **All geographies:** Submit in a timely manner after the investigator first learns of the information.
EC	**India:** Investigator shall promptly report new information that may adversely affect safety of the subject or the conduct of the study. *(Indian GCP section 3.3.4.4*) **All geographies:** Submit to EC per local reporting requirement.
Sponsor submit to:	
Regulatory authorities	**All geographies:** Submit to regulatory authority per local reporting requirement.
EC	**All geographies:** Submit to EC per local reporting requirement[iii] .

8.5 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

iii For Japan, required reports per Clinical Study Act which will be in effect from April 2018 will be provided under separate cover

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.

Abuse: Abnormal use (definition acc. #4.1 of Meddev 2.12-1 rev6)

Misuse: Use error (definition acc. #4.20 of Meddev 2.12-1 rev6)

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

9. RISK ANALYSIS

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.

A summary of the risk analysis and risk assessment will be listed in the Investigator Brochure. The Investigator's Brochure will be available upon request.

9.1 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. Medtronic has also attempted to minimize risk to subjects implementing a Data Monitoring Committee to review safety issues as part of the study.

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.

9.2 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.

9.3 Risk-to-Benefit Analysis

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

10. PLANNED STUDY CLOSURE, EARLY TERMINATION OF STUDY OR STUDY SUSPENSION

10.1 Planned study closure

Study Closure is a process initiated by distribution of a study closure letter. Study closure is defined as closure of a 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 HOMI notifies the Ethics Committee and Medtronic thereof in writing. In all geographies, ongoing Ethics Committee oversight is required until the overall study closure process is complete.

10.2 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.

10.2.1 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)
- Recommendation of early termination by the Data Monitoring Committee (DMC) based on interim analyses or concerns about study enrollment or conduct, or event rates.
- (Temporary) unavailability of the study devices
- Medtronic may stop the study due to lack of enrollment, if the average enrollment rate is less than 0.25 subjects enrolled per active center per month over any 6 consecutive months during the study.

10.2.2 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)

10.3 Procedures for termination or suspension

10.3.1 Medtronic-initiated and regulatory authority-initiated

- Medtronic will promptly inform the clinical investigators of the termination or suspension and the reasons and inform the 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 HOMI, will promptly inform the Ethics Committee of Medical Institution
- 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

10.3.2 Investigator-initiated

- The investigator will inform Medtronic and provide a detailed written explanation of the termination or suspension.
- The investigator will promptly inform the institution (where required per regulatory requirements)
- The investigator will promptly inform the Ethics Committee
- The investigator 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.

10.3.3 Ethics committee-initiated

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

11. STATISTICAL METHODS AND DATA ANALYSIS

11.1 General

Medtronic employed statisticians will perform the statistical analyses described in this section. Interim analyses will be performed by a Medtronic statistician other than the lead statistician for the study. The lead study statistician will be blinded to all interim analyses. All tests of treatment effects will be conducted in order to preserve an overall two-sided alpha level of 0.05 unless otherwise stated. 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 Statistical Analysis Plan (SAP) will be created before the first interim analysis 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.

11.2 Study design

The AdaptResponse study is a prospective, randomized, controlled, interventional, single-blinded, multi-center, post-market, global Cardiac Resynchronization Therapy (CRT) in heart failure (HF) clinical study. Patients will be randomized in equal numbers between a treatment arm that will receive CRT therapy with ambulatory optimization and preferential LV-only pacing (aCRT ON, programmed to “Adaptive Bi-V and LV”) and a control arm that will receive standard bi-ventricular CRT therapy (aCRT OFF, programmed to “Nonadaptive CRT”). Further details are given in section 5.4. Study subjects will be followed until the required number of endpoint events is reached.

11.2.1 Rationale

As described in detail in section 2, the Adaptive CRT study has demonstrated equivalence of aCRT with echo-optimized bi-ventricular CRT, with respect to the Clinical Composite Score at 6 months post-implant. A retrospective analysis on the subgroup of patients with LBBB and normal AV conduction suggested the hypothesis that aCRT reduces the incidence of the combined endpoint of death or heart failure hospitalization. The AdaptResponse study is designed to prospectively test this hypothesis.

The primary endpoint is the composite of all-cause death and any intervention for heart failure decompensation. The heart failure event definition is broader than the more traditional heart failure hospitalization, adding in-patient treatment for decompensation with oral diuretics and out-patient treatment with IV diuretics. The reasons for this choice are that the incidence rate of heart failure hospitalizations has decreased over the years due to advances in the treatment of heart failure, and the fact that there are geographic differences in the treatment of heart failure and the definition of hospitalization that lead to different rates of heart failure hospitalization. The broader definition is intended to ensure that the event rate is high enough to have an achievable sample size and to accommodate geographic differences due to differing health care systems. Independent blinded endpoint adjudication will ensure an unbiased comparison between randomized arms.

11.2.2 Randomization

Patients will be randomized in a 1:1 ratio using permuted blocks with random block sizes. Randomization will be stratified by center and by NYHA class. Randomization schedules will be generated by a Medtronic statistician using computer-generated random numbers.

11.2.3 Sample size

The AdaptResponse study will be event-driven. The study is designed to observe a primary endpoint in 1100 patients. To that end, the study will randomize approximately 3500 patients. The DMC will review accruing data and will advise on continuation of enrollment and patient follow up.

11.2.4 Interim analyses

Three interim analyses are planned to be performed after 275, 550, and 825 first primary endpoints. Under the assumptions of the sample size calculation, the interim analyses will take place approximately 3.5, 5.0, and 6.5 years after first enrollment. See section 11.4 for more details.

11.3 Primary objective

The primary objective is to test the hypothesis that aCRT reduces the incidence of the combined endpoint of all-cause mortality and intervention for heart failure decompensation, compared to standard CRT therapy, in patients with a CRT indication, LBBB and normal AV conduction.

11.3.1 Endpoint definition

The primary endpoint is the composite of all-cause death and any intervention for heart failure decompensation as adjudicated by the EAC. The date of the endpoint will be the date of death or the date of initiation of treatment for decompensation as determined by the EAC.

11.3.2 Hypothesis, analysis methods and performance requirements

The null hypothesis that will be tested is that the hazard ratio for aCRT versus control is equal to 1. It will be tested against the alternative hypothesis that the hazard ratio is unequal to 1.

Let $S_T(t)$ and $S_C(t)$ denote the proportion of patients in the treatment arm and control arm, respectively, that have not experienced a primary endpoint up to time t. Let $h_T(t)$ and $h_C(t)$ be the associated hazard functions. Under the proportional hazards model, $h_T(t) = HR\ h_C(t)$, where HR is the hazard ratio of treatment compared to control. The null and alternative hypotheses can be expressed as:

$$H_0 : HR = 1$$

$$H_A : HR \neq 1$$

The hypothesis will be tested using a Cox proportional hazards regression model with a random center effect (frailty), stratified by baseline NYHA class. The hazard ratio for treatment arm versus control arm will be reported with its associated p-value and 95% confidence interval. The null hypothesis will be rejected when the p-value is below the critical value for the (interim or final) analysis, and it will be concluded that aCRT reduces the incidence of the primary endpoint when the hazard ratio is below 1. Kaplan-Meier graphs for incidence will also be reported, together with an estimate for the absolute event rate difference at 2 years post randomization.

Two further analyses of the primary objective are planned. First, a Cox regression model will be reported with a random center effect and a risk score as fixed effect. The risk score will be derived from baseline data. Second, an analysis will be done including only the patients for whom the ECG Core Laboratory confirmed the presence of LBBB.

11.3.3 Determination of patients and data for analysis

The primary analysis will follow the intent-to-treat principle. All randomized patients will be included in analysis, and for each patient the endpoints will be attributed to the arm that the patient was randomized to irrespective of the actual treatment that the patient received. Event dates will be entered in the analysis relative to the date of randomization (which will be time zero for the survival analysis). Patients will be censored if no primary endpoint has occurred prior to the end-of-study exit visit, or the last documented follow-up visit if the patient was exited early.

11.3.4 Sample size rationale

A total of 1100 patients experiencing a primary endpoint will give 90% power to show a significant reduction of the incidence of the primary endpoint, accounting for 3 equally spaced interim analyses and assuming a true intent-to-treat hazard ratio of 0.82 for aCRT ON compared to aCRT OFF.

Version 1.0 of the CIP specified the total number of patients randomized as follows: With the inclusion of 2874 randomized patients enrolled over 3 years and followed for 2.3 more years, 1100 primary endpoint events are expected when the true control arm event-free rate is 75% at 2 years.

Version 2.0 of the CIP increases the total number of patients randomized to accommodate a lower event rate: With the inclusion of 3326 randomized patients enrolled over 4 years and followed for 3.5 more years, 1100 primary endpoint events are expected when the true control arm event-free rate is 85% at 2 years.

The study will randomize approximately 3500 patients in order to accommodate attrition due to early exit. The study will be event-driven and the DMC may advise to stop enrollment early when the primary endpoint rate is higher than expected.

Through simulation it was confirmed for version 1.0 of the CIP that the study will have 90% power under the following assumptions:

- 3000 patients randomized in 3 years with a uniform rate

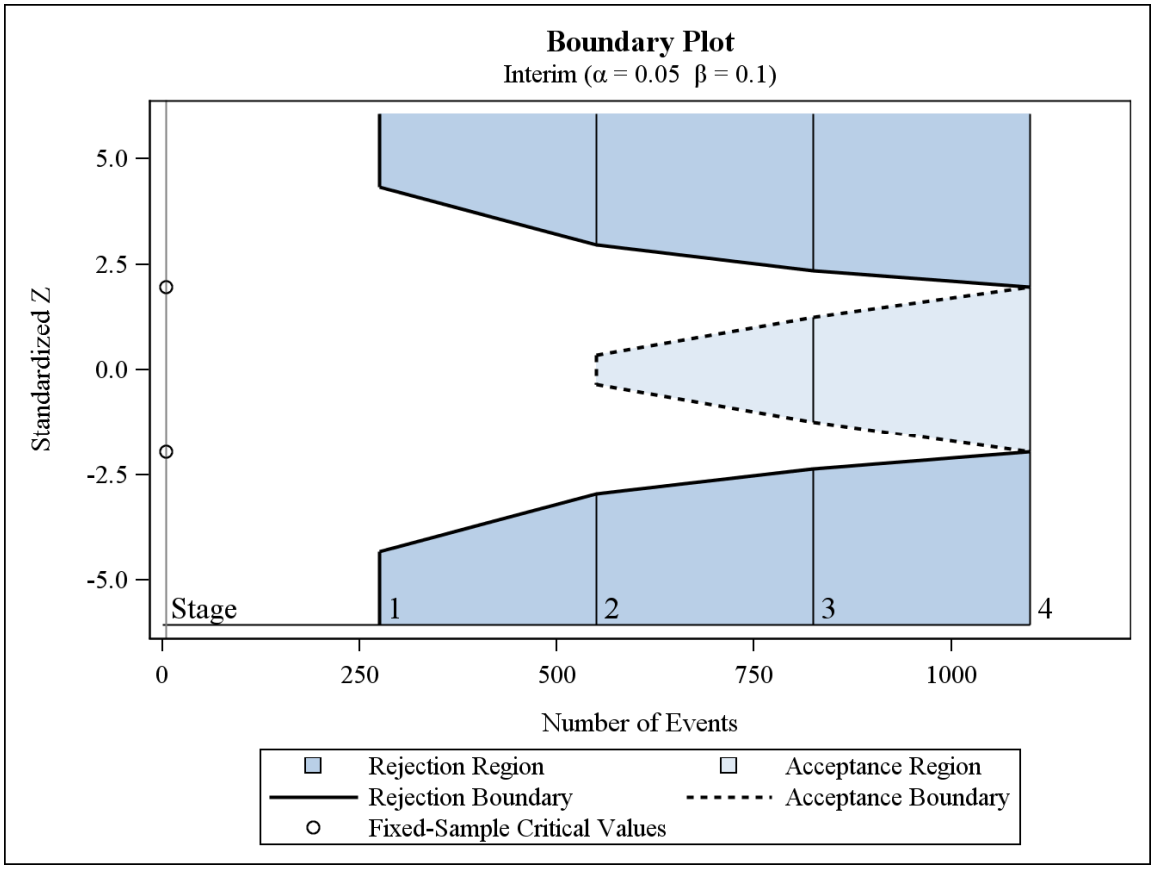
- control arm event-free rate is 75% at 2 years
- LBBB is not confirmed by the ECG Core Laboratory in 10% of patients
- aCRT hazard ratio is 0.78 in confirmed LBBB patients, 1.0 in unconfirmed patients
- crossover rate is 5% at 2 years in aCRT arm and 8% at 2 years in control arm
- loss-to-follow-up rate is 5% at 2 years in both arms
- final analysis is done when 1100 events are accrued

For version 2.0 of the CIP, the simulation was updated and the power of 90% was confirmed with updated control group event rate expectation.

11.4 Interim analysis methodology

The 3 interim analyses will follow a symmetric group sequential design using the alpha-spending methodology of Lan and DeMets[17] with O'Brien-Fleming[18] type boundaries. The statistical stopping rules are illustrated in the figure below.

Figure 2. Statistical stopping boundaries



The horizontal axis shows the number of events, indicating the timing of interim analyses after 275, 550, and 825 events, and the final analysis when 1100 events are accrued. If at any interim analysis the standardized Z statistic for the primary objective is in the darker blue area with solid boundary line, the DMC may advise to stop the study claiming the null hypothesis is rejected. This corresponds to a cumulative α-level of 0.00002, 0.00304, 0.0193 and 0.05 spent at the subsequent stages. If the Z Statistic is in the lighter blue area with dashed boundary line, the DMC may advise to stop the study for futility.

In case the study is stopped for efficacy after an interim analysis, the secondary objectives will be analyzed using a total significance level derived from a Pocock-type alpha-spending function. This corresponds to a cumulative α-level of 0.018, 0.031, 0.041 and 0.05 spent at the subsequent stages[19].

11.5 Secondary and ancillary objectives

Interpretation of results will be guided by a formal multiple testing procedure to achieve strict control of the family wise error rate, also accounting for the interim analysis plan. Secondary objectives will be analyzed when the study has stopped after an interim analysis or has reached the final analysis stage. A Hommel procedure[20,21] will be applied to the secondary objectives (excluding the cost-effectiveness objective) using an overall α-level as determined by the stage in the interim analysis plan as described in section 11.4 above.

Secondary objectives for which the hypothesis is rejected under the adjusted significance level of the Hommel procedure will be reported as significant with strictly controlled family wise error α=0.05.

Secondary objectives include the components of the primary endpoint, patient status at 6 months, the incidence of atrial fibrillation, and cost-effectiveness.

11.5.1 Secondary objectives

To assess all-cause mortality in the aCRT ON arm compared to aCRT OFF.

Mortality will be illustrated with Kaplan-Meier graphs. A Cox proportional hazards regression model will be used to estimate the HR of aCRT compared to control, which will be reported with its p-value and 95% confidence interval. The model will include the stratification variables also included in the primary objective model.

To assess the rate of intervention for heart failure decompensation for aCRT ON compared to aCRT OFF.

Incidence of intervention for heart failure decompensation will be illustrated with cumulative incidence graphs. A Cox regression model will be used to estimate the cause-specific HR of aCRT compared to control, which will be reported with its p-value and 95% confidence interval. The model will include the stratification variables also included in the primary objective model. Additionally, recurrent event survival analysis will be performed to compare rates of interventions for heart failure decompensation.

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 Clinical Composite Score classifies patients according their clinical status at 6 months post randomization into categories Improved, Unchanged, and Worsened[22]. 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.

The proportion of patients who Improved will be compared between the arms of the study with a logistic regression model, correcting for the stratification variables also included in the primary objective model.

To test the hypothesis that aCRT reduces the incidence of AF compared to aCRT OFF.

Incidence of AF will be determined from device data, and the endpoint for the primary analysis will be the first day after randomization on which there is >6 hrs of AF reported in the device's Cardiac Compass Trends. The analysis will compare incidence of AF using survival analysis methods. As secondary analyses device measured AF burden and treatment for AF will be analyzed.

To test the hypothesis that the change in quality of life, measured by the KCCQ, in the aCRT ON group is better than the change in the aCRT OFF group.

The parameter of interest is the KCCQ overall summary score (range, 0 to 100; higher scores indicate better health status) which will be assessed at baseline and at the 3, 6, 12, 18, and 24 months follow-up visits. The summary score at the follow-up visits will be analyzed using a linear mixed effects regression model that will account for the correlation of scores within each patient. The treatment arm allocation will be included as a main effect. The baseline KCCQ score as well as the stratification variables included in the primary objective model will be included as covariates in the model. Analysis will be corrected for time trends if needed.

To test the hypothesis that the change in health outcome, measured by the EQ-5D, in the aCRT ON group is better than the change in the aCRT OFF group.

The parameter of interest is the EQ-5D index, which will be assessed at baseline and at the 3, 6, 12, 18, and 24 months follow-up visits. Derivation of the index will follow instructions provided by the EuroQol Group (www.euroqol.org). The index at the follow-up visits will be analyzed using a linear mixed effects regression model that will account for the correlation of measurements within each patient. The treatment arm allocation will be included as a main effect. The baseline EQ-5D index as well as the stratification variables included in the primary objective model will be included as covariates in the model. Analysis will be corrected for time trends if needed.

To test the hypothesis that aCRT reduces the incidence of all-cause re-admissions after a heart failure (HF) admission within 30-days of the index event.

A negative binomial model will be used to estimate and compare incidence rates of all-cause re-admissions after an HF admission. For each patient the number of hospital admissions that falls within 30 days of discharge from an HF admission (as classified by the investigator) will be determined. All patients will be included in the model, with a count of zero in case no 30-day readmissions occurred. The model will include an offset based on the total follow-up experience of all patients.

To assess cost-effectiveness of CRT devices with the aCRT algorithm relative to traditional CRT devices.

Analysis method for this objective will be defined in the Economic Analysis Plan. There will be no hypothesis test and therefore the objective will not be included in the Hommel multiple testing procedure.

11.5.2 Ancillary objectives

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

12. DATA AND QUALITY 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 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 patient charts, ECGs, device interrogation files, worksheets, and lab results, must be created and maintained by the investigational site team. For source documentation, the investigational center study team must sign and date any copies or printouts of original source documents with a statement that this is complete and true reproduction of the original source document.

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. Study sites should inform Medtronic upon notification of an audit by a regulatory body immediately.

13. WARRANTY/INSURANCE INFORMATION

13.1 Warranty

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

13.2 Insurance (Europe, Russia and Middle East)

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

13.3 Insurance (Japan)

Information regarding warranty and compensation will be provided under separate cover per the local regulation. Documentation explaining compensation to the subjects in the event of study-related injuries will be submitted to Ethics Board if required.

13.4 Insurance (Australia)

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

13.5 Insurance (India)

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

13.6 Insurance (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 Board.

13.7 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 Board.

13.8 Insurance (Latin America)

Medtronic USA Inc. 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 Board.

14. 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 Monitoring Visits

The study follows a risk-based monitoring approach. 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, risk based analysis, and any suspected inconsistency in data that requires investigation. Monitoring for the study, including but not limited to site qualification visits, site initiation visits, interim monitoring visits, and closeout visits will be done 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.

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 (In U.S. and Canada, signed by subject. In Europe, Russia, Middle East, Taiwan, Australia, Korea, Latin America, and Japan, 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 PIC
- All approved versions of the Investigator's Brochure, if required by local law
- 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 (Europe, Russia, Middle East, India, Australia, Korea, Taiwan and Latin America only)
- Final Study Report including the statistical analysis
- List of investigational sites
- 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 section 8.4 of the Adverse Event section.

Table 11 Investigator reports applicable for all geographies 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.

Table 12 Investigator reports applicable to Japan

Investigator reports applicable to Japan per Ethical Guidelines for Medical and Health Research Involving Human Subjects[iv]		
Report	**Submit to**	**Description/Constraints**
Withdrawal of Ethics Committee approval	Head of Medical Institution	The principal investigator must report a withdrawal of Ethics Committee approval which occurred in other study site.
Progress Report	Head of Medical Institution	The investigator shall submit written summaries of the status of the study and record retention information relevant to the study to the Head of Medical Institution periodically per the site procedure.
Study Deviations	Head of Medical Institution	When an investigator, etc. becomes aware of any serious concern with respect to human rights of the study subject, etc. or with respect to implementing of the study, such as leakage of information related to the study, the investigator, etc. shall report promptly to the Head of Medical Institution and the principal investigator. When a principal investigator becomes aware of any fact or obtains any information that ethical justification or scientific validity of the study is, or might be, impaired, and if the continuation of the study will be hindered, the principal investigator shall report to the Head of Medical Institution without delay and, as necessary, suspend or terminate the study or revise the CIP. When a principal investigator becomes aware of any fact or obtains any information that appropriateness of implementing the study he/she is engaged in or reliability of results of the research is, or might be, impaired, the principal investigator shall report to the Head of Medical Institution promptly and, as necessary, suspend or terminate the study or revise the CIP. Any deviation from the clinical investigational plan shall be recorded together with the explanation of the deviation and report if required by the site procedure.
Study closure and/or premature termination	Head of Medical Institution	When a principal investigator has completed or terminated any study, the principal investigator shall submit to the Head of Medical Institution without delay, in writing, a statement to that effect and a summary of the results of the study.
Study registration and publication	Head of Medical Institution	If the study involves invasiveness (not including minor invasiveness) and intervention, the principal investigator shall, without delay, report to the Head of Medical Institution, when the final publication of results of the study is done.

Table 13 Investigator reports applicable to India

Report	Submit to	Description/Constraints
Agreed termination or suspension	Subjects, Ethics Committee and regulatory authorities	In case the investigator and sponsor agree to prematurely terminate or suspend the study for any reason, the investigator / institution should promptly inform the study Subjects, the Ethics Committee as well as the Regulatory Authorities. The investigators should also ensure appropriate therapy and follow-up for the subjects. *(India GCP section 3.3.8)*
Not agreed termination or suspension	All concerned parties	If the investigator or the sponsor or the ethics committee decide to terminate or suspend the study without prior agreement of all parties concerned then the party initiating the suspension / termination should promptly inform all the concerned parties about such suspension / termination and suspension along with a detailed written explanation for such termination / suspension. *(India GCP section 3.3.8)*
Final report	Institution and Ethics Committee	The completion of the study should be informed by the investigator to the institution, the sponsor and the ethics committee. *(India GCP section 3.3.8)*

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 (Europe, Russia, Middle East, India, Australia, Korea, Taiwan and Latin America only)

iv Required reports per Clinical Study Act which will be in effect from April 2018 will be provided under separate cover

- Names/contact addresses of monitors
- Statistical analyses and underlying supporting data
- Final report of the clinical study
- The Clinical Investigation Plan, Patient Informed Consent, Investigator's Brochure , 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 (by geography). 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 section 8.4 of the Adverse Event section.

Table 14 Sponsor reports for Australia

Report	Submit to	Description/Constraints
Premature termination or suspension of the clinical investigation	Investigators, Ethics Committee and relevant authorities	Provide prompt notification of termination or suspension and reason(s).
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.

Table 15 Sponsor reports for Canada

Report	Submit to	Description/Constraints
Premature termination or suspension of the clinical investigation	Investigators, Ethics Committee	Provide prompt notification of termination or suspension and reason(s). *(ISO 14155:2011)*

Report	Submit to	Description/Constraints
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.
Recall and device disposition	Investigators, Ethics Committee,	Notification within 30 days and will include the reasons for any request that an investigator return, repair, or otherwise dispose of any devices. (Mandatory Devices Regulation Mandatory Problem Reporting 63-65.1)

Table 16 Sponsor reports for Europe, Russia, Middle East, Taiwan, Korea, Latin America

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.

Report	Submit to	Description/Constraints
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	For studies with sites complying to ISO 14155:2011: • The investigator shall have the opportunity to review and comment on the final report. • If a clinical investigator does not agree with the final report, his/her comments shall be communicated to the other investigator(s). • The coordinating investigator shall sign the report. If no coordinating investigator is appointed, then the signature of the principal Investigator in each center should be obtained. *(ISO 14155:2011)*
Study deviation	Investigators	Ensure that all deviations from the Clinical Investigation Plan are reviewed with the appropriate clinical investigator(s), are reported on the case report forms and the final report of the clinical investigation. Site specific study deviations will be submitted to investigators periodically.

Table 17 Sponsor reports for Japan[v]

Report	Submit to	Description/Constraints
Premature termination or suspension of the clinical investigation	Investigators and Ethic Committees	Provide prompt notification of termination or suspension and reason(s).
Recall and device disposition	Ethics Committee	Submit per local reporting requirement.
Audit report	Principal investigator and Head of Medical Institution	Those engaged in audit shall report to the principal investigator and the Head of Medical Institution concerning results of the audit. (Ethical Guidelines for Medical and Health Research Involving Human Subjects)
Final report	Investigators and Ethics Committee	A final report will be submitted if requested after completion or termination of this study.

v Required reports per Clinical Study Act which will be in effect from April 2018 will be provided under separate cover

Report	Submit to	Description/Constraints
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, if requested.

Table 18 Sponsor reports for the United States

Report	Submit to	Description/Constraints
Premature termination or suspension of the clinical investigation	Investigators IRB/MEC Relevant authorities Head of the Institution	Provide prompt notification of termination or suspension and reason(s).
Withdrawal of Ethics Committee approval	Investigators Ethics Committee Relevant authorities	Investigators, Ethics Committees will be notified only if required by local laws or by the Ethics Committee.
Final report	Investigators, IRB/MEC, Regulatory authorities upon request	A final report will be submitted to investigators, and IRBs/MECs within six months after completion or termination of this study.
Study deviation	Investigators	Ensure that all deviations from the Clinical Investigation Plan are reviewed with the appropriate clinical investigator(s), are reported on the case report forms and the final report of the clinical investigation. Site specific study deviations will be submitted to investigators periodically.

Medtronic records and reports will be stored in locked file cabinets at Medtronic during the course of the study. Electronic versions of the 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.

APPENDIX A: CASE REPORT FORMS

Case report forms for the AdaptResponse study will be provided under separate cover upon request.

APPENDIX B: PRELIMINARY PUBLICATION PLAN

Publications from the AdaptResponse study will be handled according to Medtronic Standard Operating Procedures and as indicated in the Clinical Trial Agreement.

Publication Committee

For AdaptResponse the Steering Committee will comprise the Publication Committee. Medtronic personnel may serve as members of the committee. This committee will manage study publications with the goal of publishing findings from the data. The Publication Committee will develop the final Publication Plan as a separate document.

The Publication Committee's role is to:

1) manage elements addressed in the publication plan as outlined in this appendix

2) develop the final Publication Plan including writing group selection criteria, under separate cover

3) execute the Publication Plan

4) oversee the publication of primary, secondary and ancillary study results

5) review and prioritize publication proposals

6) provide input on publication content, and

7) determine authorship.

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

Management of Primary, Secondary and Ancillary Publications

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

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

The committee may decide that no publications, including abstracts, will be published prior to the end of the study or with individual center data. Requests for publications on study objectives

utilizing subset data (e.g., regional) will be evaluated for scientific validity and the ability of Medtronic to provide resources.

Criteria for Determining Authorship

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

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

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

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

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

Transparency

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

- a final report, describing the results of all objectives and analysis, will be distributed to all investigators, MECs and Competent Authorities of participating countries when required by local law
- registering and posting the study results on ClinicalTrials.gov based on the posting rules stipulated
- submitting for publication the primary study results after the study ends
- disclosing financial interests of the co-authors of publications according to the policies set forth by the corresponding journals and conferences
- making an individual center’s study data accessible to the corresponding investigator after the completion of the study, if requested

APPENDIX C: DATA MONITORING COMMITTEE (DMC)

Point	Examples
DMC will be used	Ongoing oversight for this study will be provided by an independent Data Monitoring Committee (DMC).
Who will be involved	The DMC will have one statistician, at least one physician specializing in electrophysiology and at least one specializing in heart failure management. None of the DMC members are participating in the AdaptResponse study. A chairperson from among those members will be identified.
Responsibility of the DMC	The DMC will be responsible for monitoring patient safety and treatment efficacy data while the AdaptResponse study is ongoing. The DMC will safeguard the interests of study participants and the scientific soundness of the study, by reviewing the accumulating data including interim analysis results, monitoring the overall conduct of the clinical study, and reviewing external developments. The DMC will regularly review data on patient safety and study conduct, review results of the interim analyses, and provide recommendations to the Steering Committee and study sponsor regarding continuation of the study and modifications in design and conduct.
Recommendations	The DMC will be advisory to the sponsor and the Steering Committee. The DMC may provide recommendations for early termination of the study. Review and consensus by the entire committee is required to recommend that the study should be stopped. The DMC may also make recommendations related to the selection, management and retention of subjects, improvement of adherence to protocol-specified regimens, and procedures for data management and quality control. The DMC will monitor the event rates of the study, and if necessary, they may recommend randomizing more subjects and/or extending follow-up in order to ensure the minimum number of events occurs.

Point	Examples
Decision Boundaries	Statistical decision boundaries for the study are outlined in the statistical methods section of this document. These are to be used only as guidelines by the DMC when deciding whether the study should continue as no statistical methods can adequately capture the complexity of all data in a clinical study. The DMC may provide recommendations for early termination of the study. At interim analyses, the DMC assessment will balance the evidence on the primary objective and the secondary objectives of all-cause mortality and heart failure decompensation incidence. If a mortality benefit is detected early, the study will stop. In addition other considerations for early stopping for efficacy will include, but are not limited to, the magnitude of effect, secondary objectives, data quality, and consistency of results across subgroups.
Operation	Together with the Steering Committee and Medtronic, the DMC will develop a charter that defines in further detail the role and operation of the DMC. The charter may deviate from the above, in which case the DMC charter takes priority.

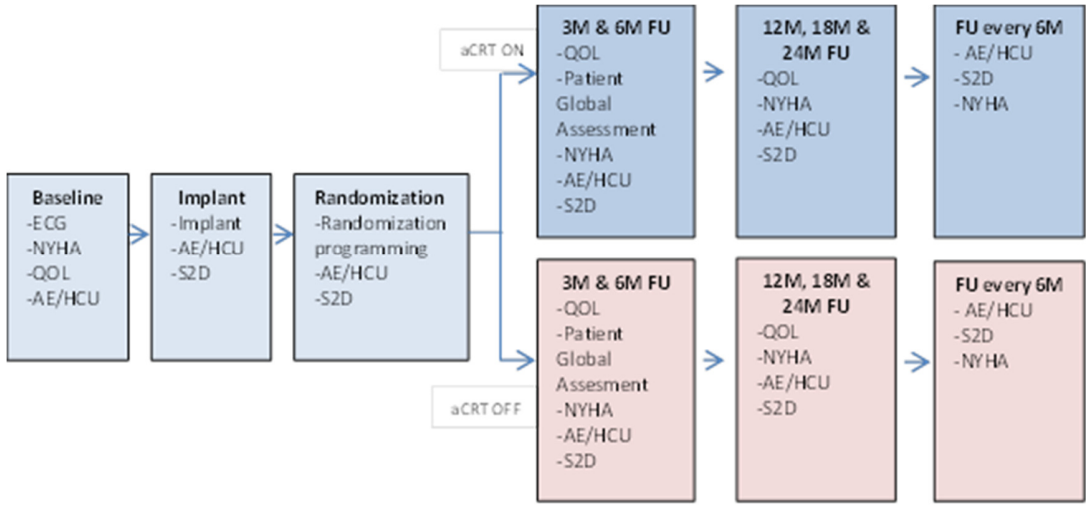
APPENDIX D: ENDPOINT ADJUDICATION COMMITTEE (EAC)

Point	Examples
EAC will be used	Ongoing review of events contributing to the primary endpoint for this study will be provided by an independent blinded Endpoint Adjudication Committee (EAC).
Who will be involved	The EAC will have at least three members, including at least one physician specializing in electrophysiology, and at least one specializing in heart failure management. A chairperson from among those members will be identified. None of the EAC members will be participating investigators in the AdaptResponse study.
Responsibility of the EAC	The EAC will establish standards for adjudicating HF events, using the ACC/AHA and ESC Guidelines as a basis for diagnosis and adjudication. The EAC will be responsible for assessing applicable Healthcare Utilizations and events during the study, assessing the cause of hospitalizations and outpatient treatment, to determine HF relatedness for study objectives. The EAC will meet at regular intervals throughout the course of the study to assess events, and determine whether these events should contribute to the primary and secondary endpoints of the AdaptResponse Study.
Recommendations	The EAC will be advisory to the sponsor and the Steering Committee. The EAC will determine events that will contribute to the primary and secondary endpoints of the study. Review and quorum adjudication by the committee is required to govern any event to the primary and/or secondary endpoint(s).
Heart Failure Relatedness definition	The category for heart failure relatedness will include 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 certain treatment devices. Intervention for heart failure decompensation (HF event) is defined as an event requiring “invasive intervention (i.e. IV diuretics, ultrafiltration, or equivalent) or inpatient hospitalization”
Decision Boundaries	The EAC will make decisions as to the relatedness of the HF event. They will not be responsible for evaluating adverse events, deaths or the safety of the patients in the study (See DMC).

APPENDIX E: STUDY OVERVIEW

Title	AdaptResponse Clinical Study
Study Purpose	The AdaptResponse study is a prospective, randomized, controlled, interventional, single-blinded, multi-center, post-market, global Cardiac Resynchronization Therapy (CRT) in heart failure (HF) clinical study. The purpose of this clinical study is 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).
Background	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] Evidence from the Medtronic pre-market approval Adaptive CRT 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] Importantly, a post-hoc sub-analysis of the Adaptive CRT Clinical 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] 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 (81% vs.69%, p=0.041) and 12 months (77% vs. 66%, p=0.076) than echocardiography-optimized control patients.[14] Furthermore, over the longer term follow-up (20.2 $\pm$ 5.9 months) the aCRT algorithm has been shown to reduce the risk of the incidence of 48 consecutive hours in AF (HR=0.54 [95% CI 0.31-0.93]; p=0.03) and aCRT patients without history of AF were less likely to develop persistent AF (HR=0.44 [95% CI 0.19-1.03]; p=0.05).[15] Further investigation of clinical outcomes over longer follow-up is needed to support the benefit of aCRT. Therefore the AdaptResponse study is 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.
Study Components	The following components will be used in the clinical study: • Market-released Medtronic CRT-P and CRT-D devices containing the AdaptivCRT® (aCRT) algorithm. • Compatible market-released right atrial, right ventricular, and Medtronic left ventricular pacing leads • Medtronic Model 2090 CareLink programmer
Study Design	Following enrollment and baseline assessment, eligible subjects will be implanted with a CRT system containing the aCRT algorithm and randomized in a 1:1 fashion to either treatment (aCRT ON, programmed Adaptiv Bi-V and LV) or control (aCRT OFF, programmed Nonadaptiv CRT) groups. Study subjects will be followed until 1100 primary endpoints are accrued or until study closure, whichever comes first. Refer to the figure below for an overview of the study design.



Study Scope	The study is expected to be conducted at approximately 250 centers including Australia, Canada, Europe, Russia, India, Japan, Korea, Latin America, Middle East, Taiwan and the US. Approximately 3500 subjects will be randomized in the study. The study utilizes an "event-driven" study design. Enrollment will end when approximately 3500 patients are randomized or there is reasonable certainty that the required number of events will be reached as determined by the Data Monitoring Committee (DMC), whichever occurs first.
Study Objectives	**Primary objective** To test the hypothesis that AdaptivCRT® reduces the incidence of the combined endpoint of all-cause mortality and intervention for heart failure decompensation, compared to standard CRT therapy, in patients with a CRT indication, LBBB and normal AV conduction. Intervention for heart failure decompensation (HF event) is defined as an event requiring "*invasive intervention (i.e. IV diuretics, ultrafiltration, or equivalent) or inpatient hospitalization".* **Secondary Objectives** • To test the hypothesis that aCRT ON reduces all-cause mortality compared to aCRT OFF. • To test the hypothesis that aCRT ON reduces the rate of intervention for heart failure decompensation compared to aCRT OFF. • 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. • To test the hypothesis that aCRT ON reduces the incidence of AF compared to aCRT OFF. • To test the hypothesis that the change in quality of life, measured by the KCCQ, in the aCRT ON group is better than the change in the aCRT OFF group. • To test the hypothesis that the change in health outcome, measured by the EQ-5D, in the aCRT ON group is better than the change in the aCRT OFF group. • To test the hypothesis that aCRT reduces the incidence of all-cause re-admissions after a heart failure (HF) admission within 30-days of the index event. • To assess cost-effectiveness of CRT devices with the aCRT algorithm relative to traditional CRT devices.

Inclusion Criteria	Exclusion criteria
▪ Subject is willing to sign and date the study Patient Informed Consent (PIC) Form. ▪ Subject is indicated for a CRT device according to local guidelines. ▪ Subject has minimally: o Sinus rhythm at time of enrollment. o Left Bundle Branch Block (LBBB) as documented on an ECG (within 30 days prior to enrollment). Criteria for complete LBBB should include: ▪ Intrinsic QRS duration ≥140 ms (men) or ≥130 ms (women), ▪ QS or rS in leads V1 and V2, ▪ Mid-QRS notching or slurring in ≥2 of leads V1, V2, V5, V6, I, and aVL. o Intrinsic, normal AV conduction as documented on an ECG by a PR interval less than or equal to 200ms (within 30 days prior to enrollment). o Left ventricular ejection fraction less than or equal to 35% (documented within 180 days prior to enrollment). o 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 Aldosterone Antagonist.	▪ Subject is less than 18 years of age (or has not reached minimum age per local law). ▪ Subject is not expected to remain available for at least 2 years 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 the exclusion criteria required by local law.

APPENDIX F: INFORMED CONSENT TEMPLATE

Geography specific Informed Consent form templates will be provided under separate cover.

APPENDIX G: FORESEEABLE ADVERSE EVENT LIST

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

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 23 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 19 Observed System and Implant Procedure Related Adverse Events

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††	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%)
Diarrhoea	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%)

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

	Events	Complications††	Events	Complications	Events	Complications
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%)
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%)

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 20.

Table 20 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 21 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)

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 (%)
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)
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 H: PARTICIPATING INVESTIGATORS AND INSTITUTIONS

A complete list of participating investigators and institutions where study activities are conducted will be distributed under separate cover.

APPENDIX I: ETHICS COMMITTEE LIST

A complete list of participating Ethics Committee and the Chairperson(s) will be distributed under separate cover.

APPENDIX J: LABELING

Labeling for all market approved system components can be found with each package insert. Manuals can be found on http://manuals.medtronic.com.

APPENDIX K: BIBLIOGRAPHY

A complete bibliography, summary of relevant literature, and summary and results of previous clinical investigations is provided in the Investigator's Brochure. The Investigator's Brochure is available upon request.

APPENDIX L: ADDITIONAL INFORMATION FOR CENTERS BY COUNTRY

Regulations for the conduct of clinical trials vary by country. Required information for centers in each country, such as detailed sponsor contact information, names of monitors, detailed CRF instruction, etc. not outlined in the Clinical Investigational Plan will be provided under separate cover.

APPENDIX M: PREVIOUS CLINICAL INVESTIGATIONS

A summary and results from the Adaptive CRT study, which is the clinical study evaluating the AdaptivCRT algorithm, are provided in the Investigator's Brochure. The Investigator's Brochure is available upon request.

APPENDIX N: CLINICAL INVESTIGATION PLAN SIGNATURE PAGE (IF APPLICABLE)

AdaptResponse Study

The AdaptResponse study is a prospective, randomized, controlled, interventional, single-blinded, multi-center, post-market, global Cardiac Resynchronization Therapy (CRT) in heart failure (HF) clinical study. 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, 28 February 2018

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**

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APPENDIX P: DOCUMENT CHANGE HISTORY

Revision	Description of Change	Author
1.0	First issue	[redacted]
2.0	1. General: a. Updated information related to sponsor contact, Core laboratory, Steering Committee to reflect the current situation b. Updated availability of study related documents to the current situation c. Updated regulatory requirements to reflect the current situation d. Used the wording in the device manuals to explain the programming in the 2 arms e. Corrected typo's 2. Paragraph 1.1: Study purpose and description a. Used the wording in the device manuals to explain the programming in the 2 arms b. Removed sentence referring to the number of CRT systems in the study as not aligned with the study change to enroll 3500 randomized subjects 3. Paragraph 1.2: Study scope a. Aligned the text with the study change: randomization increase from 3000 to 3500 randomized subjects, an increase of participating sites from 200 to approximately 250, and an increase in study duration b. Added Russia to the participating regions 4. Paragraph 2: Background and justification a. Updated with analyses results and aCRT related manuscripts published since b. Updated aCRT study post-hoc sub-analysis results table 5. Paragraph 3.1: System description and intended use a. Removed the name of the CRT devices used in the study, as the study is about the aCRT algorithm, not about the devices itself. All CRT devices used in the study are commercially available. 6. Paragraph 4: Regulatory compliance a. Updated local laws and regulations to the current situation 7. Paragraph 6.1: Site activation a. Added clarity regarding study training for site personnel 8. Paragraph 6.2: Equipment requirements a. Updated computer requirements to be compatible with the current data base 9. Paragraph 6.3: Data collection	Lidwien Vainer

Revision	Description of Change	Author
	a. Explained acronyms b. Added cardiovascular medications which are recommended for heart failure treatment according to the current guideline 10. Paragraph 6.4: Patient Informed Consent process a. Due to regional regulation differences, added “per local requirements” to the informed consent sign off possibility of a legally authorized representative or guardian 11. Paragraph 6.5: Enrollment a. Added the need to document subject’s participation in the source docs, per current regulations 12. Paragraph 6.6: Baseline a. Changed names of medication to CV medication to also include newly guideline recommended CV medication 13. Paragraph 6.8: Randomization a. Table Programming requirements: Corrected and updated programming requirements according to the current available devices, added recommended programming 14. Paragraph 6.9: Scheduled follow-up visits a. Added follow-up visit windows to table 7 to implement the longer participation of some patients 15. Paragraph 8.4: Adverse event records and reporting requirements a. Added the need for source docs for endpoint adjudication b. Updated tables to the current local reporting requirements 16. Paragraph 10.3: Procedures for termination or suspension a. Added sentence to implement new MDT CIP requirements 17. Paragraph 11.2: Study design a. Added stratification by NYHA class: this was implemented from the start of the study, on request of the Steering Committee. b. Updated timelines for interim analyses based on the current actuals 18. Paragraph 11.3: Primary objective a. Updated sample size rationale to align with the study change (increase randomized subjects from 3000 to 3500) 19. Paragraph 11.5: Secondary and ancillary objectives a. Changed type of regression model 20. Paragraph 13: Warranty/insurance information a. Added Russia b. Updated insurance sections according to current local regulations 21. Paragraph 15: Required records and reports a. Updated according to current local regulations 22. Appendix A:	

Revision	Description of Change	Author
	a. Removed “draft” as the Case Report Forms are final 23. Appendix E: Study overview a. Aligned with CIP V2.0 24. Updated appendix H, I, to the actual status 25. Updated appendix O with new references	