Medtronic Statistical Analysis Plan	
Clinical Investigation Plan Title	Mid-Q Response
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1. Version History

Version	Summary of Changes	Author(s)/Title
1.0	Not Applicable, New Document	[redacted], Principal Statistician

2. List of Abbreviations and Definitions of Terms

Abbreviation	Definition
aCRT	Adaptive Cardiac Resynchronization Therapy, or AdaptivCRT®
AE	Adverse Event
AF	Atrial Fibrillation
Bi-V	Biventricular, e.g. both left and right ventricles
CIP	Clinical Investigation Plan
CCS	Clinical Composite Score
CRT	Cardiac Resynchronization Therapy
CV	Cardiovascular
ECG	Electrocardiogram
HF	Heart Failure
ITT	Intention-To-Treat
KCCQ	Kansas City Cardiomyopathy Questionnaire
LBBB	Left Bundle Branch Block
LOCF	Last Observation Carried Forward
LV	Left Ventricle; alternatively, Left Ventricular
LVEF	Left Ventricular Ejection Fraction
MAR	Missing At Random
MCAR	Missing Completely At Random
NMAR	Not Missing At Random
NYHA	New York Heart Association
SAP	Statistical Analysis Plan

3. Introduction

The purpose of the Statistical Analysis Plan (SAP) for the Mid-Q Response trial is to provide pre-analysis documentation and rationale for the statistical procedures that will be employed in the planned analyses that are performed throughout this study. Specifically, this plan outlines methods used in the study's final report. It does not limit the analysis that will be completed, as further analysis beyond what is specified in this document is likely.

This SAP was developed based on version 1 of the Mid-Q Response Clinical Investigation Plan (CIP), dated 28-MAR-2019. Topics addressed in this document but not the CIP include analysis methods for the ancillary objectives (sections 6.2.6 – 6.2.9), pooling methods (section 6.3), handling of missing data (section 6.4) and validation requirements (section 8). Details about randomization will be documented in the study-specific Randomization and Blinding Plan, but are considered out of scope for this SAP.

The objective of the Mid-Q Response study is to provide stronger evidence about the effectiveness of the AdaptivCRT® (aCRT) algorithm compared to standard CRT therapy in heart failure patients with moderate QRS duration (hence, in the **Mid**dle of the **Q**RS range), left bundle branch block (LBBB) and preserved atrioventricular conduction. Currently, a limited evidence base from a few retrospective studies exists to support the hypotheses that patients in this subgroup who are of Asian ethnicity or of smaller body size may experience aCRT benefit. Thus, a demonstration of benefit from aCRT in this subpopulation may help to give additional heart failure patients access to a beneficial therapy, and, in addition, provide insights regarding guidelines for CRT in Asian countries.

4. Study Objectives

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

4.1 Primary Objective

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

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

4.2 Secondary Objectives

- To evaluate the change in New York Heart Association (NYHA) class at 6 and 12 months between the aCRT ON group and the aCRT OFF group.
- To characterize occurrence of hospitalizations for worsening heart failure in the aCRT ON group and the aCRT OFF group at 12 months.
- To characterize all-cause and cardiovascular related mortality in the aCRT ON group and the aCRT OFF group at 12 months.

4.3 Ancillary Objectives:

[redacted]

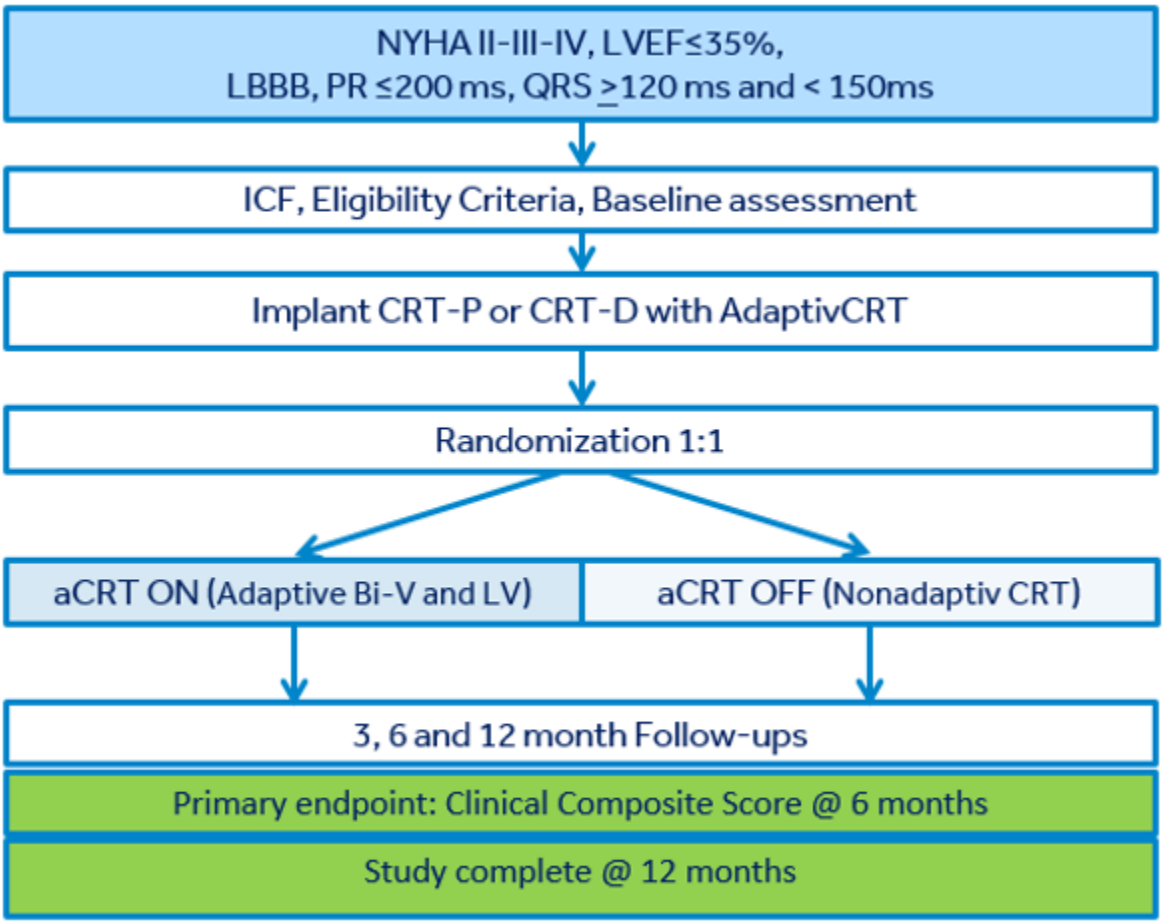
5. Investigation Plan

Medtronic Inc. and Medtronic Japan Co., Ltd. are sponsoring the Mid-Q Response study; a prospective, randomized, controlled, interventional, single-blinded, multi-center, post-market Cardiac Resynchronization Therapy in heart failure clinical study. The study is expected to be conducted at approximately 55 centers in Asia, including Japan, China, Taiwan, South Korea, Hong Kong, Malaysia, Singapore, Indonesia, Brunei, and the Philippines. Proposed study start is mid-2019.

The purpose of this study is to assess if CRT indicated patients with normal AV conduction, LBBB, and QRS ≥120 and <150 ms treated with aCRT (aCRT ON: Adaptive Biventricular [Bi-V] and Left Ventricular [LV]), have a better Clinical Composite Score at 6 months than patients treated with standard BiV pacing (aCRT OFF: Nonadaptive CRT). To assess the superiority of CRT devices containing the aCRT algorithm, the primary objective of the Mid-Q Response study is to test the hypothesis that aCRT ON increases the proportion of patients that improve on the Clinical Composite Score (CCS) compared to aCRT OFF at 6 months of follow-up. Eligible subjects will be randomized after baseline assessment and implant of a CRT system containing the aCRT algorithm. Randomization will be done in a 1:1 ratio to either treatment (aCRT ON, Adaptive Bi-V and LV) or control (aCRT OFF, Nonadaptive CRT) groups. All subjects, independent of randomization assignment, will have a Medtronic CRT system. Study subjects will be followed for 12 months. A single analysis of objectives will be performed after all subjects have exited the study; no interim analyses are planned. See figure 1 below for a diagrammatic representation for these aspects. Further rationale for the study design can be found in the CIP.

A total of 220 randomized patients followed through 6 months are needed for the study's primary analysis. To achieve this, we anticipate enrolling 232 patients.

5.1 Figure 1: Study Flow



6. Statistical Methods

6.1 Study Subjects

6.1.1 Disposition of Subjects

Subjects will have their eligibility assessed at baseline. The final report will provide a listing of any subjects that fail to satisfy the study's entry criteria. In the final report, a diagram or figure will describe (at a minimum) the following:

- Number of eligible subjects who consented and enrolled
- Of consented and enrolled, number randomized to aCRT ON and number randomized to aCRT OFF
- Subjects withdrawing consent or withdrawn by investigator prior to therapy initiation
- Subjects with initiation of therapy.
- Subjects with LBBB confirmed on ECG by core lab

- Withdrawals, early exits, deaths and planned study exits (i.e. after the 12-month follow-up visit) that occur after treatment initiation.

For the final report, these will be described by randomized group wherever appropriate. For any study progress reports prepared prior to the final report, descriptions of withdrawals, early exits, deaths and other events occurring after randomization will be presented for both treatment groups in aggregate.

6.1.2 Clinical Investigation Plan (CIP) Deviations

Protocol deviations will be described using frequency tables and listings. Subjects will be excluded from analysis of the primary efficacy objective if the subject withdraws consent to be studied prior to randomization. Handling of visit window deviations as it affects the study's primary endpoint is discussed further in section 6.2.2.4.

6.1.3 Analysis Sets

The **Full Analysis Set** consists of all enrolled subjects who provide informed consent (as determined by local regulations for the enrolling site at the time consent is given). The Full Analysis Set will not be used for any pre-planned objectives; its principal uses are in enabling the reporting of adverse events that occur prior to randomization, and in describing subjects who initially consent, but do not go on to be randomized. It is further noted that no such analyses are currently planned and that these would be ad-hoc.

An Intention-to-Treat analysis will be performed and will serve as the primary basis for inference about all objectives in this study. **The Intention-to-Treat (ITT) Set will include all randomized subjects.** Per the ITT principle, subjects' will be considered as part of the "aCRT on" or "aCRT off" treatment groups solely by their assigned randomization, regardless of their adherence with the entry criteria, regardless of the treatment they actually received, and regardless of subsequent withdrawal from treatment or deviation from the protocol (Fisher 1990). For purposes of brevity, such an approach will be described using the shorthand of "ITT analysis" throughout this SAP. For example, "analysis for this endpoint will be ITT" means that (as described above) all randomized subjects will be included and analyzed according to random assignment, and the ITT dataset will be used.

Two objectives (the analysis of the primary endpoint and the ancillary objective of comparing KCCQ scores by treatment) will also feature sensitivity analyses that will be conducted in the subset of subjects treated 'per-protocol'. This cohort of randomized subjects is defined by all of the following:

- LBBB and QRS duration ≥ 120 ms and < 150 ms at the baseline ECG, as confirmed by the ECG Core Lab
- no documented inclusion or exclusion criteria violations at baseline
- no non-assigned aCRT programming between day 7 after randomization and the subject's 6-month visit
- no deviations for crossover between treatment groups

This grouping of subjects will be referred to as the **per-protocol** cohort.

6.2 General Methodology

6.2.1 Overview

The analysis described in this SAP will be conducted by Medtronic statisticians. Prior to evaluation of the study's primary objectives, a descriptive analysis will be performed: demographic and other key baseline characteristics, attrition, follow-up experience, adverse events (AE's), and study deviations will be summarized by randomization group for the ITT dataset. All data will be reported; data that is not used for the analysis of objectives, such as data from subjects that were not randomized, will be summarized separately. Additional exploratory analyses may be conducted as deemed appropriate. Subgroups will be considered, which include age, gender, body height, heart failure etiology, LVEF, NYHA class, and QRS duration. Statistical tests will be two sided with alpha = 0.05 unless stated otherwise. Where applicable, absolute and relative effect sizes will be reported.

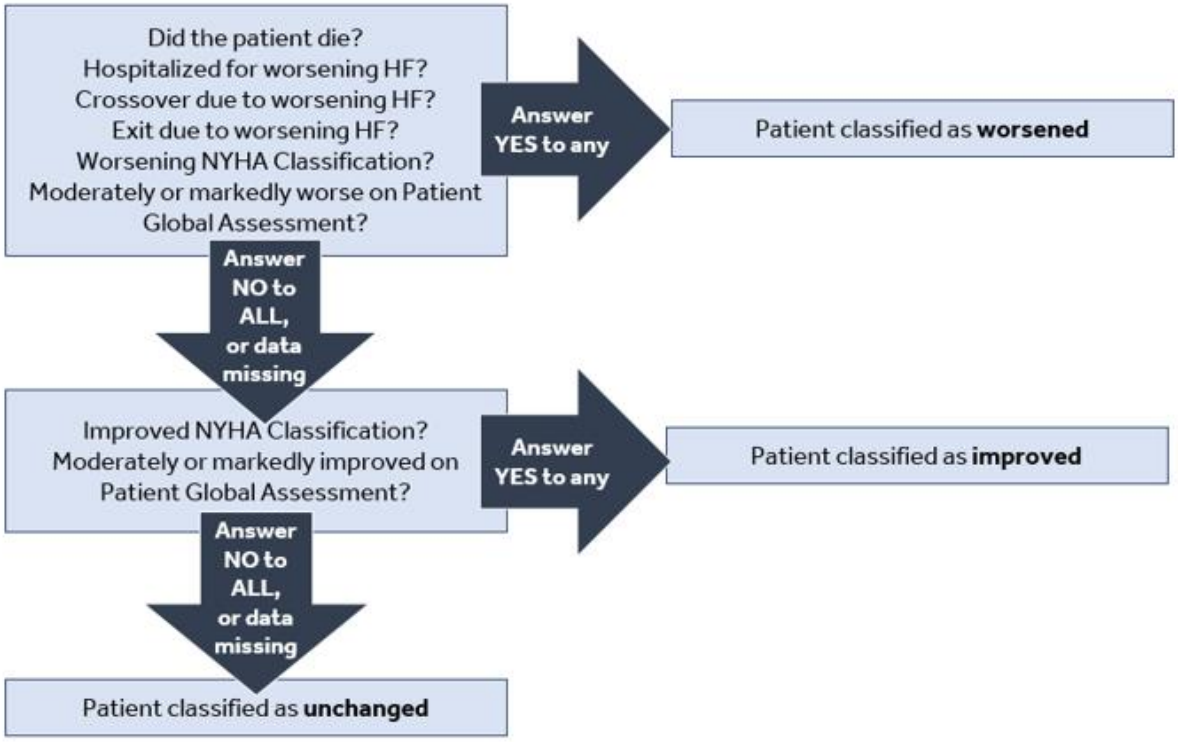
The expected mortality rate from subjects in Mid-Q Response is 4%, so we expect 4% of NYHA values at 12-month follow-ups, as well as a few less at 6-month and 3-month visits, to be missing for subjects who have died while under study. In these cases, the NYHA value will be set to "class V", and treated as being a level of heart failure more severe than NYHA class IV for purposes of all objectives.

6.2.2 Primary Objective: Compare Percent of Subjects with Clinical Composite Score Improvement from Baseline to 6 Months

6.2.2.1 Endpoint Definition

The primary endpoint for the study will be the Clinical Composite Score (CCS) at 6 months (Packer, 2001). The CCS classifies patients according their clinical status at 6 months post-randomization into categories Improved, Unchanged, and Worsened. A patient is classified Worsened in case of death, hospitalization for worsening heart failure, worsened NYHA class (using last observation carried forward), or worsened status on the Global Assessment Score. Also, patients that exit the study or cross over because of worsening heart failure are classified Worsened. A patient is classified Improved when not Worsened and there is an improvement in NYHA class or Global Assessment Score. Patients that are not Worsened or Improved are Unchanged including all patients with missing NYHA class and Global Assessment Score data who are not classified Worsened because of death, HF hospitalization, exit or crossover (see flowchart in Figure 2 below). The main analysis will look at the percentage of patients with Improved CCS.

6.2.2.2 Figure 2: Clinical Composite Score Flowchart



6.2.2.3 Hypothesis

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

H_0 : $p_{on} = p_{off}$

H_a : $p_{on} \neq p_{off}$

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

6.2.2.4 Analysis Methods

Subjects' CCS will be classified according to the algorithm described in Figure 2 and section 6.2.2.1. All subjects' 6-month visits will contribute to the 6-month CCS assessment regardless of when they occur relative to the protocol-defined windows (183 to 223 days from randomization). Non-missing values for dates of death, exit or crossover due to worsening heart failure, or a heart failure event that occur within the interval of 0 to 182 days post-randomization will necessarily lead to a CCS value of 'Worsened' and therefore a value of non-improvement for the primary outcome variable. To be

considered as endpoint events, crossovers and study exits must be indicated on the following respective crossover and exit CRF fields:

Was this an intentional crossover due to worsening heart failure o NO o YES

Was the exit due to worsening heart failure o NO o YES

NYHA and patient global assessment scores at 6 months will be used for subjects when available, and will be carried forward from the month 3 visit if this data is not available from the 6 month visit. For subjects having neither a 3-month or a 6-month classification, the baseline value will be carried forward (thus leading to a CCS of 'Unchanged' and a primary outcome value of non-improvement).

SAS code for the derivation of the CCS at 6 months, taken from the AdaptResponse study, is available under separate cover, shortened and with modifications made to reflect differing 6-month visit windows in Mid-Q Response.

The main analysis will use a Chi-square test comparing the binary proportion of subjects classified as improved (e.g., the proportion not worsened and not unchanged) between randomized arms. The null hypothesis will be rejected if the two-sided p-value is < 0.05. In the event this occurs, and the point estimate of the proportion improved in the aCRT ON group is higher compared to the aCRT OFF group, it will be concluded that aCRT ON causes a higher proportion of subjects classified as improved. The following SAS code provides an example of what may be used for this analysis:

```
proc freq data = analysis.PrimaryObj;
table aCRT_ITT*CCS_Improved/chisq nocol nopercent riskdiff;
run;
```

It is noted that this analysis will be slightly conservative due to not stratifying by site, even though randomization will be blocked within sites. The cost to statistical power from having the site-to-site variability subsumed into the overall error is expected to be minimal, and provides the benefit of having a parsimonious model for the analysis of the study's primary endpoint. Possible effects of clustering within sites will be addressed in a sensitivity analysis described below in section 6.2.2.7.

The absolute effect size will be expressed in terms of the difference in proportions of subjects with CCS improvement between ITT groups, and the associated asymptotic 95% confidence interval of that difference in proportions. The output from the SAS code cited above contains this in the fields highlighted here:

Column 2 Risk Estimates						
	Risk	ASE	(Asymptotic) 95% Confidence Limits		(Exact) 95% Confidence Limits	
Row 1						
Row 2						
Total						
Difference						
Difference is (Row 1 - Row 2)						

6.2.2.5 Determination of Subjects

The analysis of the primary endpoint for this study will be ITT.

6.2.2.6 Missing Data

The definition of the CCS ensures that no subject will have a missing value for the primary outcome. For example, if a subject is randomized and lost to follow-up immediately afterward, they will be classified as "unchanged" according to the algorithm defined above, and therefore "not improved" for the primary analysis. Precautions will be taken to ensure that every subject has a baseline NYHA classification prior to assignment of a treatment group, but if a subject without a baseline NYHA value is randomized despite these efforts, they will be included in the analysis of the primary endpoint with the conservative assumption that the subject was NYHA class II at baseline.

6.2.2.7 Sensitivity Analysis 1: Adjusting for Subject Gender and NYHA

To test the potential effect of differential distribution of NYHA class and subject sex among treatment groups, a sensitivity analysis will be done using a logistic regression model with randomization arm, gender and NYHA class as fixed effects, and site as the random effect. Sites with a low number of enrollments will be grouped into clusters according to methods outlined in section 6.3 (Center Pooling) below. Example SAS code is as follows:

```
proc glimmix data=analysis.secObj1;
class aCRT_ITT NYHA Sex site;
model CCS_Improved  = aCRT_ITT NYHA Sex/ dist=bin link=logit solution;
random intercept / subject=site  type = vc;
run;
```

It is noted that, under ideal circumstances, the p-value based on the resulting score test would be used in this case, as that is the direct analog to the chi-square test in the ITT analysis, rather than the more powerful test based on the Wald estimator provided by Proc Glimmix in SAS (see sample size simulations available under separate cover). Should Proc Glimmix fail to converge on parameter estimates, the equivalent model specification will be fit using the nlme package in R. If that also fails to converge, a conditional logistic regression model will be used instead (i.e., SAS Proc Logistic with site

specified in a strata statement). This sensitivity analysis will be performed in the ITT dataset; subjects who cross over and subjects treated in violation of major inclusion/exclusion criteria will still be analyzed according to their assigned randomization.

6.2.2.8 Sensitivity Analysis 2: Per-protocol Analysis in Confirmed Cases of Mid-Q LBBB

A second sensitivity analysis will be performed to analyze the per-protocol effect of the treatment upon the CCS at 6 months, in the subset of subjects treated per-protocol (i.e., in the per-protocol cohort defined in section 6.1.3). This second sensitivity analysis will proceed in the same manner as the main (ITT) analysis of the primary endpoint, with a chi-square test being used for the comparison of interest. Example SAS code is as follows:

```
*** Primary objective - sensitivity analysis #2;
proc freq data = analysis.PrimaryObj;
where perProtocol = 1;
table aCRT_act*CCS_Improved/nocol nopercent chisq;
run;
```

6.2.2.9 Sensitivity Analysis 3: Effect from Out of Window Visits

As stated in the CIP, data analyses include follow-up visits, regardless of whether the visit occurs within the window. However, in the presence of many subjects having late visits, the classification of the primary endpoint as a 6-month outcome becomes less accurate. Therefore, a description of visit compliance and a summary of actual days to 6 month assessments will be performed by treatment group. If a Wilcoxon test shows an imbalance in days from randomization to 6 month assessments between aCRT ON and aCRT OFF, or if > 20% of subjects from either study arm have late 6-month visits, one further sensitivity analysis will be performed. In this analysis, CCS will be calculated as above, except that for subjects who have 6 month visits occurring after the visit window has closed (i.e., 224 or more days after randomization), the NYHA and Global Assessment scores used in determining CCS will be carried forward from the baseline or 3 month visit, as available. If a subject's 6 month visit is late and out of window, and they have no post-randomization NYHA or Global Assessment Score data to carry forward, they will be assigned a score of "Unchanged" in the absence of any events that would lead to them being classified as "Worsened". This sensitivity analysis will mirror the main ITT analysis, with ITT assignments for treatment, and using a Chi-square test with two-sided alpha = 0.05 to determine whether the alternative formulation of CCS is associated with treatment, as exemplified in the following SAS code:

```
*** Primary objective - sensitivity analysis #3;
proc freq data = analysis.PrimaryObj;
table aCRT_ITT*CCS_Improved_inWind/nocol nopercent chisq;
run;
```

Differences observed between this analysis and the main ITT analysis of the primary endpoint can provide evidence about the main endpoint's sensitivity to being measured within the protocol-defined visit windows.

6.2.3 Secondary Objective #1: Change in NYHA Class at 6 and 12 Months

Secondary objective #1 is to test the hypothesis that the odds of being in a higher NYHA class is different in the aCRT ON compared to those in the aCRT OFF group.

6.2.3.1 Hypothesis

Let NYHA class be an ordinal variable with a multinomial distribution. The odds ratio (OR) for being in the next higher stratum for aCRT ON versus aCRT OFF will be tested. The null and alternative hypotheses are:

H_0 : OR = 1

H_a : OR ≠ 1

6.2.3.2 Analysis Methods

NYHA class is an ordinal variable with higher classes indicating a worse degree of heart failure. NYHA class will be collected at baseline and at the 3, 6, and 12-month follow-up visits. NYHA class at follow-up assessments (hence excluding the baseline in the outcome variable) will be analyzed with a proportional odds logistic regression model that will account for the correlation of repeated assessments within each subject. The treatment arm allocation will be included as a main effect. The baseline NYHA class and time will also be included in the model as fixed covariates. Example SAS code is shown below:

```
*** Secondary objective #1: Change in NYHA class;
proc sort data = analysis.secObj1;
by PT t;
run;
proc glimmix data=analysis.secObj1;
class PT aCRT_ITT NYHA_base t;
model NYHA = aCRT_ITT NYHA_base t/ dist=multinomial link=cumlogit solution;
random intercept / subject=PT  type = ar(1);
run;
```

The proportional odds assumption will be assessed graphically using methods described in Harrell, 2001 with an outline and proprietary R code provided under separate cover. The assessment of whether the assumption is justified, given the observed effects, will be left to the statistician conducting the analysis. Should the assumptions underlying the proportional odds model seem insufficiently justified after this investigation, modifications to the general form may be made, including fitting a partial proportional odds model or collapsing the outcome variable to allow for a simpler logistic regression model with a binary response. An alternative specification (for example, collapsing levels of NYHA by grouping classes III/IV/V together and classes I and II together, and then using a standard binary response logistic regression) will also be considered should fewer than 5 subjects with NYHA > 3 exist in one of the two treatment arms at 6 or 12 months.

6.2.3.3 Determination of Subjects

The comparison of NYHA class by treatment group will be an ITT analysis.

6.2.3.4 Missing Data

It is expected that the primary cause of missing or unobserved NYHA values in this study will be due to death. As mentioned in section 6.2.1, the NYHA value will be set to class V for deceased subjects. Values at follow-ups that are unobserved for reasons other than mortality will be assumed to be Missing Completely At Random (MCAR) and will be excluded from the analysis; this assumption may be revisited if post-randomization attrition is unexpectedly high. As with the analysis of the primary objective, any subjects missing a NYHA class value at baseline will be assumed to be starting the study with NYHA class II.

6.2.4 Secondary Objective #2: Heart Failure Hospitalizations

6.2.4.1 Hypothesis

The hypothesis tested per secondary objective #2 is that the risk of Heart Failure (HF) hospitalization is lower for subjects randomized to aCRT ON as compared to subjects randomized to aCRT OFF. The null hypothesis is that the hazard for HF hospitalization is the same in both groups, and it will be tested against the two-sided alternative that the hazard differs between groups as follows:

H_0: $HR_{HF} = 1$

H_a: $HR_{HF} \neq 1$

where HR_{HF} is the hazard ratio in the aCRT ON group vs. the aCRT OFF group.

6.2.4.2 Analysis Methods

This analysis will investigate the effect of treatment group upon the time to first hospitalization for HF after randomization. Subsequent HF hospitalizations for a subject will be ignored for this objective. The risk of HF hospitalization during the 12 months after randomization will be assessed using a Cox proportional hazards regression model, with randomized group as a predictor variable. NYHA class and sex will also be included as covariates to partially account for informative censoring from the competing risk of death.

```
/*Secondary objective #2*/
proc phreg data = analysis.secObj2;
class aCRT_ITT;
model HFhospDays*HFhosp(0) = aCRT_ITT NYHA Sex/rl ties=exact;
hazardratio aCRT_ITT;
run;
```

A graphical comparison of the incidence of first HF Hospitalization will be made using plots of cumulative incidence functions in the aCRT ON and aCRT OFF groups with mortality as competing risk.

6.2.4.3 Determination of Subjects

The hypothesis test for differing risks of HF hospitalization by treatment group will be an ITT analysis.

6.2.4.4 Missing Data

A very high rate of capture for HF hospitalizations is expected for this study. It is noted that the risk of undercounting (i.e., sites failing to report a HF hospitalization event) is much higher than overcounting (reporting an event as an HF hospitalization when it does not, in actuality, meet the protocol-defined criteria). However, it is unclear why the rate of HF hospitalization misclassification would differ between randomization groups, and the simplifying assumption will be made that false positives and false negatives occur independently of treatment. It is acknowledged that censoring of HF hospitalizations may be informative due to the competing risk of death, with higher mortality rates and larger effects of aCRT upon mortality leading to greater distortions in parameter estimates for this objective. Given expected event rates, a sensitivity analysis will be performed to estimate the effect of one possible informative censoring regime, and is described below in section 6.2.4.5. The sensitivity analysis will be foregone in the presence of very low mortality rates (<=5 deaths in both treatment arms combined) as it is less likely that censoring will be informative in that scenario. If both mortality and HF hospitalization rates are very low, informative censoring from mortality may exert more of an influence on the hazard estimates, but the sensitivity will still be regarded as optional in that situation as the type II error rate of the analysis will be high under any imputation plan.

6.2.4.5 Sensitivity Analysis: Informative Censoring of HF Hospitalization Due to Mortality

In the Adaptive CRT study, 31/478 subjects (6.5%) died within 365 days of randomization. These subjects combined for 21 first hospitalizations in 15.4 subject-years. Under the strong assumption that all deceased subjects would have experienced a hospitalization for HF had they survived at least 365 days after randomization, an additional 10 events would have been observed. Given a similar set of event rates, the Mid-Q Response study can expect 14.3 deaths, with 9.5 observed HF hospitalizations, and up to 5.8 unobserved first HF hospitalizations in the affected subjects. The sensitivity to unobserved events in deceased subjects will be assessed by creating an alternate outcome variable which copies observed HF events, in which all subjects from the study arm with the higher death rate who experience mortality on day t (for all times t < 365 days) are assigned a HF event on day t + 1. This outcome will have a slightly higher event rate compared to its complete cases equivalent, and will then be substituted its place into the Cox regression model specified in section 6.2.4.2. If the treatment effect is associated with time to first HF hospitalization (i.e., if $p < 0.05$) in the sensitivity analysis but not in the complete cases analysis, or vice versa, then the results of both will be presented together. In this situation, a further sensitivity analysis involving a less extreme assumption about unobserved events (for instance, if only CV deaths would have had an associated HF hospitalization) may be performed as well. In the event the sensitivity analysis does not lead to a different conclusion regarding the effect of aCRT ON upon HF hospitalization, only the complete cases analysis will be presented as part of the objective, and the sensitivity analysis may be referenced and presented in an appendix to the final report.

6.2.5 Secondary Objective #3: All-cause and CV Mortality

The third secondary objective is to test two hypotheses about differences in (A) all-cause mortality and (B) mortality only from CV causes, between subjects randomized to aCRT ON and subjects randomized to aCRT OFF.

6.2.5.1 Hypothesis

The first hypothesis tested per this objective is that the proportion of subjects dying from any cause 365 days or less after randomization is different in subjects with aCRT ON compared to subjects with aCRT OFF. The following hypothesis will be tested in a two-sided test with $\alpha = 0.05$:

$H_0: \pi_{On} = \pi_{Off}$

$H_a: \pi_{On} \neq \pi_{Off}$

where π_{On} and π_{Off} are the Kaplan-Meier estimates of all-cause mortality in the intention-to-treat aCRT ON and aCRT OFF groups, respectively.

6.2.5.2 Analysis Methods for All-cause Mortality Comparison

The probability of a subject surviving for 365 days past randomization will be estimated using Kaplan-Meier methods. A two-sided 95% log-log confidence interval will be constructed, using Greenwood's formula to approximate the standard error. A log-rank test will be used to assess whether mortality differs between aCRT ON and aCRT OFF groups. This can be accomplished in SAS using code such as the following:

```
proc lifetest data = analysis.secObj3 plots =survival(atrisk failure) outsurv = kmout;
time SurvivalDays*Death(0);
survival conftype = loglog;
strata aCRT_ITT;
run;
```

Subjects will be censored at the last date of study contact (randomization, scheduled or unscheduled visits, termination/study exit date, AE or HCU event dates, or system modification dates) or at day 365 post-randomization, whichever comes first.

6.2.5.3 Determination of Subjects for All-cause Mortality Comparison

The comparison of all-cause mortality will be an ITT analysis.

6.2.5.4 Hypothesis

The second hypothesis to be tested for this objective is:

$H_0: HR_{CV} = 1$

$H_a: HR_{CV} \neq 1$

where HR_{CV} is the hazard ratio for cardiovascular-related mortality in the (ITT) aCRT ON group compared to the aCRT OFF group.

6.2.5.5 Analysis methods for CV-related Mortality Comparison

Medtronic safety personnel will classify each death per definitions in section 10.3.2 of the CIP as being a cardiac death (or otherwise), a sudden death (or otherwise), or unknown. An effort to sparingly categorize deaths as unknown will be made and that grouping will be reserved for cases only when there is insufficient information to classify. The CIP uses the term cardiac death to refer to "A death related to the electrical or mechanical dysfunction of the heart", but frames secondary objective #3 in terms of characterizing "cardiovascular mortality". For purposes of this SAP, this endpoint includes all cardiac deaths as well as any cardiovascular deaths that are not directly a result of mechanical or electrical heart dysfunction (for example, stroke or embolism).

Subjects will be censored at the last date of study contact (randomization, scheduled or unscheduled visits, termination/study exit date, AE or HCU event dates, or system modification dates), upon death from all other competing (non-cardiovascular) causes, or at day 365 post-randomization, whichever comes first. The probability of cardiovascular (CV) mortality within 365 days of randomization will be modeled using Cox proportional hazards regression. The model may be fit in SAS using the following code:

```
/*Secondary objective #3b*/
proc phreg data = analysis.secObj3;
class aCRT_ITT;
model CVdeathDays*CVdeath(0) = aCRT_ITT/rl ties=exact;
hazardratio aCRT_ITT;
run;
```

Additionally, a graphical representation of the CIF for CV mortality, along with the competing risk of non-CV mortality, will be displayed by group.

6.2.5.6 Determination of Subjects for CV-related Mortality Comparison

The comparison of CV-related mortality will be an ITT analysis.

6.2.5.7 Missing Data

For this objective, we will assume that (A) all mortality that occurs in enrolled subjects who are under study will be observed, and (B) all observed mortality will be correctly classified as CV mortality when the cause is, in fact, cardiovascular in nature. Censoring is assumed to be non-informative, allowing for a "complete cases" analysis with statistically unbiased estimates.

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

6.3 Center Pooling

Site will be included as a random effect in a sensitivity analysis of the primary endpoint to account for the site-by-site variability in the assessment. Descriptive statistics for the primary endpoint will be reported study-wide and by investigational sites. In the circumstance where the statistical model described in section 6.2.2.8 cannot converge due to low enrollments of some sites, sites with fewer than 5 randomized subjects will be combined, first to other small sites within country. If all small sites in a country still have fewer than 5 randomized subjects combined, they will be combined with the smallest site from that country with 5 or more subjects. For the study's final report, no formal assessments of country-to-country or site-to-site heterogeneity are planned, and data from all participating study centers will be pooled for all primary, secondary and ancillary objectives. For purposes beyond the final report, additional subsetting of any pre-specified analyses may be performed as needed if required by local regulatory authorities.

6.4 Handling of Missing, Unused, and Spurious Data and Dropouts

All available data will be summarized in tables and listings. Predetermined plans for handling and/or assessing the effects of missing data for the primary and secondary objectives are specified separately within each section 6.2.2 – 6.2.5 along with the other accompanying analytical procedures. Missing data procedures referenced in this SAP use terminology and definitions as described in Carpenter, Pocock and Lamm (2002). It is noted that for the primary objective, the Clinical Composite Score endpoint is defined for all subjects, even if contributing data is missing. For each other objective, all expected data points that are missing data will be reported, along with the number of affected subjects. Data management practices to identify and correct spurious data will be performed in accordance with Medtronic Standard Operating Procedures (SOPs). There are no predetermined plans to perform anything other than complete cases analyses for all ancillary objectives at the time of this SAP, although

ancillary objective #1 (KCCQ) will have an associated sensitivity analysis performed under certain conditions. If, under the course of the study, it becomes apparent that the Missing Completely At Random (MCAR) or MAR assumptions are unlikely to be met for ancillary endpoints, appropriate sensitivity analyses may be devised and performed at that time.

6.5 Adjustments for Multiple Comparisons

A Hommel multiple testing procedure will be utilized to maintain an overall type I error rate of 0.05 for the four hypotheses being tested among the study's three secondary objectives. These four hypotheses are that NYHA class, hazard for HF hospitalization, all-cause mortality, and CV mortality differ between ITT treatment groups, and are described in sections 6.2.3.1, 6.2.4.1, 6.2.5.1 and 6.2.5.4, respectively.

The Hommel procedure is a "step-up" method of error adjustment.

This adjustment may be done using an implementation such as the code below for SAS Proc Multtest:

```
proc multtest inpvalues = analysis.results hommel;
where find(Objective,"Secondary") > 0;
run;
```

It is noted that each p-value will be reported without adjustment in the final report. This multiplicity procedure is performed strictly to aid in the interpretation of the combined results of the secondary objectives.

6.6 Interim Analyses

No interim analyses will be performed for the Mid-Q Response study and there are no criteria defined for termination of the study on statistical grounds.

6.7 Subgroup Analyses

A limited number of additional analyses may be performed to evaluate evidence for a differential effect of aCRT upon the primary endpoint and secondary endpoints of HF hospitalization, CV mortality, and all-cause mortality within subgroups of subjects. NYHA class as a secondary endpoint (measured at 3, 6 and 12 months) may or may not be analyzed within subgroups, depending on characteristics of the variable that are evident from analyses outlined in sections 6.2.3. The CIP identifies the following variables as the basis for subgroup analyses: age, sex, etiology of HF, Left Ventricular Ejection Fraction (LVEF), NYHA class, body height, and QRS duration. It is noted that race and ethnicity, which are typically identified in subgroup analyses in US-based clinical studies, are not collected in the Mid-Q Response study. It is also noted that the effect of NYHA and sex on the CCS will be investigated separately as part of the sensitivity analysis outlined in section 6.2.2.7, and that the effects of height and QRS duration upon the primary outcome will be estimated as part of ancillary objective #2 (see section 6.2.7).

In the context of subgrouping strata, values for the variables of age, sex, height, and NYHA class refer data recorded on the Baseline CRF, while QRS duration and LVEF refer to values captured on the enrollment CRF. Etiology of HF will be categorized as either ischemic or non-ischemic. Subgroups among continuous variables (age, height, LVEF and QRS duration) may be divided into quartiles, allowing the simultaneous presentation of odds ratios (or hazard ratios, for secondary endpoints) within subgroups in

a Forest plot. Subgroup analyses will be ITT and, to the degree that is possible, will conserve the methods of the corresponding primary or secondary objective.

6.8 Changes to Planned Analysis

Additional details on analysis methods have been added to this SAP, but no changes to the methods defined in the Mid-Q Response CIP version 1 are noted. Future revisions of the Mid-Q response SAP may occur, but deviations from the Mid-Q Response CIP version 1 will require a corresponding CIP revision or, alternatively, a description in the final report, along with the rationale for the deviation. Likewise, deviation from this SAP in the analysis methods of any pre-defined objectives will be documented and explained in the final report.

7. Determination of Sample Size

Sample size calculations were performed to find the number of enrollments required such that a Pearson's chi-squared test with two-sided $\alpha = 0.05$ would have >80% power when 75% of subjects assigned to aCRT ON and 55% of subjects assigned to have aCRT OFF have improved CCS at six months after randomization. Over the first six months of study, a crossover rate of 3% between both treatment groups is assumed. Given these constraints, it was determined that 220 subjects would need to be randomized, and assuming an attrition rate of 5% from baseline to 6-months post-randomization, **a total of 232 subjects will need to be enrolled in the Mid-Q Response study**. Rationale regarding the estimates for treatment group success rate, control group success rate and six-month crossover rates is provided in the Mid-Q Response CIP. Sample size was estimated by simulation in SAS version 9.4, and independently verified using a simulation in R version 3.4.3. The R code for the sample size calculation is provided under separate cover.

8. Validation Requirements

Verification of analysis of the study's primary objective will be completed with level I validation (independent programming). Secondary and ancillary objectives will be validated with a minimum of level II validation. Analyses that are not related to primary objectives or ancillary endpoints will be validated at a minimum of level II validation if being presented externally in an abstract or publication.

9. References

1. Allison P. "For Causal Analysis of Competing Risks, Don't Use Fine & Gray's Subdistribution Method". *Statistical Horizons Blog*, March 24, 2018. https://statisticalhorizons.com/for-causal-analysis-of-competing-risks
2. Carpenter J, Pocock S, and Lamm CJ (2002). Coping with missing data in clinical trials: A model-based approach applied to asthma trials. *Statistics in Medicine*, 21(8), 1043-66. doi:10.1002/sim.1065
3. Fisher LD, Dixon DO, Herson J, Frankowski RK, Hearron MS, Peace KE. Intention to treat in clinical trials. In: Peace KE, editor. Statistical issues in drug research and development. New York: Marcel Dekker; 1990. pp. 331–50.

4. Green CP, Porter CB, Bresnahan DR, Spertus JA (2000). KCCQ: A New Health Status Measure for CHF. *JACC* 35(5), 1245-55.
5. Harrell FE (2001). *Regression modeling strategies: With applications to linear models, logistic regression, and survival analysis*. New York: Springer.
6. Hommel G (1988). A stagewise rejective multiple test procedure based on a modified Bonferroni test. *Biometrika*, 75, 383-6.
7. Packer M (2001). Proposal for a new Clinical End Point to Evaluate the Efficacy of Drugs and Devices in the Treatment of Chronic Heart Failure. *Journal of Cardiac Failure*, 7(2), 176-82.