Statistical Analysis Plan

Clinical Investigation Plan Title	Attain Stability™ Quad Clinical Study
Clinical Investigation Plan Version	Version 3.0 20 March 2017
Sponsor/Local Sponsor	Medtronic, Inc. 8200 Coral Sea Street NE Mounds View, MN U.S.A. 55112 1-800-328-2518
Document Version	1.0

[redacted]

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1. Version History

Version	Summary of Changes	Author(s)/Title
1.0	• 'Not Applicable, New Document'	Joao Monteiro/ Sr Statistician Adam Himes/ Sr Pr Test Engineering

2. List of Abbreviations and Definitions of Terms

Abbreviation	Definition
ACC	American College of Cardiology
AHA	American Heart Association
BMI	Body Mass Index
CABG	Coronary Artery Bypass Graft
CIP	Clinical Investigation Plan
CEC	Clinical Events Committee
CRF	Case Report Form
CRT	Cardiac Resynchronization Therapy: Established pacing therapy for patients with heart failure
CRT-D	Cardiac Resynchronization Therapy - Defibrillator
CRT-P	Cardiac Resynchronization Therapy - Pacemaker
CS cannulation	Coronary Sinus cannulation
eCRF	Electronic Case Report Form
EMEA	Europe, Middle East, Africa
FDA	Food and Drug Administration
HRS	Heart Rhythm Society
IDE	Investigational Device Exemption
LV	Left Ventricular
MI	Myocardial Infarction
NYHA	New York Heart Association
OUS	Outside of the United States
PCT	Pacing Capture Threshold
PMA	Premarket Approval
PNS	Phrenic Nerve Stimulation

Abbreviation	Definition
PTCA	Percutaneous Transluminal Coronary Angioplasty
RA	Right Atrial
RV	Right Ventricular
SAP	Statistical Analysis Plan
US	United States

3. Introduction

The Attain Stability™ Quad LV Lead Clinical Study is a prospective, non-randomized, multi-site, global, Investigational Device Exemption (IDE), interventional clinical study. The purpose of this clinical study is to evaluate the safety and efficacy of the Attain Stability Quad MRI SureScan LV Lead (Model 4798). This study will not be considered investigational in geographies with CE Mark of the Attain Stability Quad MRI SureScan LV lead (Model 4798). However, data collected from all study subjects will be represented in the PMA Supplement (PMA-S) and all clinical reports. Subjects successfully implanted with the Attain Stability Quad MRI SureScan LV Lead (Model 4798) will be followed at implant, three months, six months and every six months thereafter until FDA approval is obtained or until study closure, whichever comes first.

This Statistical Analysis Plan (SAP) has been designed to document, before data is analyzed, the rationale for the study design, and the planned analyses related to the primary objective and secondary objectives. Additional analysis of the study data beyond this plan may be conducted to provide evidence further supporting the market approval of the lead and additional publications. The statistical analyses conducted for publications and/or ad-hoc requests may not be limited to this document.

The Attain Stability™ Quad Clinical Study CIP Version 3.0, dated 20 March 2017 was used to create this SAP.

4. Study Objectives

4.1. Primary objective

The primary objective of the study is to assess the safety and characterize the efficacy of the Attain Stability Quad MRI SureScan LV Lead (Model 4798).

Primary Safety Objective: Lead complication-free rate at 6 months

The Attain Stability Quad MRI SureScan LV Lead (Model 4798) will be considered safe if the probability of subjects free of Model 4798 lead-related complications at 6 months post-implant is greater than 87%.

Primary Efficacy Objectives: Lead pacing capture thresholds at 6 months

To demonstrate the effectiveness of the Attain Stability Quad MRI SureScan LV Lead (Model 4798), the study will evaluate the likelihood that there are at least two programmable vectors for each patient post

implant. The effectiveness of this lead will be evaluated based on two primary efficacy objectives. More specifically, both primary efficacy objectives must be met simultaneously.

Primary Efficacy Objective #1
The Attain Stability Quad MRI SureScan LV Lead (Model 4798) will meet this objective if the proportion of subjects with at least one LV lead pacing vector having a pacing capture threshold less than or equal to 2.5 V at 0.5 ms pulse width (with absence of Phrenic Nerve Stimulation (PNS) at 5.0 V) at 6 months post-implant is greater than 80%.

Primary Efficacy Objective #2
The Attain Stability Quad MRI SureScan LV Lead (Model 4798) will meet this objective if the proportion of subjects with at least one additional (or second) LV lead pacing vector having a pacing capture threshold less than or equal to 4.0 V at 0.5 ms pulse width (with absence of PNS at 5.0 V) at 6 months post-implant is greater than 80%.

4.2. Secondary Objectives

The secondary objectives are descriptive in nature and are intended to provide additional information about the Attain Stability Quad MRI SureScan LV Lead (Model 4798). There will be no established performance requirements for these secondary objectives.

- To summarize implant procedure related information: success rate, implant related times
- To estimate 6-month reliability: post implant lead failure modes (i.e. complication rate)
- To estimate electrical measurement values (Pacing Capture Thresholds (PCTs) and Lead Impedance) at 6 months post-implant

5. Investigation Plan

The Attain Stability™ Quad Clinical Study is a prospective, non-randomized, multi-site, global, IDE, interventional clinical study. Up to 471 subjects may be enrolled in the study.

The inclusion and exclusion criteria to be enrolled in the study are as follows:

Inclusion criteria

- Patient meets CRT implant criteria as determined by local regulatory and/or hospital policy (i.e. US subjects should meet CRT device indications per the HRS/ACC/AHA guidelines)
- Patient (or legally authorized representative) has signed and dated the study-specific Consent Form
- Patient is 18 years of age or older, or is of legal age to give informed consent per local and national law
- Patient is expected to remain available for follow-up visits

Exclusion criteria

- Patient has had a previous unsuccessful LV lead implant attempt
- Patient has a previous CRT system or LV lead implanted (for example, transvenous or epicardial)
- Patient is currently implanted with a recalled (i.e. market-withdrawn, recalled or safety alert) RA and/or RV lead
- Patient has known coronary venous vasculature that is inadequate for lead placement
- Patient has unstable angina pectoris or has had an acute myocardial infarction (MI) within the past 30 days
- Patient has had a coronary artery bypass graft (CABG) or percutaneous transluminal coronary angioplasty (PTCA) within the past 90 days

- Patient has contraindications for standard transvenous cardiac pacing (e.g., mechanical right heart valve)
- Patient has had a heart transplant (patients waiting for heart transplants are allowed in the study)
- Patient has known renal insufficiency and/or significant allergy to contrast dye that would prevent them from receiving an occlusive venogram during the implant procedure
- Patient is contraindicated for <1mg dexamethasone acetate
- Patient is enrolled in any concurrent drug and/or device study that may confound the results of this study
- Patient has a terminal illness and is not expected to survive more than six months
- Patient meets exclusion criteria required by local law (e.g. age, pregnancy, breast feeding, etc.)
- Patient is unable to tolerate an urgent thoracotomy

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

- Subjects will be evaluated at baseline to confirm eligibility for enrollment with defined inclusion/exclusion criteria
- Subject demographics and medical history will be collected at baseline and differences that may affect primary endpoints will be identified
- To ensure widespread distribution of data between sites, the maximum number of subjects allowed per site is 50
- All implanters in the study will be experienced in the implant of CRT-P and/or CRT-D systems
- Data collection requirements and study procedures will be standardized across all sites and geographies
- All study site personnel and Medtronic personnel will be trained on their respective aspects of the study using standardized training materials, and required to follow the CIP
- Per the specifications in the Monitoring Plan, monitoring visits will be conducted for adherence to the CIP and to verify the CRF data against source data
- Pre-defined statistical methods specified in the CIP and the Statistical Analysis Plan (SAP) will be followed
- The Steering Committee members will not have influence on the treatment decisions by study site investigators during the trial
- An independent and blinded CEC will regularly review and adjudicate reported adverse events and deaths
- Registration of the trial on ClinicalTrials.gov and the publication plan will ensure that study results will be reported
- All study investigators are required to meet 21 CFR Part 54, Financial Disclosure by Clinical Investigators, to identify potential bias due to financial interest in the outcome of the study

6. Determination of Sample Size

The sample size requirement at 6-months for each of the study objectives is displayed in

Table 1. The first row does not account for attrition, while the second row is inflated by 15% attrition which accounts for 5% pre-procedure and 10% post procedure attritions. The sample size requirement for Secondary Objective #2 was given by the FDA as a requirement for evaluating post implant lead failures. Therefore, the overall sample size for the study is 471.

Table 1: Require Sample size by Study Objective

	Primary Safety Objective	Primary Efficacy Objective #1	Primary Efficacy Objective #2	Secondary Objective #1	Secondary Objective #2 (post-implant failure modes)	Secondary Objective #3	Overall
Number needed at 6-months	170	145	50	NA	400	NA	400
Number of enrollments	200	171	59	NA	471	NA	471

7. Statistical Methods

7.1. Study Subjects

7.1.1. Disposition of Subjects

A STROBE flow diagram will be used to describe the disposition of study subjects.

Figure 1 shows an example of a blank STROBE flow diagram.

Allocation:

Since the Attain Stability™ Quad Clinical Study is not a randomized study, all study subjects that are enrolled are allocated to the intervention (i.e. implanted with Attain Stability™ Quad Clinical Study).

Follow-up:

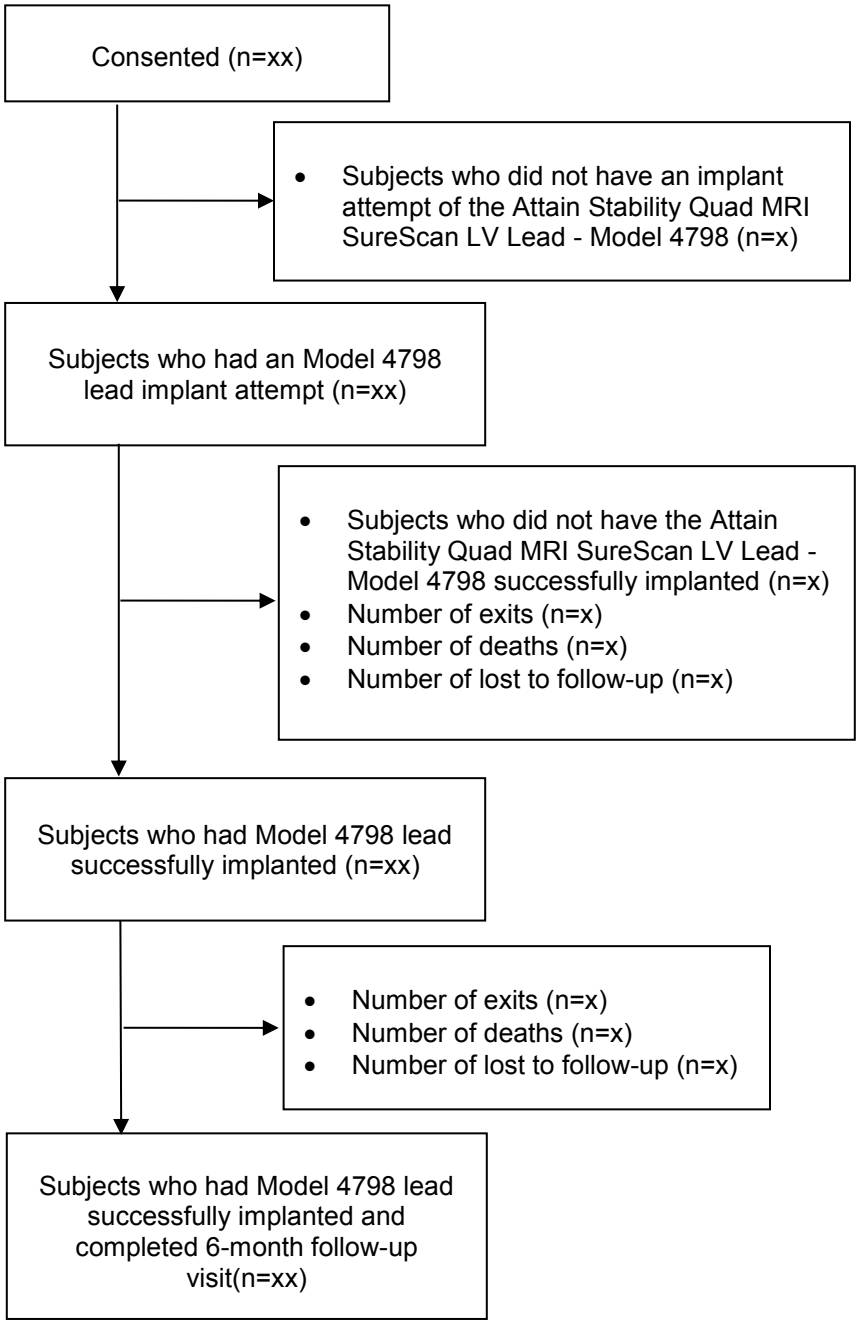
All Model 4798 lead implanted subjects will be followed until study closure or subject exiting from the study due, but not limited, to the following reasons:

- Study subject withdrawal of consent
- Study subject death
- Lost to follow-up
- Investigator withdraws subject from the study
- Other reasons described by the study subject

Analysis:

Analyses of study objectives will be completed for subjects with valid data entries, e.g. save-complete case report forms and CEC fully adjudicated adverse events, etc. If there is missing data that prevents the analysis of a pre-specified objective then those test subjects will be excluded from that objective. Unless otherwise specified, there will be no imputation for missing data. Additional sensitivity analysis will be carried out to assess impact of missing data on study objectives.

Figure 1 – Attain Stability™ Quad Clinical Study



7.1.2. CIP Deviations

Deviations from the CIP will be collected on the Study Deviation CRF. Deviations will be summarized in the final report in a table by coded category. Deviation coding will be performed by Medtronic. The number of deviations per category, and the number and percentage of subjects with a deviation in each category will be reported.

7.1.3. Analysis Sets

There will be three analysis sets used in this study:

Analysis Set #1:
All subjects who undergo Model 4798 lead implant attempt procedure.

Analysis Set #2:
All subjects who are successfully implanted with a Model 4798 lead and with valid[1] pacing data collected at 6 months post implant follow-up visit.

Analysis Set #3:
All subjects who are successfully implanted with a Model 4798 lead and who completed the 6-month post implant follow-up visit or experienced lead failure prior to 6-months.

If a subject experienced multiple Model 4798 lead implant procedures (e.g. a second lead was implanted due to a system modification of the initialed implanted lead), only first experience will be included for the analysis. Multiple lead attempts during this same procedure will not be counted as multiple procedures.

7.1.4. Primary Endpoints

Primary Safety Endpoint
The study primary safety endpoint is Attain Stability Quad MRI SureScan LV Lead (Model 4798) related complications through 6 months post implant. All reported system and procedure-related adverse events will be reviewed by an event review committee for LV lead relatedness and severity.

Primary Efficacy Endpoint #1
The Model 4798 LV lead has sixteen (16) programmable pacing vectors. The endpoint for the primary efficacy objective is whether there is at least one Model 4798 LV lead pacing vector with pacing capture voltage thresholds less than or equal to 2.5V (with absence of PNS at 5.0 V). This endpoint will be measured at the 6-month post implant follow-up visit.

Primary Efficacy Endpoint #2
The co-primary efficacy endpoint is whether a second Model 4798 lead configuration has a pacing capture threshold less than or equal to 4V (with absence of PNS at 5.0 V), excluding the pacing vector that is already counted to the primary efficacy endpoint #1. This endpoint will be measured at 6-month post implant follow-up visit.

[1] PCT measured at pulse width ≤ 0.5 ms

7.1.5. Secondary Endpoints

To summarize implant procedure related information
Implant procedure related endpoints will include implant success rate and procedure durations.

To estimate 6-month reliability
The Model 4798 LV lead 6-month reliability endpoint is Model 4798 lead related complications.

To estimate electrical measurement values (PCTs and Lead Impedance) at 6 months post-implant
The electrical measurements endpoints are pacing capture thresholds and impedance values collected at each time point (i.e. Implant, 6 months, etc.).

7.2. Center Pooling

The Attain Stability™ Quad Clinical Study is expected to be conducted at up to 56 sites worldwide, with a total enrollment of 471 subjects across all study centers. Participating geographies are expected to include, but are not limited to: the United States (US), Canada, EMEA, Malaysia, and Hong Kong. Per the CIP, each center will enroll between 0 and 50 subjects.

The primary analysis for all study objectives will include valid data entries from all study sites. In additional, sensitivity analysis will be conducted to assess in characteristics of each region and/or study site impact the overall study results. Specifically, this analysis will investigate whether sites exhibit significant heterogeneity in event rates, and whether geography (a binary variable representing whether a site is located in the US or outside United States (OUS)) moderates any statistically significant heterogeneity that is observed. Models will be fit separately for each primary outcome; in the analysis of each, centers within the US having ≤5 subjects with complete data will be considered as coming from one center, here denoted as 'US small'. Similarly, `OUS small' will be the collection of data from centers outside the US having ≤5 subjects with complete data. If a Cochran's Q-test for heterogeneity shows $p<0.05$, it will be taken as evidence of significant heterogeneity between sites. Evidence of between-site heterogeneity will not necessarily preclude pooling data; rather, it will prompt further investigation into the sources of the apparent differences in event rates between sites. At a minimum, findings of analyses on heterogeneity between study sites and between all US and OUS sites will be shown in the final report in a table by endpoint.

In addition, summary statistics for baseline characteristics and primary endpoints by study center may be provided in clinical reports. See examples below (actual format may vary).

Table A: Baseline Characteristics by Center

Site	Number of Subjects Underwent Model 4798 Implant Attempt	Mean LVEF (± SD)	Mean QRS (± SD)	% Subjects with NYHA Class III/IV
Medical Center X				
Medical Center Y				
Medical Center Z				

Primary Objective Results by Site					
Site	**Number of Subjects Underwent Model 4798 Implant Attempt**	**Number of Subjects implanted successfully with Model 4798 Lead**	**Number of Subjects with Model 4798 Related Complications through 6-months post-implant**	**% of Subjects with at least 2 vectors with PCT≤ 4.0V**	**% of Subjects with at least one vector with PCT≤2.5V**
Medical Center X					
Medical Center Y					
Medical Center Z					

7.3. Handling of Missing Data and Dropouts

Unless otherwise specified, if data is missing then there will be no imputation of the data. Instead, subjects with missing data will be excluded. Survival analyses will consider time to event censored at the last contact for lost to follow-up subjects.

7.4. Adjustments for Multiple Comparisons

No adjustments will be made for multiple comparisons.

7.5. Demographic and Other Baseline Characteristics

Several characteristics will be reported for each enrolled subject at time of enrollment. The variables collected will include, but not limited to, subject age, gender, body mass index (BMI), left ventricular ejection fraction (LVEF), intrinsic QRS duration, New York Heart Association (NYHA) class and medical history. Tables and descriptive statistics will be used to summarize subject data with respect to these variables. For quantitative variables, the mean, standard deviation, median, first and third quartiles, minimum and maximum will be presented. For qualitative variables, counts and percentages will be given.

Sensitivity analysis will also be carried out using a similar method as outlined in section 7.2 to assess in subject gender affects overall study outcome.

7.6. Treatment Characteristics

Statistical summaries for treatment characteristic variables (on the LV Lead Implant Procedure CRF) will be reported. Continuous variables will be reported as mean, standard deviation, median, minimum, maximum, and quartiles. Categorical variables will be reported as number and percentage of subjects. The procedure variables to be summarized will include, but not limited to, CRT implant timing, operative time, LV lead implant timing, number of LV lead implant attempts, reason for being unable to implant the LV lead, diameter of the cardiac vein at final LV lead tip position, final location of LV tip electrode, final location of helix, final vector programmed for LV pacing configuration, reason for choosing final programmed vector.

7.7. Interim Analyses

The study protocol specified one non-formal interim analysis for secondary objective #2 (6-month reliability). See Section 7.8.4 for details. No formal interim analysis is planned for study primary objectives; or other secondary objectives.

7.8. Evaluation of Objectives

7.8.1. Primary Safety Objective

The Attain Stability™ Quad MRI SureScan LV Lead (Model 4798) will be considered safe if the probability of subjects free of Model 4798 lead-related complications at 6 months post-implant is greater than 87% (i.e., the lower bound of a one-sided 97.5% confidence interval must be greater than 87%).

Hypothesis:
H_0: $S_{(6\text{-month})} \leq 87\%$
H_1: $S_{(6\text{-month})} > 87\%$

where $S_{6\text{-month}}$ is the probability that a subject remains free from Model 4798 lead related complications through 6 months since implant.

Analysis Dataset:

Analysis set #1 per section 7.1.3.

Analysis Method:

A standard time to first event survival analysis type will be performed to investigate the hypothesis proposed in the primary safety objective. More specifically, the Kaplan-Meier method will be used to estimate the probability of a subject surviving from any Model 4798 lead-related complication as a function of time; the 1-sided 97.5% confidence limit lower bound for the survival probability at 6 months (183 days) will be calculated using the log-log survival function approach (Kalbfleisch and Prentice 2002)[2]. For the purposes of this analysis, time 0 is defined as the day a subject undergoes the implant procedure of the Attain Stability Quad MRI SureScan LV Lead (Model 4798), which is independent of success status of this implant procedure. For the survival analysis, an event is defined as an Attain Stability Quad MRI SureScan LV Lead (Model 4798) related complication according to Clinical Events Committee (CEC) adjudication. Event date is the onset date of a subject's first complication that is related to the Attain Stability Quad MRI SureScan LV Lead (Model 4798). The definition of "complication" and "LV lead related" can be found on the study CIP. Subjects who undergo an Attain Stability Quad MRI SureScan LV Lead (Model 4798) implant attempt and do not experience any LV lead related complications will have their time to event censored at their last known time to exposure to the initial Attain Stability Quad MRI SureScan LV Lead (Model 4798). For any lost to follow-up subject, the last contact date will be used as the censor date.

Additional Analysis:

Sensitivity analyses will be performed to assess the robustness of the results. In particular,

[2] Kalbfleisch, J.D. and Prentice, R.L. (2002). *The Statistical Analysis of Failure Time Data*. Second Edition. John Wiley & Sons, Inc. New York.

- In the event a site investigator disagrees with the CEC's classification of an event, site investigator's event classification will be disclosed, however only CEC final adjudication results will be used for the statistical analysis. In the event when CEC final adjudication of relatedness of an event is "unknown", the "worst-case" scenario analysis will be carried out where the event will be counted as a lead related event in addition to the primary analysis of this objective.

- A tipping point survival analysis will be performed. In particular, subjects having time to event censored before 6 months will be considered one-by-one (by implant date) as observed events. Therefore, the 6-month survival intervals will be calculated for all scenarios in which a censored subject becomes an event.
- A similar survival analysis will be performed, but considering the first 200 subjects who had at least an implant attempt of the Attain Stability Quad MRI SureScan LV Lead - Model 4798. The first 200 subjects will be selected based on the date of implant. In case of a tie (for the 200th position) among subjects who are implanted on the same day, the initial procedure time (converted to U.S. central time) will be used to select the first 200 subjects.

7.8.2. Primary Efficacy Objective

To demonstrate the effectiveness of the Attain Stability Quad MRI SureScan LV Lead (Model 4798), the study will evaluate the likelihood that there are at least two programmable vectors for each patient post implant. The effectiveness of this lead will be evaluated based on two primary efficacy objectives. Both primary efficacy objectives must be met simultaneously.

Primary Efficacy Objective #1

The Attain Stability Quad MRI SureScan LV Lead (Model 4798) will meet this objective if the proportion of subjects with at least one LV lead pacing vector having a pacing capture threshold less than or equal to 2.5 V at 0.5 ms pulse width (with absence of Phrenic Nerve Stimulation (PNS) at 5.0 V) at 6 months post-implant is greater than 80%.

Hypothesis
H_0: $P1_{6\text{-month}} \leq 80\%$
H_A: $P1_{6\text{-month}} > 80\%$

where $P1_{6\text{-month}}$ is the proportion of subjects with pacing voltage thresholds ≤ 2.5V at 0.5ms (with absence of PNS at 5.0 V) at 6 months follow-up visit post-implant for at least one LV lead pacing vector.

Primary Efficacy Objective #2

The Attain Stability Quad MRI SureScan LV Lead (Model 4798) will meet this objective if the proportion of subjects having the two following conditions satisfied at the 6-month follow-up visit is greater than 80%:

- At least two LV lead pacing vectors having PCT less than or equal to 4.0 V at 0.5 ms pulse width and absence of PNS at 5.0V
- At least one LV lead pacing vector having PCT less than or equal to 2.5 V at 0.5 ms pulse width and absence of PNS at 5.0V

Hypothesis
H_0: $P2_{6\text{-month}} \leq 80\%$
H_A: $P2_{6\text{-month}} > 80\%$

where $P2_{6\text{-month}}$ is the proportion of subjects meeting the two conditions above.

Analysis Dataset:

Analysis set #2 per section 7.1.3.

Analysis Method:

The lower bound of the 1-sided 97.5% Confidence Interval for $P1_{6\text{-month}}$ and $P2_{6\text{-month}}$ will be calculated using the Clopper-Pearson method. More specifically,

- For the primary efficacy objective #1, the number of successes observed is defined as the number of subjects who had at the 6-month follow-up visit at least one vector with pacing voltage thresholds ≤ 2.5V at 0.5ms and absence of PNS at 5.0 V.

- For the primary efficacy objective #2, the number of successes observed is defined as the number of subjects who had a) at least two LV lead pacing vectors having PCT less than or equal to 4.0 V and absence of PNS at 5.0V b) At least one LV lead pacing vector having PCT less than or equal to 2.5 V at 0.5ms and absence of PNS at 5.0 V.

For both objectives, only Model 4798 lead successfully implanted subjects who had the 6-month follow-up and performed the PNS testing will be considered.

Additional Analysis:

Sensitivity analyses will be performed to assess the robustness of the results. In particular,

- A tipping point analysis will be performed to find how many more failures are necessary to not meet the primary efficacy objectives.

- Repeat these analyses using the first 200 subjects who are successfully implanted with a Model 4798 lead and have valid pacing data collected at 6 months post implant follow-up visit. In case of a tie (for the 200th position) among subjects who are implanted on the same day, the initial procedure time (converted to U.S. central time) will be used to select the first 200 subjects.

7.8.3. Secondary Objective #1

The first secondary objective is to summarize implant procedure information.

Analysis Dataset:

Analysis set #1 per section 7.1.3.

Analysis Method:

Descriptive statistics will be computed. The Attain Stability Quad LV lead implant success rate will be estimated as the number of subjects with Attain Stability Quad MRI SureScan LV Lead (Model 4798) successfully implanted divided by the total number of subjects who undergoes an Attain Stability Quad MRI SureScan LV Lead (Model 4798) implant attempt. A 2-sided 95% Confidence Interval will be calculated using the Clopper-Pearson method.

Procedure times are collected via eCRF. Only subjects with the Attain Stability Quad MRI SureScan LV Lead (Model 4798) successfully implanted will be included in this calculation.

- The total implant procedure time is defined as time from initial incision to final skin closure.
- Fluoroscopy time is defined as the total time the fluoroscope is imaging.
- Cannulation time is defined as the time from insertion of the first CS cannulation catheter to the first successful CS cannulation.
- Successful lead placement time is defined as the time from lead insertion of the successfully placed lead to the time when the lead is placed in its first acceptable pacing location. If a subject

experienced multiple implant attempts during the same procedure, only the final successful attempt will be included in this analysis.

Statistical summaries (e.g. mean, standard deviation, min, max, median) will be compute for these procedure times.

7.8.4. Secondary Objective #2

The second secondary objective aims to estimate the probability of post implant lead failure through 6 months for each individual failure type (e.g. lead dislodgement, infection, device capturing issue).

Analysis Dataset:

To proactively address FDA reviewer's potential questions at the time of PMA-s submission, two approaches will be considered: (a) standard frequentist approach and (b) Bayesian approach borrowing information from historical datasets. Per FDA requirement, the study reports will provide standard frequentist estimates as primary results. The analysis dataset will consist of all subjects successfully implanted with the Attain Stability Quad MRI SureScan LV Lead (Model 4798) and who completed at least 6-month follow-up or experienced lead failure prior to 6-months (i.e. Analysis set #3 per section 7.1.3.). For the Bayesian approach, analysis will be performed using data from the first 360 subjects successfully implanted with the Attain Stability Quad MRI SureScan LV Lead (Model 4798) and who completed the 6-month follow-up. In addition, the Bayesian approach will use historical datasets from the Attain Stability and Attain Performa clinical studies, described in more detail below.

Analysis Method:

Standard Frequentist Approach

For each lead failure mode, the Attain Stability Quad LV lead failure rate will be estimated as the number of subjects with Attain Stability Quad MRI SureScan LV Lead (Model 4798) failure before 6 months (183 days) divided by the total number of subjects successfully implanted with an Attain Stability Quad MRI SureScan LV Lead (Model 4798) successfully implanted and who completed at least the 6-month follow-up or had a lead failure before 6 months post-implant. A 2-sided 95% Confidence Interval will be calculated using the Clopper-Pearson method.

Bayesian Approach

The Bayesian analysis will be conducted as a virtual adaptive study. The interim look dataset will be constructed as it would have been available after the 360th patient was enrolled, and the additional enrollment will be computed. The final analysis will be conducted using only the data from the interim and additional enrollment, along with the historical prior data, to simulate the results of an adaptive study.

Methodology

Historical data from the Attain Stability and Attain Performa Clinical studies will be incorporated using the power prior methodology with a discount function[3]. A maximum weight of 37 effective patients will be

[3] Haddad, Tarek, et al. "Incorporation of stochastic engineering models as prior information in Bayesian medical device trials." *Journal of Biopharmaceutical Statistics* (2017): 1-15.

given to the historical data, equal to the number of subjects in the Attain Stability OUS study that had follow up data at six months or longer with an Attain Stability lead. Historical data will be scaled to create an effective weight of 37 patients in the case of the Attain Performa historical data because the actual study enrolled 401 patients.

The Attain Stability data will be applied only to complications associated with lead fixation: dislodgement and perforation. There were 0 events for 37 patients in the Attain Stability study. The Attain Performa data will be applied to all other complications. There were 10 non-fixation complications in the Attain Performance study, out of 401 patients.

There are three steps in the methodology:

1. Compare the historical and current data to create a measure of similarity, p
2. Compute the effective sample size a_0 of the historical data using a discount function based on the level of similarity
3. Combine the historical data y_0 and current data y using the calculated weight a_0 to get the combined data set $y + a_0 y_0$

These three steps are performed at the interim analysis and at the final analysis.

Comparison

Let y and y_0 be the number of events that occur for the current data and historical data respectively and let n and n_0 be the total number of subjects for the current and historical studies that reach the 6 month time point or had an event. A discount function is used to adjust the strength of the prior according to the agreement between current and historical data.

Suppose we develop the posterior distribution of $\tilde{\theta}$ and θ_0 for the current data and historical data, respectively, both with minimally informative priors. Calculate θ as:

$$\tilde{\theta} \sim beta(\mathrm{y}+1, \mathrm{n}-\mathrm{y}+1) \quad (1)$$

$$\theta_0 \sim beta(y_0+1, n_0-y_0+1) \quad (2)$$

We can stochastically compare the distribution of $\tilde{\theta}$ to θ_0 as follows:

$$p = P(\tilde{\theta} \leq \theta_0 | y, n, y_0, n_0) \quad (3)$$

Equation (3) can be calculated by drawing m samples of $\tilde{\theta}$ and θ_h from (1) and (2) (i.e. $\widetilde{\theta^1}, \widetilde{\theta^2} \ldots \widetilde{\theta^m}$ and $\theta_0^1, \theta_0^2 \ldots \theta_0^m$)

$$p = P(\tilde{\theta} \leq \theta_0) = \frac{1}{m} \sum I\{\tilde{\theta}^i < \theta_0^i\}$$

The resulting p-value is then used to compute the discount function.

Compute the discount function

The weight of the historical data will be computed with a discount function based on the measure of similarity p. The historical data will be scaled from 0 to 37 effective patients as:

Prior weight from Attain Stability	Prior weight from Attain Performa

$\widehat{a_0} = 1 - e^{-(p*5)^2}$	$\widehat{a_0} = \frac{37}{401}\left[1 - e^{-(p*5)^2}\right]$

The discount function for the Attain Stability data set is given below:

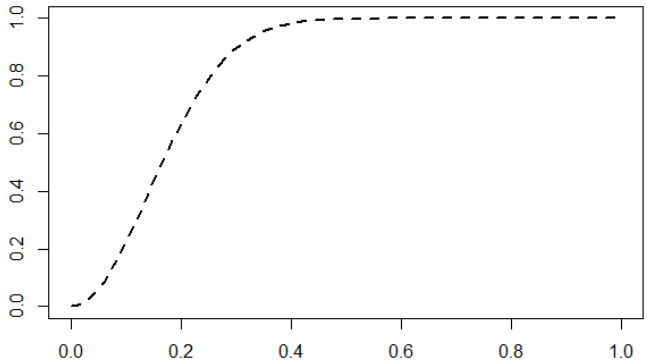


Figure 2: Loss function $\widehat{a_0} = 1 - e^{-(p*5)^2}$

Combine the current and historical data

Let y and y_0 be the number of events that occur for the current data and historical data respectively and let n and n_0 be the total number of subjects for the current and historical studies that reach the 6 month time point or had an event. Following the work of Ibrahim and Chen [1], the posterior probability for event rate θ using the power prior is given as:

$$P(\theta|y, n, y_0, n_0, \widehat{a_0}) = beta(\alpha, \beta)$$

where

$$\alpha = y + \widehat{a_0}\, y_0 + 1$$

$$\beta = (n - y) + \widehat{a_0}\,(n_0 - y_0) + 1$$

Interim analysis

This analysis will be conducted with data retrospectively analyzed as it would have been available for the first consecutively enrolled 360 subjects. Within this data set, some patients will not have completed the full evaluation period. A longitudinal model will be employed to enable final observations to be imputed for those subjects with incomplete information.

There are 3 types of subjects at a given interim analysis:

1. Subjects that have complete data
2. Subjects that have partial data (censored value at a particular time)
3. Subjects that have no information (subjects that have not been enrolled)

We will construct predictive probabilities for types 2 and 3. The predictive probability model that will be used is a piecewise exponential. This will allow us to impute final outcomes for the subjects who have not had an event and have not completed 6 month follow up.

We assume a gamma distribution prior for each of the exponential segments, which allows us to estimate the hazard rate using closed form conjugacy. Therefore, the posterior is also a gamma distribution.

We partition duration time into 3 intervals across six months (0-2, 2-4, and 4-6 months) and assume the hazard is constant within each interval. The event times are therefore modeled as:

$$T_{event} \sim PE(\lambda_1,\lambda_2,\lambda_3)$$

where $\lambda_1,\lambda_2,\lambda_3$ are the hazards for the three segments.

The purpose of the interim look is to determine the number of additional patients to enroll in order of have a high probability of meeting the required effective sample size of $n_{effective} = 400$ (after accounting for attrition). The effective sample size is the sum of enrolled patients and effective historical patients at the final analysis. The interim analysis may result in as few as 363 patients enrolled. This study follows methods from Berry, et.al.[4]

Adaptive Bayesian sample size algorithm:

1. If the predictive probability of $n_e \geq 400$ is larger than 80% then enrollment will stop.
2. If the predictive probability of $n_e \geq 400$ is less than 80%, enroll sufficient additional patients to make the probability of $n_e \geq 400$ at least 80%.

Final Analysis

The final analysis will be performed using the 6-month data from the patients enrolled at the interim analysis time point, along with the 6-month data from the number of additional patients resulting from the interim analysis. The same three steps (Compare, Compute, Combine) will be performed to incorporate the historical data sources.

The estimates for rates of lead failure modes will be presented as a point estimate and 95% credible intervals.

7.8.5. Secondary Objective #3

The third secondary objective aims to estimate electrical measurement values (PCTs and Lead Impedance) at 6 months post-implant.

Analysis Dataset:

Analysis set #2 per section 7.1.3.

Analysis Method:

Mean, standard deviation, minimum, median and maximum for PCTs and lead pacing impedance at the 6-month follow-up visit will be presented for the final programmed LV lead pacing polarity. In addition, the frequency of each LV lead pacing polarity being used at the final programmed configurations will be presented.

Electrical values may be collected via eCFR and Save-to-Media files (i.e. Save-to-Diskette and Carelink Transmissions). The statistical analysis will prioritize documented values from eCRF over save-to-media data. If discrepancies of over 1 volt is identified comparing values from two data sources, data queries may be initiated for resolution.

8. Validation Requirements

Minimum validation requirements for the programs written to execute the analyses in this SAP:

[4] S.M. Berry, B.P. Carlin, J.J. Lee, P. Muller, Bayesian adaptive methods for clinical trials. CRC press, 2010.

- Primary objective: Level II
- Secondary objectives: Level II
- Description of patient population (baseline demographics, patient characteristics, etc.): Level II
- Deviation table and listing: Level III