Statistical Analysis Plan

Clinical Investigation Plan Title	Imaging Study of Lead Implant for His Bundle Pacing (IMAGE-HBP)
Clinical Investigation Plan Version	Version 2.0 29 June 2017
Sponsor/Local Sponsor	Medtronic, Inc. 8200 Coral Sea Street NE Mounds View, MN U.S.A. 55112 1-800-328-2518
Document Version	Version 1.0

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1. Version History

Version	Summary of Changes	Author(s)/Title
1.0	• 'Not Applicable, New Document'	Tracy Bergemann/Sr Pr Statistician

2. List of Abbreviations and Definitions of Terms

Abbreviation	Definition
CIP	Clinical Investigation Plan
CRF	Case Report Form
HBP	His-Bundle Pacing
MUO	Medtronic Use Only
SAP	Statistical Analysis Plan

3. Introduction

The Imaging Study of Lead Implant for His Bundle Pacing (IMAGE-HBP) Study is a prospective, non-randomized, multi-site, clinical research study.

The purpose of this research study is to assess the implant success proportion of the Medtronic SelectSecure™ MRI SureScan™ Model 3830 pacing lead at the bundle of His for His bundle pacing, evaluate implant lead electrical measurements and changes over time, evaluate changes in QRS duration over time, estimate the correlation between lead location and selective vs. non-selective His-Bundle Pacing (HBP), and estimate the correlation between long-term lead performance and implant characteristics. Data from the study may be used to standardize the implant workflow to help improve the ease and predictability of His bundle pacing implants.

Up to 55 subjects will be enrolled from three sites to ensure 50 subjects undergo an implant procedure. Subjects will complete visits at enrollment/baseline, implant, pre-hospital discharge, 1 week, 3 months, 6 months and 12 months. The study duration is expected to be approximately 28 months from first center activation until closure.

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, secondary objectives and ancillary objectives. This SAP does not limit the analysis in reports, and additional analysis of the study data beyond this plan is expected.

The Imaging Study of Lead Implant for His Bundle Pacing study CIP Version 2.0, dated 29 Jun 2017 was used to create this SAP.

4. Study Objectives

4.1. Primary objective

The primary objective is to assess the implant success proportion of the Medtronic SelectSecure™ MRI SureScan™ Model 3830 pacing lead at the bundle of His for His bundle pacing. Implant success will be defined as the presence of a H wave on the implanted lead EGM and a HB pacing capture threshold equal to or less than 2.5V at 1.0ms.

4.2. Secondary Objectives

The secondary objectives are descriptive in nature and are intended to provide additional information about HBP with the SelectSecure™ MRI SureScan™ Model 3830 pacing lead. There will be no established performance requirements for these secondary objectives.

1. Estimate the correlation between the lead position and selective vs. non-selective HBP occurrence at implant
2. Assess changes in lead electrical measurements over time
3. Assess changes in QRS duration over time
4. Estimate the correlation between implant characteristics and long-term lead electrical performance at 12 months
5. Characterize the occurrence of complications related to the procedure or lead for His bundle pacing up to 12 months

4.3. Ancillary Objectives

Additional analyses may be done on data and images collected during the study as outlined below. These analyses are descriptive in nature and are intended to provide additional information about His bundle pacing with the Medtronic SelectSecure™ MRI SureScan™ Model 3830 lead.

The ancillary objectives are:

1. To characterize performance of existing delivery tools and Medtronic SelectSecure™ MRI SureScan™ Model 3830 lead for HBP
2. To summarize implant procedure information
3. To characterize the survival for subjects up to 12 months post-implant.

5. Investigation Plan

The IMAGE-HBP Study is a prospective, non-randomized, multi-site, clinical research study.

All subjects included in the study will be implanted with a Medtronic market released de novo Implantable Pacemaker, Medtronic SelectSecure™ MRI SureScan™ Model 3830 lead at the bundle of His for His bundle pacing, and compatible market released Medtronic Right Atrial lead (if applicable). The subjects with an implant of the Medtronic SelectSecure™ MRI SureScan™ Model 3830 lead for His bundle pacing will undergo a Cardiac CT Scan and be followed up to twelve months post implant for electrical testing. Subjects that do not receive an implanted SelectSecure™ MRI SureScan™ Model 3830 pacing lead for His bundle pacing will be exited from the study at the time of the unsuccessful implant or after any reportable Adverse Events are resolved. Up to 55 subjects may be enrolled in the study.

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

Inclusion criteria

- Subject has a Class I or II indication for implantation of an implantable pacemaker according to ACC/AHA/HRS 2008 guidelines and any national guidelines[15]
- Subject (or legally authorized representative) has signed and dated the study-specific Consent Form
- Subject is 18 years of age or older, or is of legal age to give informed consent per local and national law
- Subject is expected to remain available for follow-up visits

Exclusion criteria

- Subject is contraindicated for Cardiac CT
- Subject has an existing or prior pacemaker, ICD or CRT device implant
- Subject is intended to receive an implant of a Left Ventricle lead or CRT device
- Subject life expectancy is less than 1 year
- Pregnant women or breastfeeding women, or women of child bearing potential and who are not on a reliable form of birth regulation method or abstinence
- Subjects with exclusion criteria required by local law (e.g. age or other)
- Subject with a medical condition that precludes the patient from participation in the opinion of the investigator
- Subject is enrolled in a concurrent study that may confound the results of this study. Co-enrollment in any concurrent clinical study (including registries) requires approval of the study manager or designee.

Subjects who meet all the inclusion and none of exclusion criteria are eligible to be enrolled in the study.

6. Determination of Sample Size

The goal of the study is to assess the implant success proportion of the Medtronic SelectSecure™ MRI SureScan™ Model 3830 pacing lead at the bundle of His for His bundle pacing. A sample size of 50 subjects with an implant attempt will produce a two-sided 95% confidence interval with a width equal to 0.17 (using the Wilson method) for the implant success proportion when the observed implant success proportion is 0.9. The sample size is not driven by a power calculation or any pre-specified threshold for success. Table 1 below shows various scenarios for the precision of the implant success proportion estimate depending on the actual observed data.

Table 1. Estimation Precision for Implant Success Proportion

Observed implant success proportion (N=50 subjects attempting implant)	Width of the two-sided 95% confidence interval
0.96	0.124
0.92	0.157
0.90	0.17
0.86	0.192
0.80	0.218

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 for analysis of the primary objective. Figure 1 shows an example of a blank STROBE flow diagram.

Allocation:

Since the IMAGE-HBP study is not a randomized study, all study subjects that are enrolled are allocated to the intervention (i.e. receive a pacing lead at the bundle of His for His bundle pacing).

Follow-up:

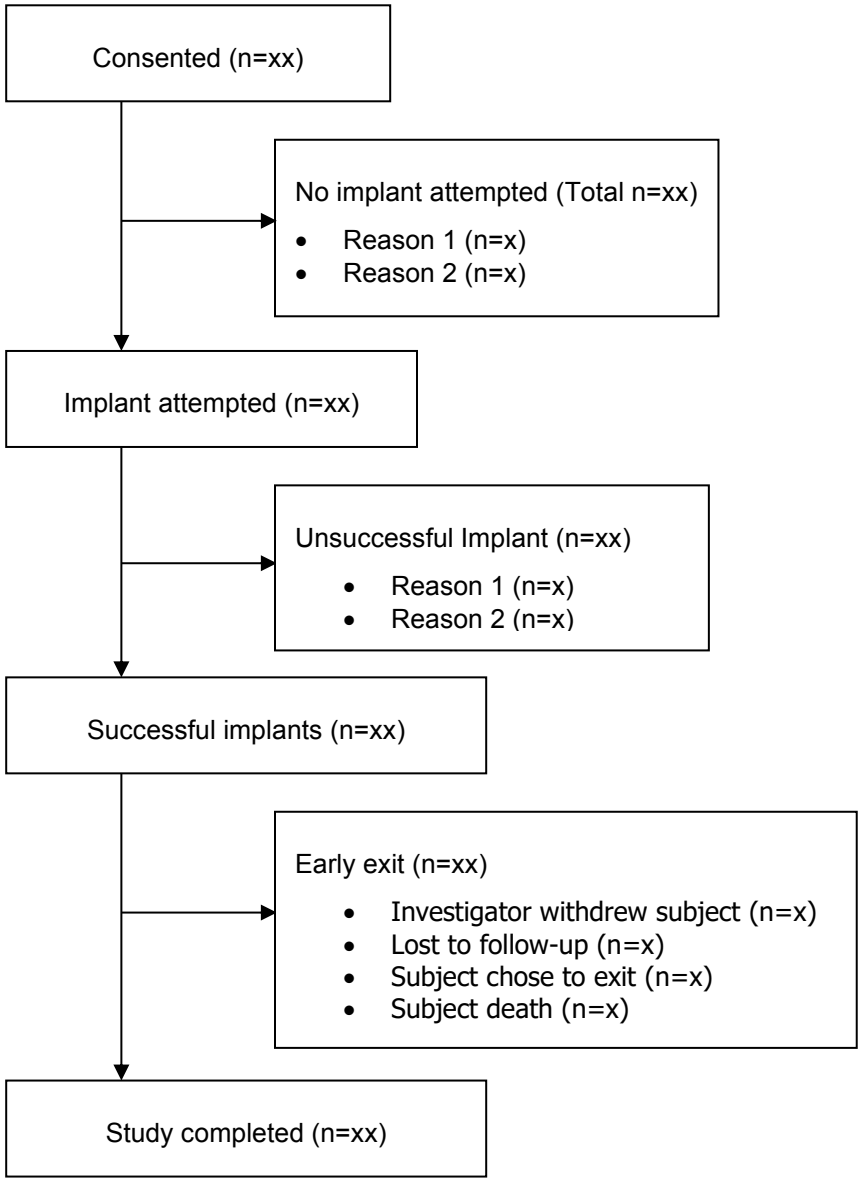
Study discontinuation might include the following reasons:

- Investigator withdrew subject
- Lost to follow-up
- Subject chose to exit
- Subject death
- Subject did not meet eligibility criteria
- Subject does not have an implant of a SelectSecure™ MRI SureScan™ 3830 lead for His bundle pacing

Analysis:

Analysis can only be completed for subjects that have case report forms saved complete. If there is missing data that prevents the analysis of a pre-specified objective then those subjects will be excluded from that objective. There will be no imputation for missing data.

Figure 1 – STROBE Flow Diagram for the IMAGE-HBP 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 two analysis sets used in this study:

Analysis Set #1:

This analysis set will be used for the primary objective (implant success), secondary objective #5 (adverse events), and ancillary objectives #1 and #2. Study subjects will be included in this analysis set if an implant is attempted.

A STROBE flow diagram per section 7.1.1 will outline the specific exclusions.

Analysis Set #2:

This analysis set will be used for secondary objectives #1-#4 and ancillary objective #3. Study subjects will be included in this analysis set if they have a successful implant.

7.2. General Methodology

7.2.1. Primary Objective

The primary objective is to assess the implant success proportion of the Medtronic SelectSecure™ MRI SureScan™ Model 3830 pacing lead at the bundle of His for His Bundle Pacing.

The observed implant success proportion will be calculated as follows:

$$\text{Implant Success Proportion} = \frac{\#\text{ Subjects with implant success}}{\#\text{ Subjects with implant attempt}}$$

A 95% confidence interval for the implant success proportion will be constructed using the Wilson method.

7.2.2. Secondary Objective #1

This secondary objective is to estimate the correlation between the lead position and selective vs. non-selective HBP occurrence at implant.

The relationship between lead position (anterior septum, mid septum, posterior septum) and HBP selectivity (selective vs. non-selective) will be assessed using a logistic regression. Additionally, HV intervals will be compared between the three groups of lead positions using linear regression.

7.2.3. Secondary Objective #2

This secondary objective is to assess changes in lead electrical measurements over time (HB PCT, R waves and impedance).

The lead electrical measurements from each visit will be summarized using descriptive statistics (mean, median, standard deviation, minimum, maximum, etc.) and graphical displays. Longitudinal analysis will

be conducted to estimate differences in electrical measurements from implant to subsequent follow-up visits.

7.2.4. Secondary Objective #3

This secondary objective is to assess changes in QRS duration over time.

The QRS durations from each visit will be summarized using descriptive statistics (mean, median, standard deviation, minimum, maximum, etc.) and graphical displays. Longitudinal analysis will be conducted to estimate differences in QRS duration from implant to subsequent follow-up visits.

7.2.5. Secondary Objective #4

This secondary objective is to estimate the correlation between implant characteristics and long-term lead electrical performance at 12 months post-implant.

A multivariable regression analysis will be conducted to assess if there is any correlation between implant characteristics, including lead location, HB PCT, and QRS duration at implant, and the 12-month HB PCT.

7.2.6. Secondary Objective #5

This secondary objective is to characterize the occurrence of any complications related to the procedure or the lead for His bundle pacing up to 12 months post-implant.

The types of complications related to the procedure or the lead for His bundle pacing will be summarized using frequencies and percentages. The probability of a subject being free of a complication related to the procedure or the lead for His bundle pacing through 12 months post-implant will be estimated using the Kaplan-Meier method. In addition, the relationship between implant characteristics, including lead position, HB PCT at implant, and QRS duration at implant, and the occurrence of complications related to the procedure or the lead for His bundle pacing will be assessed using a Cox proportional hazard regression model.

7.2.7. Ancillary Objective #1

This ancillary objective is to characterize the performance of existing delivery tools for the Medtronic SelectSecure™ MRI SureScan™ Model 3830 lead for HBP.

Responses to the Physician Questionnaire eCRF will be summarized using frequencies and percentages.

7.2.8. Ancillary Objective #2

This ancillary objective is to summarize implant procedure information.

The implant procedure information will be summarized using descriptive statistics (mean, median, standard deviation, minimum, maximum for continuous variables, and frequencies and percentages for categorical variables).

7.2.9. Ancillary Objective #3

This ancillary objective is to characterize the survival for subjects up to 12 months post-implant.

The causes of death will be summarized using frequencies and percentages. The probability of subject survival through 12 months post-implant will be estimated using the Kaplan-Meier method.

7.3. Center Pooling

The IMAGE-HBP study will be conducted at three sites. Given the small number of sites participating, there will be no analysis to examine the impact of site on study results.

7.4. Handling of Missing Data and Dropouts

If data is missing then there will be no imputation of the data. Instead, subjects with missing data will be excluded.

7.5. Adjustments for Multiple Comparisons

No adjustments will be made for multiple comparisons.

7.6. Demographic and Other Baseline Characteristics

The total number of males and females who participate in the study will be reported. The average age and standard deviation of the study subjects will be reported. The number and percentage of subjects with a medical history of sinus node dysfunction, AV junctional arrhythmias and blocks, and heart failure will be reported. The number and percentage of subjects with an AV node ablation in their medical history will be reported.

7.7. Treatment Characteristics

Using device data from study save-to-disk files, the device longevity estimate from the last available file for each subject will used to calculate a survival function estimate for the device battery. Programmed outputs at implant and changes over time shall also be summarized. Tools used during the implant procedure will be summarized with counts and percentages including the type of delivery catheter. Further analysis of implant tools is included in Ancillary Objective #1. Other implant characteristics are included in the analysis of Ancillary Objective #2.

7.8. Interim Analyses

No interim analysis will be conducted.

7.9. Evaluation of Objectives

7.9.1. Primary Objective

The primary objective is to assess the implant success proportion of the Medtronic SelectSecure™ MRI SureScan™ Model 3830 pacing lead at the bundle of His for His Bundle Pacing.

Analysis Dataset:

Analysis set #1 per section 7.1.3.

Analysis Method:

The observed implant success proportion will be calculated as follows:

$$\text{Implant Success Proportion} = \frac{\#\text{ Subjects with implant success}}{\#\text{ Subjects with implant attempt}}$$

A 95% confidence interval for the implant success proportion will be constructed using the Wilson method. The analysis will also provide a table summarizing implant success, similar to the following:

	Number (Percentage)
Successful	N (xx%)
Unsuccessful	N (xx%)
Reason 1	N (xx%)
Reason 2	N (xx%)

The observed implant success proportion will be calculated using SAS code similar to the following:

```
proc freq data=analysisset1;
  table impsuccess / alpha=0.05 binomial(level='Yes' wilson);
  output out=impci binomial;
run;
```

Endpoint Definition:

Implant success will be defined as the presence of a H wave on the implanted lead EGM and a HB pacing capture threshold equal to or less than 2.5V at 1.0ms.

Implant success proportion is defined as the proportion of all subjects who undergo an implant attempt that is successful.

Additional Analysis:

Implant success may also be characterized in subgroups of subjects with different classifications of AV block or sinus node dysfunction. Characterizations shall only be performed if there is sufficient data (e.g. 10 patients) within each subgroup.

7.9.2. Secondary Objective #1

This secondary objective is to estimate the correlation between the lead position and selective vs. non-selective HBP occurrence at implant.

Analysis Dataset:

Analysis set #2 per section 7.1.3.

Analysis Method:

The relationship between lead position (anterior septum, mid septum, posterior septum) and HBP selectivity (selective vs. non-selective) will be assessed using a logistic regression. Additionally, HV intervals will be compared between the three groups of lead positions using linear regression. The logistic regression will be performed in SAS using code similar to:

```
proc genmod data=analysisset2;
   class leadloc;
   model nsHBP = leadloc / dist = bin link=logit;
```

```
run;
```

and the linear regression will be performed in SAS with code similar to:

```
proc glm data=analysisset2;
   class leadloc;
   model HVint = leadloc;
run;
```

Endpoint Definition:

The lead position is identified as anterior septum, mid septum or posterior septum. Location is determined by the implanting physician during implant and verified by Medtronic through evaluation of cardiac CT scan images. The location determined from CT scan will be used in the analysis.

The HBP at implant is classified as either selective or non-selective by the implanting physician based on the definitions specified in section 4.1, Table 1 of the study CIP.

Additional Analysis:

None

7.9.3. Secondary Objective #2

This secondary objective is to assess changes in lead electrical measurements over time (HB PCT, R waves and impedance).

Analysis Dataset:

Analysis set #2 per section 7.1.3.

Analysis Method:

The lead electrical measurements from each visit will be summarized using descriptive statistics (number with measure available, mean, median, standard deviation, minimum, maximum) and graphical displays. Longitudinal analysis will be conducted to estimate differences in electrical measurements from implant to subsequent follow-up visits. The analysis will be performed in SAS using code similar to:

```
proc mixed data=analysisset2;
   class time;
   model pct = time;
   random int / subj=ptid corr=exch;
run;
```

Endpoint Definition:

The lead electrical measurements that will be evaluated include HB pacing capture threshold (PCT) (in Volts) at 0.5ms, impedance (in Ohms), and R-wave amplitude (in mV) measured at the final lead location during the implant procedure, and then at the 3-month, 6-month, and 12-month follow-up visits.

Additional Analysis:

A similar analysis will be performed using the HB PCT at a pulse width of 1.0ms, instead of a pulse width of 0.5ms.

7.9.4. Secondary Objective #3

This secondary objective is to assess changes in QRS duration over time.

Analysis Dataset:

Analysis set #2 per section 7.1.3.

Analysis Method:

The QRS durations from each visit will be summarized using descriptive statistics (number with measure available, mean, median, standard deviation, minimum, maximum) and graphical displays. Longitudinal analysis will be conducted to estimate differences in QRS duration from implant to subsequent follow-up visits. The analysis will be performed in SAS using code similar to:

```
proc mixed data=analysisset2;
   class time;
   model inqrs = time;
   random int / subj=ptid corr=exch;
run;
```

Endpoint Definition:

Intrinsic QRS duration will be measured prior to the implant procedure, and then at the 3-month, 6-month, and 12-month follow-up visits.

Additional Analysis:

A similar analysis will be performed using the paced QRS duration instead of intrinsic QRS duration.

7.9.5. Secondary Objective #4

This secondary objective is to estimate the correlation between implant characteristics and long-term lead electrical performance at 12 months post-implant.

Analysis Dataset:

Analysis set #2 per section 7.1.3.

Analysis Method:

A multivariable regression analysis will be conducted to assess if there is any correlation between implant characteristics, including lead location, HB PCT, and paced QRS duration at implant, and the 12-month HB PCT. The analysis will be performed in SAS using code similar to:

```
proc glm data=analysisset2;
   class leadloc;
   model pct12 = pct0 leadloc pacedqrs0;
run;
```

Endpoint Definition:

Long-term lead electrical performance is identified as the HB PCT with a pulse width of 0.5ms at 12 months post-implant. Implant characteristics to be evaluated here include lead location, HB PCT with a pulse width of 0.5ms at implant, and paced QRS duration at implant. The lead location is determined by the implanting physician during implant and verified by Medtronic through evaluation of cardiac CT scan images. The location determined from CT scan will be used in the analysis.

Additional Analysis:

A similar analysis will be performed using the implant and 12 month HB PCT at a pulse width of 1.0ms, instead of a pulse width of 0.5ms. In addition, the number of subjects that have an increase of 1.0V in the HB PCT will be characterized, and further this characterization will be performed on the subgroups of subjects with either AV block or sinus node dysfunction.

The association between lead slack, anatomical features and HB PCT may also be analyzed. Lead slack = Arclength/Euclidean distance as determined from the CT scan. Anatomical features include right atrial size and location of right atrial dilation.

7.9.6. Secondary Objective #5

This secondary objective is to characterize the occurrence of any complications related to the procedure or the lead for His bundle pacing up to 12 months post-implant.

Analysis Dataset:

Analysis set #1 per section 7.1.3.

Analysis Method:

The types of complications related to the procedure or the lead for His bundle pacing will be summarized using frequencies and percentages. The probability of a subject being free of a complication related to the procedure or the lead for His bundle pacing through 12 months post-implant will be estimated using the Kaplan-Meier method.

The Kaplan-Meier analysis will be performed in SAS using code similar to:

```
proc lifetest data=analysisset1 conftype=loglog timelist=12;
   time monthsEvent*event(0);
run;
```

In addition, the relationship between implant characteristics, including lead position, HB PCT at implant, and QRS duration at implant, and the occurrence of complications related to the procedure or the lead for His bundle pacing will be assessed using a Cox proportional hazard regression model. The Cox proportional hazards analysis will be performed in SAS using code similar to:

```
proc phreg data=analysisset;
   class leadloc;
   model monthsEvent*event(0) = leadloc pct0 pacedqrs0;
run;
```

Endpoint Definition:

Procedure and the lead for His bundle pacing related complications will be reported via the Adverse Event eCRF. Examples include but are not limited to: lead dislodgement, exit block, loss of capture, or high threshold causing action.

Additional Analysis:

All adverse events collected in the study will be characterized. A table with MedDRA Preferred terms will be generated, which will report for each MedDRA Preferred term, the number of adverse events, the number of subjects with event, and these numbers also restricted to complications. This table will be similar to:

Table 2. MedDRA terms

MedDRA Preferred Term	Adverse events		Complications	
	lead related	procedure related	lead related	procedure related
Exit block	1 (1)	0 (0)	0 (0)	0 (0)
High threshold	1 (1)	0 (0)	1 (1)	0 (0)

MedDRA Preferred Term	Adverse events		Complications	
	lead related	procedure related	lead related	procedure related
Lead dislodgment	2 (2)	0 (0)	1 (1)	0 (0)
Loss of capture	4 (3)	1 (1)	2 (2)	0 (0)

A listing of all adverse events will be generated, with subject identifier, time of event relative to the implant procedure, event description, classification, outcome and MedDRA Preferred term.

Adverse events in subjects with an unsuccessful implant will be reported separately. Additionally, events in subjects that had no implant attempt will be reported separately. Complications will also be characterized for the subgroups of subjects with either AV block or sinus node dysfunction.

In addition, the major complication rate will be estimated using the Kaplan-Meier method where a major complication is defined as a complication that leads to:

- Death
- Permanent loss of device function due to mechanical or electrical dysfunction of the device (e.g. loss of capture, lead dislodgement)
- Hospitalization
- Prolonged Hospitalization by at least 48 hours
- System revision (reposition, replacement, explant)

These components of a major complication will be determined from the MUO Adverse Event CRF.

7.9.7. Ancillary Objective #1

This ancillary objective is to characterize the performance of existing delivery tools for the Medtronic SelectSecure™ MRI SureScan™ Model 3830 lead for HBP.

Analysis Dataset:

Analysis set #1 per section 7.1.3.

Analysis Method:

Responses to the Physician Questionnaire eCRF will be summarized using frequencies and percentages. Tables similar to the following shall be presented:

What factors were considered when determining which catheter to start with?	Number of responses
Mapping with EP catheter	N (xx%)
Patient anatomy from fluoroscopy	N (xx%)
Standard procedure to start with selected catheter	N (xx%)
How did you identify the location to start catheter placement?	Number of responses
Valve anatomy	N (xx%)
Fluoroscopy AP	N (xx%)
Fluoroscopy RAO	N (xx%)
Fluoroscopy LAO	N (xx%)
Intrinsic electrical morphology	N (xx%)

Did you reposition the lead after the initial fixation?	Number of responses
Yes	N (xx%)
Threshold not acceptable	N (xx%)
QRS morphology	N (xx%)
Selective vs Non-selective HBP	N (xx%)
His sensing not acceptable	N (xx%)
No	N (xx%)
How did you decide on the final fixated lead position?	Number of responses
Electrical outcomes	N (xx%)
HB pacing capture threshold	N (xx%)
QRS morphology	N (xx%)
QRS duration	N (xx%)
HB sensing	N (xx%)
Bundle Branch Block correction	N (xx%)
Other	N (xx%)

and

Delivery catheter and SelectSecure 3830 handling	Poor	Fair	Good	Very Good	N/A
Catheter designed to reach desired location	N (xx%)	N (xx%)	N (xx%)	N (xx%)	N
Catheter able to reach desired location	N (xx%)	N (xx%)	N (xx%)	N (xx%)	N
Stability of the catheter at the final location	N (xx%)	N (xx%)	N (xx%)	N (xx%)	N
Stability of the SelectSecure 3830 lead during catheter slitting	N (xx%)	N (xx%)	N (xx%)	N (xx%)	N
Pushability of the SelectSecure 3830 through the catheter	N (xx%)	N (xx%)	N (xx%)	N (xx%)	N
Ability to use the SelectSecure 3830 for mapping	N (xx%)	N (xx%)	N (xx%)	N (xx%)	N
Ability of the SelectSecure 3830 to fixate in desired location	N (xx%)	N (xx%)	N (xx%)	N (xx%)	N

Endpoint Definition:

Physicians will report the performance of existing delivery tools for the 3830 lead for HBP via the Physician Questionnaire eCRF to be completed after each implant procedure.

Additional Analysis:

Summary statistics for this objective will also be calculated for subgroups of successful and unsuccessful implants.

7.9.8. Ancillary Objective #2

This ancillary objective is to summarize implant procedure information.

Analysis Dataset:

Analysis set #1 per section 7.1.3.

Analysis Method:

The implant procedure information will be summarized using descriptive statistics (mean, median, standard deviation, minimum, maximum for continuous variables, and frequencies and percentages for categorical variables).

Endpoint Definition:

The implant procedure information to be characterized include: procedure times, number of fixation attempts, fluoroscopy time, and delivery systems used. This information is collected on the Implant Procedure eCRF.

Additional Analysis:

Summary statistics for this objective will also be calculated for subgroups of successful and unsuccessful implants.

The association between anatomical features and procedure time may also be analyzed. Anatomical features include right atrial size and location of right atrial dilation.

7.9.9. Ancillary Objective #3

This ancillary objective is to characterize the survival for subjects up to 12 months post-implant.

Analysis Dataset:

Analysis set #2 per section 7.1.3.

Analysis Method:

The causes of death will be summarized using frequencies and percentages. The probability of subject survival through 12 months post-implant will be estimated using the Kaplan-Meier method. The Kaplan-Meier analysis will be performed in SAS using code similar to:

```
proc lifetest data=analysisset2 conftype=loglog timelist=12;
   time monthsEvent*event(0);
run;
```

Endpoint Definition:

Deaths and corresponding cause of death and time of death will be reported via the Adverse Event eCRF and the Study Exit eCRF.

Additional Analysis:

A separate listing of all deaths will be reported for all enrolled subjects.

7.10. Changes to Planned Analysis

None

8. Validation Requirements

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

- Primary objective: Level I
- Secondary objectives: Level II
- Ancillary objectives: Level II
- Deviation table and listing: Level III

9. Appendix

9.1. Planned Analysis Not Covered by Study Objectives

9.1.1. Strength duration curve estimation

At implant and at the three month follow-up visit, subjects with selective His bundle pacing will have their HB PCT measured at the following pulse widths: 0.1 (or 0.12) ms, 0.2 (or 0.21) ms, 0.5 (or 0.52) ms, 0.76 (or 0.8) ms, 1.0 ms, and 1.5 ms. For each pulse width, the HB PCT will be summarized using descriptive statistics (number with measure available, mean, median, standard deviation, minimum, maximum) and graphical displays. Methods to estimate the strength duration curve function at implant and three months may also be explored, such as non-parametric spline smoothing or polynomial fitting in linear regression.

9.2. Mapping of Variables

Endpoint definitions are provided for all study objectives in Section 7. The locations of these study endpoints on the study eCRFs are specified in more detail and documented in RAD: MCRI/CRHF/Studies/IMAGE-HBP/General Trial Folder/8.0 Data Management/8.06 General /IMAGE HBP_CRF mapping CIP objectives.xls.