Statistical Analysis Plan

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1. Version History

Version	Summary of Changes	Author(s)/Title
1.0	• Not Applicable, New Document	Jeff Lande, Principal Statistician
2.0	• Updated to new SOP template	Jeff Lande, Principal Statistician
3.0	• Corrections made to the SAS code for statistical exact tests and revision of analysis by geography	Alex Dedrick, Senior Statistician

2. List of Abbreviations and Definitions of Terms

Abbreviation	Definition
CEE	Central and Eastern Europe
IPG	Implantable Pulse Generator
MEA	Middle East and Africa
QOL	Quality of Life
SND	Sinus Node Dysfunction

3. Introduction

This Statistical Analysis Plan has been designed to document, before data are analyzed, the rationale for the study design, and the planned analyses that will be included in study reports. The purpose of this study is to characterize the current management of subjects presenting with possible sinus node dysfunction (SND) and test the hypothesis that the use of a practice-specific process improvement intervention consisting of education, diagnostic algorithm(s) and documentation tools that advocate and reinforce adherence to consensus treatment guidelines will improve the quality of care for patients with SND.

4. Study Objectives

4.1. Primary Objective(s) or Main Objective(s)

This study is exploratory in nature and there are no specified hypotheses or performance requirements for the Primary Objectives. All mentions of the intervention in the objectives below refer to the process improvement intervention that will be implemented at the start of Phase II. All mentions of the diagnosis of SND refer to symptomatic SND.

4.1.1. Primary Objective #1

Evaluate the impact of the intervention on the diagnosis of SND.

4.1.1.1. Endpoint Definition

The absolute change in the proportion of subjects diagnosed with SND at pre-specified time points (%=number diagnosed/number enrolled x 100 at time point t where t= 6, 12, and any additional 6-month interval for which there is sufficient follow-up information) and the absolute change in the number of subjects diagnosed with SND per person-year. An SND diagnosis will be determined by the response on the Diagnosis Form on the CRF. If any response under the heading of Sinus Node Dysfunction is selected, the subject will be considered to have been diagnosed with SND. Responses under the heading of Sinus Node Dysfunction include

- Minimally symptomatic SND, with heart rate less than 40 bpm while awake and no evidence of chronotropic incompetence (Class IIb)
- SND, with heart rate less than 40 bpm and no symptom rhythm correlation present (Class IIa)
- Symptomatic bradycardia, brady-tachy syndrome (Class I)
- Symptomatic bradycardia, sinus arrest/pause/exit block (Class I)
- Symptomatic bradycardia, sinus brady (Class I)
- Symptomatic Chronotropic incompetence (Class I)
- Symptomatic SND/bradycardia, drug induced (Class I)
- Symptomatic SND, sinus tachycardia (Class I)
- Syncope, spontaneous or induced in EP study (Class I)
- Syncope of unknown origin with EP findings (Class IIa)

If none of these diagnoses were indicated on the Diagnosis Form on the CRF, the subject will be considered to not have been diagnosed with SND.

4.1.2. Primary Objective #2

Evaluate the impact of the intervention on SND subjects receiving an indicated IPG device.

4.1.2.1. Endpoint Definition

The absolute change in the proportion of subjects receiving indicated therapy at pre-specified time points (% = number receiving IPG/number with SND diagnosis x 100 at time point t where t= 3, 6, and any additional 3-month interval for which there is sufficient follow-up information) and the absolute change in the number of subjects implanted per person-year.

4.2. Secondary Objectives

4.2.1. Secondary Objective #1

Describe the diagnosis and treatment of Phase I subjects.

4.2.1.1. Endpoint Definition

The proportion of subjects receiving an SND diagnosis (as described in section 4.1.1.1) and the number of diagnoses that result in indicated therapy at pre-specified time points and the number of subjects diagnosed and implanted per person-year.

4.2.2. Secondary Objective #2

Evaluate the change in the time to diagnosis of SND before and after intervention.

4.2.2.1. Endpoint Definition

Time to diagnosis in days (date of diagnosis – date of enrollment); number of visits to diagnosis

4.2.3. Secondary Objective #3

Evaluate the change in the time to receiving an indicated IPG device for SND subjects before and after intervention.

4.2.3.1. Endpoint Definition

Time to treatment in days (date of implant – date of diagnosis); number of visits to treatment

4.2.4. Secondary Objective #4

Evaluate the Caregiver burden between pre-implant and 6 months post-implant.

4.2.4.1. Endpoint Definition

Compare the difference in caregiver burden from pre-implant to 6 months post-implant. The Zarit survey will be used for assessment.

4.2.5. Secondary Objective #5

Evaluate change in quality of life (QOL) and functional status between pre-implant and 6 months post-implant.

4.2.5.1. Endpoint Definition

Compare the difference in QOL and functional status between pre-implant and 6 months post-implant. The composite physical and mental scores from Version 2 of the SF-12 Health Survey will be used to assess QOL.

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5. Investigation Plan

Study Design Overview

The study may be conducted in countries located in Central and Eastern Europe (CEE), Greater China, India, Latin America, Asia, and Middle East and Africa (MEA). Countries from other geographies may be added in the future. The distribution of centers will be approximately 10 per geography or country and is determined by local evidence needs.

Approximately 1,650 subjects per geography/country, or up to 14,850 subjects worldwide, will be enrolled in the study. An enrollment target of 6 subjects per center per month is desired to make center-specific outcomes more meaningful and reliable in measuring changes in diagnostic rates and patient acceptance of indicated therapy. Centers that enroll faster than others will be allowed to enroll until 20% of the sample size for the geography/country has been reached for a maximum of 330 subjects per site - 110 maximum in Phase I and 220 maximum in Phase II.

All study subjects will be followed until the study exit criteria are met or until official study closure. Study closure is defined as closure of a clinical study that occurs when Medtronic and/or regulatory requirements have been satisfied per the Clinical Investigation Plan and/or by a decision by Medtronic or regulatory authority, whichever occurs first. The expected study duration per geography/country, from first enrollment to last follow-up, is approximately 4.5 years per geography/country.

Subjects will have successfully completed the study if one of the following criteria has been met:

1. Subject does not meet a class I or class II SND indication for pacing therapy
2. Subject meets an indication for pacing but not an SND indication for pacing therapy
3. Subject has met an SND indication for pacing therapy and did not receive a market released pacemaker from the Medtronic family of devices
4. Subject has met an SND indication for pacing therapy but will not be receiving pacing therapy
5. Subject has completed the final scheduled follow-up visit (in Phase II).

6. Geography/country completion of Phase I follow-up
7. Study closure

The IMPROVE Brady study will not use randomization to divide subjects into treatment groups, but rather will implement a two-phase design. Since the current rates of SND diagnosis and IPG therapy are not known, it is not feasible to construct a study with two simultaneous treatment arms and adequately power the comparison. Thus, the IMPROVE Brady study will have two sequential phases. In the first phase, the control phase, we expect to obtain baseline measurements for key variables including the rate of SND diagnosis and the rate of implantation of an IPG in subjects with an SND diagnosis. Once phase one enrollment is complete for a geographic region, patients will be followed for six months and then will be exited from the study. Physicians at participating centers will then receive an educational intervention and comprehensive disease state management tools on the adoption of ACC/AHA/HRS and ESC indications. In the second phase, the experimental phase, patients will have scheduled follow-up to collect questionnaire data if they are implanted with an IPG manufactured by Medtronic.

Each of the geographies currently participating has differing rates of SND diagnosis and implantation. Early enrollment figures anticipate the accrual of 60 subjects per month per geography, to be obtained through ten or more clinical centers. Given that baseline disease and treatment rates differ by geography, we anticipate that statistical analysis will stratify by geography and thus sample size calculations shall be stratified also. It may also be necessary to look more finely at rates by site within geography. All primary and secondary objectives will be investigated within each geography, in addition to the overall testing of primary and secondary objectives, which will include geography as a covariate.

Baseline IPG Rates

Table 1 shows WHO estimates of new implantation rates per million people (Mond *et al*)

Table 1

Region	Country	Centers	New Implants/Million (2005)
Eastern Europe	Russia	99	101
Asia	China	417	13
	Hongkong	20	157
	South Korea	100	29
	Taiwan	78	119
Southeast Asia	India	417	7
	Singapore	10	91
	Thailand	46	22

Latin America	Argentina	NA	294
	Chile	50	153
	Panama	5	80
	Uruguay	14	287

The rates in Table 1 are lower than those in developed countries such as Canada (550 implants per million) and the US. The number of new implants in the US in 2009 was 616/million (Greenspon *et al*). Thus, it is estimated that the number of IPGs implanted due to SND would be about 50-70% or 308-431 implants/million (Rodriguez *et al*, P3 Patient Profiling Study Final Report). The implantation rates in other geographies outside of the US are lower, suggesting that current pacing therapies may be underused in bradycardia subjects worldwide.

The current plan is to enroll by site in two phases. The first phase would enroll for 10-12 months and the second phase would be twice as long. If the study plan uses 10 months of Phase I subjects, this will result in roughly 550 subjects per geography. This is based on the anticipated ability to enroll subjects at the rate of 55 subjects per month per geography. The study team anticipates that enrollment timing and rates will vary between the geographies. Phase II is currently planned to enroll subjects for twice as long as Phase I, resulting in roughly 1100 subjects per geography. This is based on the anticipated ability to enroll subjects at the rate of 55 subjects per month per geography. In general the study will start with a 1:2 collection ratio for Phase I and Phase II sample sizes. Twice as many subjects are enrolled in Phase II of the study design so that the study may also examine any temporal drift in the outcomes of interest or subject demographics.

6. Revision from Version 2.0 of the Statistical Analysis Plan

Study closures by Geography Prior to Phase II

This section has been added to this study SAP following the completion of Phase I in all geographies. While the initial investigation plan intended for the study to be conducted in two phases across multiple geographies, only one geography has opted to complete both phases of the study. The geographies that have completed Phase I of the study are CEE, Latin America and South Asia. Only South Asia has proceeded into Phase II of the study with sites in both India and Bangladesh participating in both phases. CEE and Latin America both terminated their participation in IMPROVE Brady after completing Phase I of the study. Accordingly, planned statistical analyses that were going to investigate study objectives within geography or country can no longer be performed. Therefore, for any analysis comparing phases, it will be performed on the South Asia geography only. Analyses by site within the South Asia geography will only include sites enrolling in both Phase I and Phase II.

7. Determination of Sample Size

Calculations of Phase II Sample Size Adaptation

The planned sample size in Phase II is up to 1100 enrollments. This sample size assumes that, in Phase I, 20% of enrolled subjects obtain an SND diagnosis and that 10% of subjects with an SND diagnosis then go on to receive indicated therapy with an IPG. This sample size also assumes that 10% of enrolled subjects will be lost to follow-up. The sample size in Phase II will be adapted, however, if the results from Phase I within each geography differ from the original assumptions about diagnosis and implant rates. The adaptation is described below.

Summary

Enrolling 500 subjects in Phase I and 1000 subjects with complete follow-up in Phase II powers the study to detect increases in the SND percentage of 9% or greater. The study is also powered to detect an increase in the IPG implant percentage by 15%. This assumes that the Phase I SND percentage is 20% or greater and that the percent of diagnoses does not decrease in Phase II.

Synopsis of Phase II Preliminary Power and Sample Size Calculations

For Phase II, we will outline many different possible scenarios and the sample sizes required for each. Actual Phase II calculations will depend on what is observed in Phase I within each geography.

Section 4.1 Primary objective #1 for SND

The following assumptions are made for all calculations.

Assumptions:

1. 90% power and type I error of 0.05
2. Phase I enrolled 500 subjects with complete follow-up
3. Overall goal is 2:1 sampling for Phase II versus Phase I
4. Calculation via methods in Fleiss JL, Tytun A, Ury HK (1980): A simple approximation for calculating sample sizes for comparing independent proportions. Biometrics 36:343–6.

Table 2. Subjects Required to Observe Changes in SND Diagnosis

SND % Phase I	SND % Phase II	Phase II Subjects	Higher SND % Phase II	Phase II Subjects

10%	20%	N=405	25%	N=203
20%	30%	N=593	35%	N=279
30%	40%	N=717	45%	N=327
40%	50%	N=778	55%	N=347
45%	55%	N=785	60%	N=346
50%	60%	N=776	65%	N=338
60%	70%	N=711	75%	N=302
70%	80%	N=582	85%	N=237
80%	90%	N=390	95%	N=144

There is clear power to attain the first primary objective with 873 subjects or fewer in Phase II, accounting for 10% attrition.

Section 4.2 Primary objective #2 for IPG implants

Scenario 1 -- Additional assumptions:

1. No change in SND diagnosis between Phase I and Phase II, i.e., the first primary objective is not met.
2. Futility is assumed when more than 1000 subjects with complete follow-up are needed for Phase II. Areas of futility are not included in **Error! Reference source not found.** and **Error! Reference source not found.**.

Table 3. For SND diagnosis rates less than 50%

	IPG % Phase I	IPG % Phase II	Phase II Subjects Needed	Accounting for Attrition	CI width for IPG % with Half of Phase II Data
10% SND = 50 SNDs	80%	95%	>1000	>1000	0.06
	85%	100%	856	952	0.03
20% SND = 100 SNDs	5%	20%	769	855	0.18
	10%	**25%**	**1013**	**1126**	0.17
	15%	30%	>1000	>1000	0.16

	70%	85%	>1000	>1000	0.07
	75%	90%	968	1076	0.07
	80%	95%	717	797	0.06
	85%	100%	428	476	0.03
30% SND = 150 SNDs	5%	20%	513	570	0.18
	10%	25%	676	752	0.17
	15%	30%	814	905	0.16
	20%	35%	929	1033	0.16
	25%	40%	1021	1135	0.15
	30%	45%	>1000	>1000	0.15
	55%	70%	>1000	>1000	0.14
	60%	75%	1004	1116	0.14
	65%	80%	908	1009	0.13
	70%	85%	788	876	0.13
	75%	90%	645	717	0.12
	80%	95%	478	532	0.10
	85%	100%	286	318	0.08
40% SND = 200 SNDs	5%	20%	385	428	0.18
	10%	25%	507	564	0.17
	15%	30%	611	679	0.16
	20%	35%	697	775	0.16
	25%	40%	766	852	0.15
	30%	45%	817	908	0.15
	35%	50%	850	945	0.15
	40%	55%	866	963	0.15
	45%	60%	864	960	0.14

	50%	65%	845	939	0.14
	55%	70%	808	898	0.14
	60%	75%	753	837	0.14
	65%	80%	681	757	0.13
	70%	85%	591	657	0.13
	75%	90%	484	538	0.12
	80%	95%	359	399	0.10
	85%	100%	214	238	0.08
50% SND = 250 SNDs	5%	20%	308	343	0.18
	10%	25%	406	452	0.17
	15%	30%	489	544	0.16
	20%	35%	558	620	0.16
	25%	40%	613	682	0.15
	30%	45%	653	726	0.15
	35%	50%	680	756	0.15
	40%	55%	693	770	0.15
	45%	60%	691	768	0.14
	50%	65%	676	752	0.14
	55%	70%	646	718	0.14
	60%	75%	603	670	0.14
	65%	80%	545	606	0.13
	70%	85%	473	526	0.13
	75%	90%	387	430	0.12
	80%	95%	287	319	0.10
	85%	100%	172	192	0.08

Table 4. For SND diagnosis rates greater than 50%

	IPG % Phase I	IPG % Phase II	Phase II Subjects Needed	Accounting for Attrition	CI width for IPG % with Half of Phase II Data
60% SND = 300 SNDs	5%	20%	257	286	0.18
	10%	25%	338	376	0.17
	15%	30%	407	453	0.16
	20%	35%	465	517	0.16
	25%	40%	511	568	0.15
	30%	45%	545	606	0.15
	35%	50%	567	630	0.15
	40%	55%	577	642	0.15
	45%	60%	576	640	0.14
	50%	65%	563	626	0.14
	55%	70%	539	599	0.14
	60%	75%	502	558	0.14
	65%	80%	454	505	0.13
	70%	85%	394	438	0.13
	75%	90%	323	359	0.12
	80%	95%	239	266	0.10
	85%	100%	143	159	0.08
70% SND = 350 SNDs	5%	20%	220	245	0.18
	10%	25%	290	323	0.17
	15%	30%	349	388	0.16
	20%	35%	399	444	0.16
	25%	40%	438	487	0.15
	30%	45%	467	519	0.15

	35%	50%	486	540	0.15
	40%	55%	495	550	0.15
	45%	60%	494	549	0.14
	50%	65%	483	537	0.14
	55%	70%	462	514	0.14
	60%	75%	431	479	0.14
	65%	80%	389	433	0.13
	70%	85%	338	376	0.13
	75%	90%	277	308	0.12
	80%	95%	205	228	0.10
	85%	100%	123	137	0.08
80% SND = 400 SNDs	5%	20%	193	215	0.18
	10%	25%	254	283	0.17
	15%	30%	306	340	0.16
	20%	35%	349	388	0.16
	25%	40%	383	426	0.15
	30%	45%	409	455	0.15
	35%	50%	425	473	0.15
	40%	55%	433	482	0.15
	45%	60%	432	480	0.14
	50%	65%	423	470	0.14
	55%	70%	404	449	0.14
	60%	75%	377	419	0.14
	65%	80%	341	379	0.13
	70%	85%	296	329	0.13
	75%	90%	242	269	0.12

	80%	95%	180	200	0.10
	85%	100%	107	119	0.08
90% SND = 450 SNDs	5%	20%	171	190	0.18
	10%	25%	226	252	0.17
	15%	30%	272	303	0.16
	20%	35%	310	345	0.16
	25%	40%	341	379	0.15
	30%	45%	363	404	0.15
	35%	50%	378	420	0.15
	40%	55%	385	428	0.15
	45%	60%	384	427	0.14
	50%	65%	376	418	0.14
	55%	70%	359	399	0.14
	60%	75%	335	373	0.14
	65%	80%	303	337	0.13
	70%	85%	263	293	0.13
	75%	90%	215	239	0.12
	80%	95%	160	178	0.10
	85%	100%	96	107	0.08

Additional calculations:

If the Phase II data is divided into two pieces, then there would be, ideally, an equal number of SND diagnoses and number treated with IPG in each piece. The following table describes the width of the confidence intervals around the IPG proportions estimated in Phase II, the width around the point estimate for one half of the Phase II enrollments and the width around the difference in the proportions from the two halves of Phase II.

Table 5. For SND diagnosis rates greater than 50%

IPG % Phase II	Number of SND dx in Phase II	CI width for IPG % with Half of Phase II Data	CI width for Comparison of IPG % Between Two Halves of Phase II
20%	154	0.19	0.26
25%	203	0.18	0.24
30%	245	0.17	0.23
35%	279	0.16	0.22
40%	307	0.16	0.22
45%	327	0.16	0.22
50%	340	0.16	0.21
55%	347	0.15	0.21
60%	346	0.15	0.21
65%	338	0.15	0.20
70%	323	0.15	0.20
75%	302	0.14	0.20
80%	273	0.14	0.19
85%	237	0.14	0.18
90%	194	0.13	0.16
95%	144	0.11	0.13

To compare the SND proportion between these two pieces, we have a confidence interval total width of 12% (absolute range) or less. To compare the IPG proportion between these two pieces, we have a confidence interval total width of 26% (absolute range) or less.

Futility examples

Suppose that the SND percentage is 10% and that less than 85% of those indicated will implant. Assuming 500 patients in Phase I, we will need 2,520 patients in Phase II to see an increase in the implant rate from 10% to 30%. This is an example of a scenario where we may decide not to move forward into Phase II.

Suppose that the SND percentage is 5% and that 5% of those indicated will implant. Assuming 500 patients in Phase I, we will need 5,440 patients in Phase II to see an increase in the implant rate from 5% to 30%. This is another example of a scenario where we may decide not to move forward into Phase II.

Suppose that the SND percentage is 20% and that 40% of those indicated will implant. Assuming 500 patients in Phase I, we will need more than 10,000 patients in Phase II to see an increase in the implant rate from 40% to 55%. If there are 910 patients in Phase II, this is sufficient to detect an increase in the implant rate from 40% to 60%.

8. Statistical Methods

8.1. Study Subjects

8.1.1. Disposition of Subjects

Subjects will be summarized with a STROBE diagram, including number of

- Enrolled subjects
- Subjects meeting/not meeting inclusion/exclusion criteria and lost to follow-up
- Subjects per geography (global analyses)
- Subjects with SND diagnosis (per diagnosis selected on eCRF)
- Subjects for whom investigator selected as indicated for a device on the treatment CRF
- Subjects implanted with an IPG during follow up

8.2. General Methodology

8.2.1. Special Considerations

The study will have an enrollment restriction. The maximum number of subjects to be enrolled at any given study center is 20% of the expected sample size in that geography; 20% of 1650 subjects equals 330 subjects per study center.

Sample size calculations will account for an attrition rate in the study of 10%.

An analysis will be built to examine temporal confounding. Since the study design does not randomize the treatment and control subjects it is possible that the time elapsed over Phase I and Phase II of the study will confound the results. To examine the possibility of temporal confounding, an interrupted time series regression analysis will be performed. This analysis will adapt Rubin's causal model for rate parameters.

Rubin's causal model for linear outcome Y is $Y = \beta_0 + \beta_1 X + \beta_2 D$, where X is time and D is a dummy variable for group assignment, before and after intervention. To adopt this model for rate parameters estimated in the primary objectives of the study, the model to be fit is $log(Y) = \beta_0 + \beta_1 X + \beta_2 D + log(Z)$ where Y is a binary response to indicate an SND diagnosis and Z is the amount of subject follow-up. The same model will also be fit to model the rate of IPG treatment. If an association is seen by testing β_1, then temporal confounding exists.

8.2.2. Reports for which this Statistical Analysis Plan applies

This Analysis plan shall apply to the final report. The plan will also be used for the interim analysis at the end of Phase I data collection. Statistical analysis for study related publications will not be limited to this plan.

8.3. Demographic and Other Baseline Characteristics

8.3.1. Description of Baseline Variables

A number of characteristics will be reported for each enrolled subject on baseline case report forms (CRFs) at time of enrollment. The variables collected will include demographics, medical history, symptoms, vitals, and cardiovascular medications. Tables and descriptive statistics will be used to summarize subject data with respect to these variables. For quantitative variables such as age, the mean, standard deviation, median, the first quartile and third quartile, minimum and maximum will be presented. For qualitative variables, counts and percentages will be given.

8.4. General Summaries

The Medtronic statistician who is assigned to the project will conduct all statistical analysis. Sample size package PASS 2008 was used for sample size evaluation. The two primary endpoints are the change in the proportion of subjects with an SND diagnosis after intervention and the change in the proportion of subjects receiving IPG therapy after intervention. In current practice, both of these proportions are unknown for a set of subjects meeting the study inclusion criteria. Three principles will guide the statistical analysis outlined below. The first principle is that the sample size calculations will use exact confidence intervals and tests to compare binomial proportions. The second principle of the analysis is that sample size calculations for Phase II of the study design will depend on the outcomes observed in Phase I of the study design. Due to this, the Phase II sample size calculations provided herein are preliminary calculations that will be amended once Phase I data collection is completed. In general the study will start with a 1:2 collection ratio for Phase I and Phase II sample sizes. Twice as many subjects are enrolled in Phase II of the study design so that the study may also examine any temporal drift in the outcomes of interest or subject demographics. The third principle of the analysis is that both the

statistical methods and the sample size calculations will be geography specific because the study outcomes are expected to vary by geography.

8.5. Evaluation of Objectives

8.5.1. Primary Objective #1

Evaluate the impact of the intervention on the diagnosis of SND.

8.5.1.1. Analysis Methods

A. Statistical Methodology

To compare the proportion of subjects with an SND diagnosis pre-intervention (Phase I) to the proportion post-intervention (Phase II), a chi-square test will determine statistical significance. The proportion of subjects diagnosed will be evaluated at multiple time points because the time to diagnosis is expected to vary by geography. Thus, times are pre-specified starting at 6 months and any additional 6-month interval thereafter for which there is sufficient follow-up data available to compare study phases. Proportions calculated at all available time points will be reported. Additionally a Poisson regression will compare the average number of subjects with an SND diagnosis in Phase I and Phase II where the subject time in study is treated as an offset in the model. The above described tests will be performed only for subjects in the South Asia geographical region as per section 6.

[redacted]

B. Determination of Patients/Data for Analysis

All subjects that are enrolled in the study will be included in the determination of the proportion estimates. The proportion estimates will be calculated based on information from fixed time points at 6 months of follow-up, 12 months of follow-up, and any additional 6-month interval thereafter for which there is sufficient follow-up data available to compare study phases. The number of subjects that obtain an SND diagnosis by pre-specified time point t= 6, 12, etc., is included in the numerator and the number of subjects enrolled is included in the denominator.

8.5.1.2. Sample Size Methods and Assumptions

The proportion of SND diagnoses in bradycardia subjects is currently unknown within the study geographies. The PANARM HF study of 2000 subjects found that 146 out of 331 bradycardia subjects (44%) had symptomatic SND and that 15 (10%) of SND subjects opted for IPG therapy (internal data on file). The power calculations conservatively assume that the SND diagnosis will be 20% at six months of follow-up, or equivalently an SND incidence of 0.4 diagnoses per person-year. Thus, the margin of error will be ±4% in a sample of 500 subjects per geography/country, based on a 95% confidence interval. If 500 subjects are collected in Phase I and 1000 subjects are collected in Phase II, assuming a type I error of 0.05 and power of 0.90, a chi-square test will detect an increase in SND diagnosis of at least 8%. For example, the study will find a statistically significant difference between a Phase I SND percentage of 20% at 6 months and a Phase II SND percentage of 28% at 6 months. The Poisson regression for the same scenario has a power of 0.95 to compare SND incidence of 0.4 versus 0.56 diagnoses per person-year. If the proportion of SND diagnoses is smaller than 20%, there will be more power to detect significant differences in the diagnosis proportion. Thus, the Phase II sample size will be recalculated within geography/country once Phase I data collection is complete. It is expected that the study attrition rate may be 10-15% of the study population. To account for attrition, *the sample size for Phase I will be 550 subjects per geography/country* and for Phase II may be 1100 subjects per geography/country.

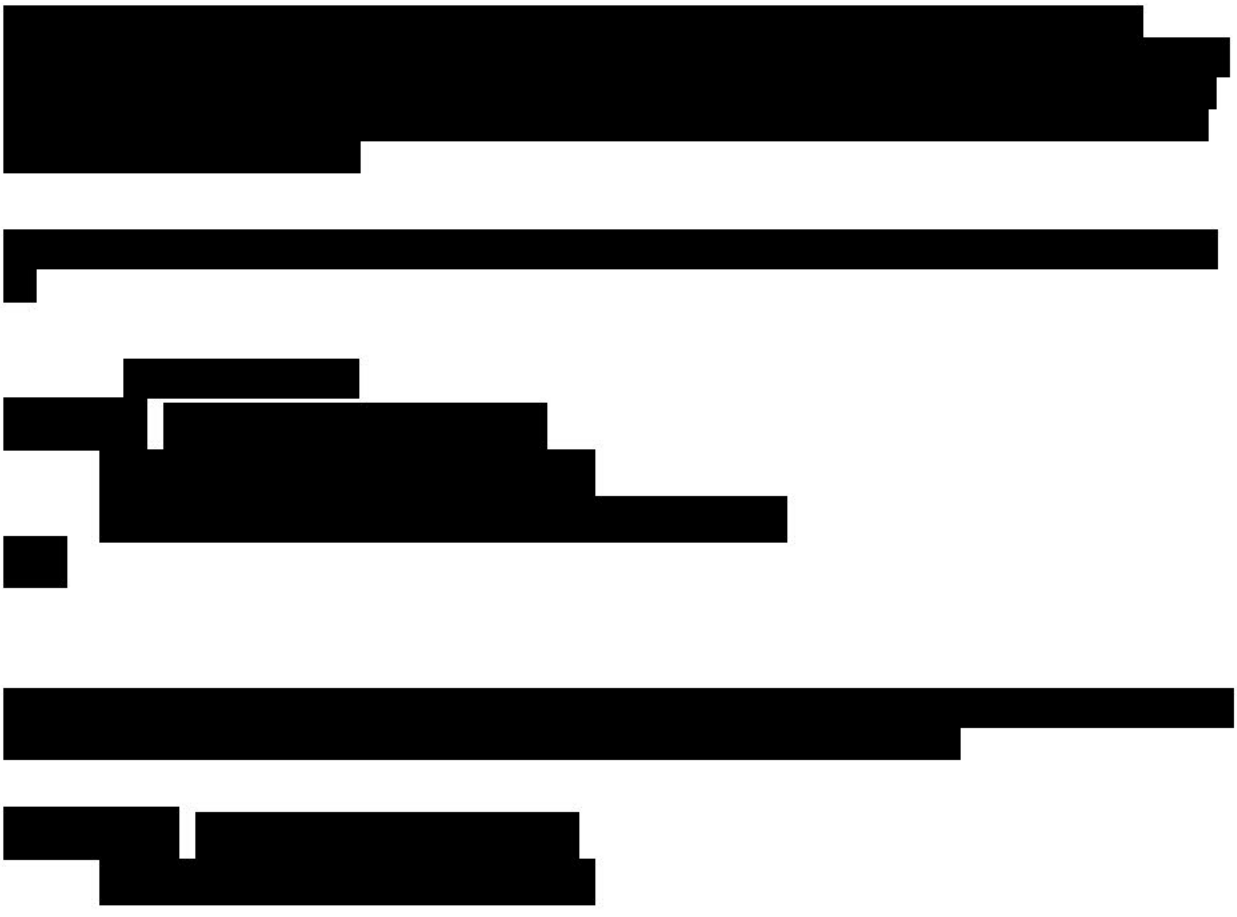
8.5.2. Primary Objective #2

Evaluate the impact of the intervention on SND subjects receiving an indicated IPG device.

8.5.2.1. Analysis Methods

A. Statistical Methodology

To compare the proportion of subjects that receive indicated therapy pre-intervention (Phase I) to the proportion post-intervention (Phase II), a Fisher's Exact test will determine statistical significance. A Fisher's exact test is recommended for smaller sample sizes. The proportion of subjects diagnosed will be evaluated at multiple time points because the time from diagnosis to implant is expected to vary by geography. Shorter time intervals will be used to evaluate the proportion of implants than for the proportion of diagnosis because time from diagnosis to implant is typically shorter than the time from enrollment to SND diagnosis. Thus, times are pre-specified starting at 3 months and any additional 3-month interval thereafter for which there is sufficient follow-up data available to compare study phases. Proportions calculated at all available time points will be reported. Additionally, a Poisson regression will compare the average number of subjects with an implant where the subject time in study beginning at the time of SND diagnosis is treated as an offset in the model. The above described tests will be performed only for the South Asia geography as described in Section 6. Further, similar tests will compare the differences in the types of therapy received in Phase I and Phase II. For example, a Fisher's exact test will compare the frequency of dual chamber device use pre- and post-intervention.



[redacted]

B. Determination of Patients/Data for Analysis

Subjects that meet inclusion criteria and obtain an SND diagnosis shall be included in this analysis. The proportion estimates will be calculated based on information from fixed time points at 3 months of follow-up, 6 months of follow-up, and any additional 3-month interval thereafter for which there is sufficient follow-up data available to compare study phases. The number of subjects that obtain an IPG by pre-specified time point t= 3, 6, etc., will be included in the numerator and the number of subjects with an SND diagnosis will be included in the denominator.

C. Additional Analyses

- In addition to the overall diagnosis and treatment rates between Phase I and Phase II, various descriptive summaries of the subjects will be explored by geography, including the following:
    - The distribution of subgroups of final diagnoses that fall under the general categorization of SND –
    - The distribution of various diagnostic tests used to determine final diagnosis
    - The association between diagnostic tests used and the type of SND indication
    - A table that describes the type and number of devices prescribed for SND
    - A summary of pacing modes for devices prescribed for SND

8.5.2.2. Sample Size Methods and Assumptions

The proportion of IPG therapy in SND subjects is currently unknown within the study geographies. The PANARM HF study of 2000 subjects found that 146 out of 331 bradycardia subjects (44%) had symptomatic SND and that 15 (10%) of SND subjects opted for IPG therapy. PANARM HF included symptomatic HF which is different than the IMPROVE Brady population. Thus, the percentages expected in IMPROVE Brady may differ from those observed in PANARM HF. Assuming that 20% of subjects will be diagnosed with SND, this suggests that there will be 100 SND subjects in Phase I and 200 in Phase II per geography/country. Further assuming that IPG therapy will be adopted by 10% of SND subjects at three months after diagnosis, or equivalently an IPG incidence of 0.25 diagnoses per person-year, this means that the margin of error will be ±8.0% in a sample of 100 subjects per geography/country, based on a 95% confidence interval. If there are 100 SND subjects in Phase I and 200 SND subjects in Phase II, assuming a type I error of 0.05 and power of 0.90, a Fisher's Exact test will detect an increase in IPG therapy of at least 16% at three months after diagnosis. This means that the objective will obtain statistical significance if 52 of 200 SND subjects in Phase II opt for IPG therapy. The Poisson regression for the same scenario has a power of 0.95 to compare IPG incidence of 0.25 versus 0.625 implants per person-year. The power of this objective will improve if the percentage of SND diagnoses is larger than 20%. In order to better account for the proportion of SND diagnosis and IPG adoption per

geography/country, the Phase II sample size will be recalculated within the geography/country once Phase I data collection is complete.

Stopping Guidelines for Futility

If Phase I of the study suggests that only 5% of enrolled subjects meet an SND indication and that only 5% of those indicated opt for IPG therapy, the study may close for futility at the end of Phase I within that geography/country. Suppose that the percent of SND diagnosis is 5% and that 5% of those indicated will opt for therapy. Assuming 500 subjects in Phase I, 5,440 subjects will be needed in Phase II to see an increase in the implant rate from 5% to 30%. This suggests a scenario with insufficient power to continue into Phase II.

8.5.3. Secondary Objective #1

Describe the diagnosis and treatment of Phase I subjects.

8.5.3.1. *Analysis Methods*

A. Statistical Methodology

An exact 95% confidence interval of a binomial proportion at each pre-determined time point will be used to calculate the margin of error for the SND and IPG proportions in Phase I of the study. [redacted]

B. Determination of Patients/Data for Analysis

All subjects that are enrolled in the study will be included in the determination of the proportion estimates of SND. The proportion estimates will be calculated based on information from fixed time points at 6 months of follow-up, 12 months, and any additional 6-month interval thereafter for which there is follow-up data available. The number of subjects that obtain an SND diagnosis by pre-specified time point t= 6, 12, etc., is included in the numerator and the number of subjects enrolled is included in

the denominator. The number of subjects that meet inclusion criteria and obtain an SND diagnosis shall be included in the determination of the proportion estimates of IPG therapy. The proportion estimates will be calculated based on information from fixed time points at 3 months of follow-up, 6 months, and any additional 3-month interval thereafter for which there is follow-up data available. The number of subjects that obtain an IPG by pre-specified time point t= 3, 6, etc., will be included in the numerator and the number of subjects with an SND diagnosis will be included in the denominator.

C. Additional Analyses

- In addition to the overall diagnosis and treatment rates of Phase I subjects, various descriptive summaries of the subjects will be explored by geography, including the following:
  - The distribution of subgroups of final diagnoses that fall under the general categorization of SND – overall and by local region
  - The distribution of various diagnostic tests used to determine final diagnosis
  - The association between diagnostic tests used and the type of SND indication
  - A table that describes the type and number of devices prescribed for SND
  - A summary of pacing modes for devices prescribed for SND

8.5.4. Secondary Objective #2

Evaluate the change in the time to diagnosis of SND before and after intervention.

8.5.4.1. *Analysis Methods*

A. Statistical Methodology

A log-rank test of two Kaplan-Meier curves will determine if there is a significant difference in the time to diagnosis before and after intervention, within the South Asia geography. [redacted]

[redacted]

Cox models may also be fit to examine independent variables of interest that may affect SND diagnosis, such as gender and age. Descriptive statistics will be used to characterize the number of visits that occur before an SND diagnosis and further will examine number of visits separated by Phase, type of enrolling physician, and possibly other baseline characteristics. [redacted]

[redacted]

B. Determination of Patients/Data for Analysis

The subjects to include in the analysis of Secondary Objective 2 in Section **Error! Reference source not found.** are the same as specified in Section **Error! Reference source not found.** for Primary Objective 1.

C. Additional Analyses

In addition to the time to event analysis, various additional analyses of the subjects will be explored, including a description of diagnostic tests performed when there is a delay in a patient's diagnosis. The endpoint is time to diagnosis and variables of interest are the different types of diagnostic tests. A table will be created with a format as follows:

Tests performed	SND dx 0-6 months	SND dx 6-12 months	SND dx 12-18 months
ECG	Number of tests, number of subjects		
Tilt table			
ILR			
Holter			
Average number of tests performed			

8.5.5. Secondary Objective #3

Evaluate the change in the time to receiving an indicated IPG device for SND subjects before and after intervention.

8.5.5.1. *Analysis Methods*

A. Statistical Methodology

A log-rank test of two Kaplan-Meier curves will determine if there is a significant difference in the time to implant before and after intervention, within the South Asia geography. Descriptive statistics will be used to characterize the number of visits that occur between the diagnosis and implant and further will examine number of visits separated by Phase, type of enrolling physician, and possibly other baseline characteristics.

B. Determination of Patients/Data for Analysis

The subjects to include in the analysis of Objective 3 in Section **Error! Reference source not found.** are the same as specified in section **Error! Reference source not found.** for Primary Objective 2.

C. Additional Analyses

In addition to the time to event analysis, a Cox model will test covariates of interest that may include gender, age, HF, NYHA class and ejection fraction and the impact on time to implant. A characterization will also be provided that describes covariates of interest and whether or not the implant was CRT instead of an IPG

8.5.6. Secondary Objective #4

Evaluate the Caregiver burden between pre-implant and 6 months post-implant.

8.5.6.1. Analysis Methods

A. Statistical Methodology

Descriptive statistics will be used to summarize the difference in caregiver burden between pre-implant and 6 months post-implant. The Zarit Burden Interview is a 22 question survey, with each question scored on a scale of 0 to 4. The total score is the sum of all 22 question responses. A t-statistic will test the difference between the total score of the survey between pre-implant (zarit0) and 6 month post-implant (zarit6)[redacted]

[redacted]

The primary analysis will deal with missing values by scaling the total score of the non-missing responses. If at least 50% of the survey has been completed, the total score of the non-missing responses will be multiplied by (22/number of non-missing responses). If less than half of the questions were answered, the survey will not be included in the analysis. Missing values will be dealt with using a multiple imputation procedure as a sensitivity analysis.

B. Determination of Patients/Data for Analysis

Subjects in Phase II who opt to receive an indicated therapy and are implanted with a market released pacemaker from the Medtronic family of devices will be followed from implant to 6 months post-implant. The primary caregiver of these subjects will be asked to complete a questionnaire that assesses caregiver burden at the time of implant and 6 months post-implant.

8.5.7. Secondary Objective #5

Evaluate change in quality of life (QOL) and functional status between pre-implant and 6 months post-implant.

8.5.7.1. *Analysis Methods*

A. Statistical Methodology

Descriptive statistics will be used to summarize the difference in QOL and functional status between pre-implant and 6 months post-implant. The SF-12 survey results will be compared at implant and at six

months of follow-up. A t-statistic will test the difference in the survey scores between the two time points. The eight sub-domains of the SF-12 may also be tested.

Composite scores are calculated by first appropriately summarizing eight scales from the individual SF-12 questions.

- Physical Functioning (PF) - Items 2a+2b
- Role Physical (RF) - Items 3a+3b
- Bodily Pain (BP) - Item 5
- General Health (GH) - Item 1
- Vitality (VT) - Item 6b
- Social Functioning (SF) - Item 7
- Role Emotional (RE) - Items 4a+4b
- Mental Health (MH) - Items 6a+6b

If at least half of the items within any scale have been completed, any missing values within those scales can be imputed as the average response of all remaining questions from that scale for that respondent within the survey taken on that visit (Chapter 6 of SF-36 Health Survey Manual and Interpretation Guide).

Once the eight scales have been summarized, they are each normalized by their 1998 general US population means and standard deviations, and a linear combination of the scales are combined to calculate the composite physical and mental scores (Chapter 8 of How to Score Version 2 of the SF-12 Health Survey).

[redacted]

[redacted]

[redacted]

B. Determination of Patients/Data for Analysis

Subjects in Phase II who opt to receive an indicated therapy and are implanted with a market released pacemaker from the Medtronic Family of devices will be followed from implant to 6 months post-implant. These subjects will be asked to complete a questionnaire that assesses their QOL at the time of implant and 6 months post-implant.

[redacted]

[redacted]

9. Validation Requirements

All analysis of primary objectives will have level I validation.

All analysis of secondary and ancillary objectives will require level II (or better) validation.

10. References

Greenspon AJ, Patel JD et al. Trends in Permanent Pacemaker Implantation in the United States From 1993 to 2009. J Am Coll Cardiol 2012; 60(16): 1540-1545.

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Rodriguez RD, Schocken DD et al. Update on sick sinus syndrome, a cardiac disorder of aging. J Am Coll Cardiol 1990; 45(1): 26-30.

P3 Patient Profiling Study Final Report. Version 1.0, May 21, 2008.

SF-36 Health Survey Manual and Interpretation Guide. Chapter 6; 6:16-6:17.

How to Score Version 2 of the SF-12® Health Survey. Chapter 8; 45-51.