Document Approval and Change History

Medtronic	**IMPROVE Brady**	
	Clinical Investigation Plan	**Version 2.0** **16 February 2012**

Document Change History			
Version	**Version Date**	**Description of and Rationale for Change**	**Effects on Other Documents**
1.0	14 Nov 2011	Initial Release	Initial Release
2.0	16-Feb-2012	Appendix F Study Overview was added to support ethics committee submissions.	No other documents effected.

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IMPROVE Brady
Clinical Investigation Plan

Version 2.0
16 February 2012

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ADVISORY COMMITTEE

Medtronic, Inc. has assembled an independent scientific advisory committee comprised of health care professionals to help design and guide this initiative.

Advisory Committee

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1 INTRODUCTION

1.1 Study Purpose

Medtronic, Inc. is sponsoring a quality improvement study called the "Registry to Improve the Adoption of Consensus Treatment Guidelines" (IMPROVE Brady). It is hypothesized 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 sinus node dysfunction (SND). The study is expected to provide evidence to support claim(s) that:

- Education and process improvement initiatives can improve the diagnosis of and appropriate therapy application for SND
- The quality improvement methods studied have general applicability and can be used by all centers
- Appropriate treatment minimizes caregiver burden
- Appropriate treatment improves quality of life (QOL) and functional status compared to pre-implant

1.2 Study Scope

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.

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.

2 BACKGROUND AND JUSTIFICATION

The World Health Survey of Cardiac Pacing and Cardioverter-Defibrillators suggests that adoption of pacing therapy in emerging countries is lower than that

of developed countries. New device implants per million in emerging countries are 17, 31, 159 and 287 for India, China, Russia and Argentina respectively compared to 702, 782, 744 and 627 for the respective developed countries of Sweden, France, Italy and Belgium. The population for these countries in millions is as follows: 1,200 in India, 1,300 in China, 142 in Russia, and 40 in Argentina, 9 in Sweden, 62 in France, 60 in Italy and 10 in Belgium[1]. The size of the population in the emerging countries combined with data from the World Health Survey, suggests that there is an opportunity to improve adoption to consensus treatment guidelines in the emerging countries. Adoption of the pacing indications for Sinus Node Dysfunction (SND) may not be optimal due to the chronic non-specific nature of the symptoms and the lack of conclusive randomized trials supporting the efficacy of pacemaker therapy in SND patients[2,3,4]. Within the developed geographies, 21-40% of subjects participating in clinical studies receiving pacing therapy had met the indication for sinus node dysfunction. The wide range may demonstrate that SND can be a difficult indication to identify[1, 5, 6, 7, 8, 9].

A recent process improvement clinical study, IMPROVE HF, demonstrated that implementation of a defined and scalable practice-specific quality improvement process in the outpatient heart failure cardiology setting significantly improved the use of evidence-based therapies in eligible patients with systolic heart failure[10]. A baseline chart review was conducted at 167 sites, involving 34,810 patients. Physicians then attended an educational workshop, where they set treatment goals and developed a customized clinical care pathway for their practice. Sites were also provided with heart failure disease state management tools that were designed to help improve the quality of care administered to their heart failure patients. Participation did not require that any specific procedure or assessment be done[11]. After the intervention occurred, there was evidence of significant improvements in the adoption of guideline based care. Perhaps a similar clinical trial on SND developed for the emerging countries could improve the adoption of the American College of Cardiology (ACC)/American Heart Association (AHA)/Heart Rhythm Society (HRS) Guidelines for Device Based Therapy of

1 Mond HG and Proclemer A. The 11th World Survey of Cardiac Pacing and Implantable Cardiac Defibrilators: Calendar Year 2009 A World Society of Arrhythmia's Project. Pacing Clin Electrophysiol 20011 Aug;34:1013-1027
2 Mangrum JM. The Evaluation oand Management of Bradycardia. New England Journal of Medicine 2010 May;342(10):703-709
3 Epstein et al. ACC/AHA/HRS 2008 Guidelines for Device-Based Therapy of Cardiac Rhythm Abnormalities. Heart Rhythm 2008;5:e1-e62.
4 Vardas PE. Guidelines for cardiac pacing and cardiac resynchronization therapy. European Heart Journal 2007 Sep;28(18):2256-95.
5 Nowak et al. Do gender differences exist in pacemaker implantation?. Europace 2010 Feb;12(2):210-5)
6 Levander-Lindgren et al. Bradyarrhythmia profile and associated disease in 1265 patients with cardiac pacing. Pacing Clin Electrophysiol 1988 Dec;11(12):2207-15
7 Sutton et atl. Electrophysiological and haemodynamic basis for application of new pacemaker technology in sick sinus syndrome and AV block. Br Heart J 1979 May;41(5):600-12
8 Coma et al. Spanish Pacemaker Registry. Fifth Official Report of the Spanish Society of Cardiology Working Group on Cardiac Pacing. Rev Esp Cardiol 2008 Dec;61(12):1315-28
9 Hartel G. Treatment of sinoatrial syndrome with permanent cardiac pacing in 90 patients. Acta med Scand. 1975 Nov;198(5):341-7
10 Yancy CW, Fonarow GC, Albert NM, et al. Improving evidence-based care for heart failure in outpatient cardiology practices: Primary results of IMPROVE HF [abstract]. Circulation 2010 Aug 10; 122(6):585-96
11 Fonarow GC et al. Improving the use of evidence-based heart failure therapies in the outpatient setting : the IMPROVE HF performance improvement registry. Am Heart J, 2007;154:12-38.

Cardiac Rhythm Abnormalities[2] and the European Society of Cardiology (ESC) Guidelines for cardiac pacing and cardiac resynchronization therapy[3].

The aim of IMPROVE Brady is to improve adoption of consensus treatment guidelines in the emerging countries for SND indicated patients as described in the ACC/AHA/HRS guidelines[2] and ESC guidelines[3]. Implantable Pulse Generator (IPG) therapy has been integrated into the ACC/AHA/HRS guidelines and ESC guidelines without evidence from large randomized clinical trials (RCT). While the RCT is considered the gold standard for establishing that a therapy causes a clinical outcome effect, the scientific community is calling for clinical research beyond the RCT. A manuscript in Circulation in 2008[12] states that the external validity of RCTs must be supplemented by real world "effectiveness research", including pragmatic studies, meta-analyses and observational trials. Guidelines and major publications help with awareness of what is possible when treating disease and an important component of adoption is the physician's personal experience with the therapy. As such, the evidence in this study will provide personal experience, powerful information for the individual physician, and an aggregated analysis.

3 SYSTEM DESCRIPTION AND INTENDED USE

3.1 Device Description

Subjects meeting an ACC/AHA/HRS or ESC indication for pacing therapy may be implanted with any pacemaker from the Medtronic family of devices that are market released and any market released lead. There are no programming requirements for this study. All devices are used according to medical, technical and ethical standards without any change to the approved use of the device.

3.2 Medtronic Programmers

Medtronic programmers will need to be available at each implanting center to support study data collection requirements. Programmers will be used to interrogate, program devices and save device data to a disk or USB. All commercially released Medtronic programmers are available for use in this study.

4 METHODOLOGY

The IMPROVE Brady study is a prospective, interventional, sequential, post market study that may be conducted in CEE, Greater China, India Latin America, Asia and MEA. Additional countries from other geographies may be added in the future. Any market released pacemaker from the Medtronic family of devices may be used in this study. It is hypothesized 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

12 Nallamothu, et al. Beyond the Randomized Clinical Trial: The Role of Effectiveness Studies in Evaluating Cardiovascular Therapies. Circ 2008;118;1294-1303.

treatment guidelines will improve the quality of care for patients with sinus node dysfunction (SND).

The study will be conducted in compliance with the Clinical Investigation Plan, Clinical Trial Agreement, approved labeling, latest version of the Declaration of Helsinki, and laws and regulations of the country in which the study is conducted, including data protection laws.

Principles of the Declaration of Helsinki have been incorporated into this study by means of the patient informed consent/Patient Data Release process, IRB/MEC approval (if required), study training, clinical trial registration, risk benefit assessment, and publication policy, etc.

The study may enroll up to 14,850 subjects worldwide. Once enrolled, Phase I subjects may be followed for approximately 1.5 years and Phase II subjects may be followed for approximately 3 years per geography/country. IMPROVE Brady is anticipated to be completed in Spring 2017 across all geographies. Subject data will be collected at enrollment/baseline, diagnostic assessment visits, implant visit and a scheduled follow up visit. Data will continue to be collected until one of the exit criteria has been met (Section 5.7).

IMPROVE Brady requires measurement of Thyroid Stimulating Hormone (TSH & T4) and hemoglobin (HGB) prior to an IPG implant. The bloodwork can be done at any time during the diagnostic process as determined by the sites standard of care. IMPROVE Brady does not mandate specific requirements regarding any other procedures, subject visits to the clinic, clinical treatment of subjects or device programming (if applicable). Clinical data will be collected using electronic case report forms.

Centers will be eligible to enroll subjects in IMPROVE Brady upon Medtronic's receipt of required center activation materials and written approval.

4.1 Study Objectives

PRIMARY OBJECTIVE(S)

1. Evaluate the impact of the intervention on the diagnosis of SND
2. Evaluate the impact of the intervention on SND subjects that receive an indicated IPG device

SECONDARY OBJECTIVES

The key secondary objectives with pre-specified hypotheses to be tested include:

1. Describe the diagnosis and treatment of Phase I subjects
2. Evaluate the change in time to diagnosis of SND before and after intervention
3. Evaluate the change in the time to receiving an indicated IPG device for SND subjects before and after intervention
4. Evaluate the caregiver burden between pre-implant and 6 months post-implant
5. Evaluate change in Quality of Life (QOL) and functional status between pre-implant and 6 months post-implant

[redacted]

4.2 Subject Selection

Subjects of both genders meeting all the inclusion criteria and none of the exclusion criteria are eligible for the study.
Inclusion Criteria:

- Patient is at least 18 years of age
- Patient's heart rate meets at least **one** of the following:
  - Patient has a sinus rate ≤50 **OR** a junctional escape rhythm no faster than 50
  - Patient has a history of exercise intolerance
- Patient complains of general fatigue, shortness of breath, shortness of breath with exertion, syncope, light headed dizziness, palpitations, lethargy, dyspnea **OR** malaise within the last 30 days that are not related to other discovered causes (such as untreated hypothyroidism or anemia).
- Patient (or patient's legally authorized representative) is willing and able to sign and date written Patient Consent Form/Patient Data Release Consent

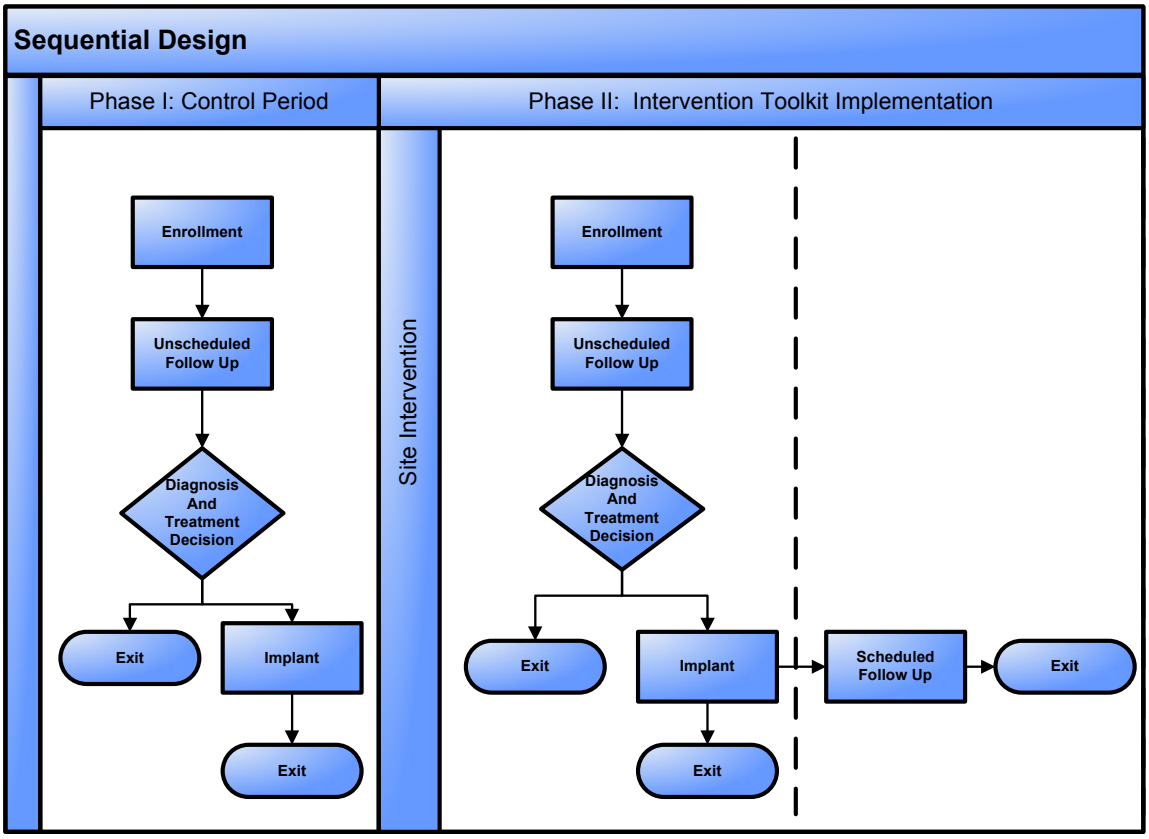
Exclusion Criteria:

- Patient has type II 2nd degree AV block, High degree AV block (2:1, 3:1, 4:1 etc.) or 3rd degree AV block
- Patient has recent history of blood loss
- Patient has a medical history leading to suspicion of neurological disorder
- Patient has a history of Chronic Atrial Fibrillation
- Patient is enrolled or planning to participate in a concurrent drug and/or device study at any time during the course of this clinical study without documented pre-approval from the Medtronic study manager
- Patient is not expected to survive for 12 months
- Patient is anticipated to be unwilling or unable to comply with the clinical investigation plan

Subjects will be screened to ensure they meet all of the inclusion and none of the exclusion criteria. Subjects are considered enrolled upon signing the Informed Consent Form/Patient Data Release.

4.3 Study Design

There are two phases to IMPROVE Brady:



Phase I: This phase of the study serves as a control period. During Phase I physicians will assess and treat subjects per their site's standard care practice. Enrollment for Phase I is anticipated to occur for approximately 12 months but will continue until 550 subjects have been enrolled for the geography/country. For subjects enrolled during Phase I, collection of diagnostic assessment and implant data will be complete 6 months after the last enrollment for the geography/country. At that time, all Phase I subjects will be exited.

If a center becomes active after the geography/country enrollment goal for Phase I has been met or the center did not enroll at least 10 subjects before Phase I enrollment stopped then the center will enroll Phase I subjects until 10 subjects have been enrolled at that center. Once 10 subjects have been enrolled at the center, enrollment will stop and the subjects will be followed for a maximum of 6 months and exited from the study.

Phase II:
The objective of the IMPROVE Brady study is to provide investigators with comprehensive resources that may be adapted by the Principal Investigator and his/her colleagues to create a practice specific process improvement intervention to improve the quality of care for patients.

At the completion of Phase I, the Principal Investigator and co-investigators will complete an educational workshop and be given access to the IMPROVE Brady toolkit. In addition, the Principal Investigator and his/her colleagues are encouraged to adapt tools from the IMPROVE Brady toolkit to create a practice specific process improvement intervention.

Immediately following completion of the educational workshop, study investigators will receive written authorization from Medtronic that they are authorized to enroll subjects in Phase II. Enrollment during this phase is anticipated to occur for approximately 18 months per geography/country.

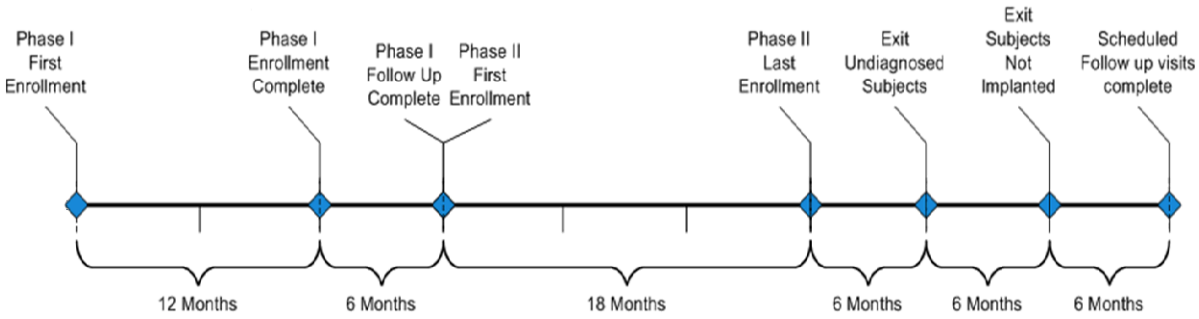
The IMPROVE Brady process improvement intervention toolkit may include an education workshop, diagnostic algorithm(s), patient video and tools for investigators to educate their patients on their disease state, available therapy options, and benefits and risks associated with the therapy options.

During Phase II a patient survey assessing the subject's quality of life and functional status, will be completed by subjects meeting an SND indication for pacing therapy and being implanted with a market released pacemaker from the Medtronic family of devices. The patient survey must be completed before the implant procedure and again at 6 months post-implant.

The caregiver of the subject being implanted with the market released pacemaker from the Medtronic family of devices will be asked to participate in a caregiver survey. The purpose of the survey is to assess how providing care to the person receiving the pacemaker impacts the caregiver. Prior to completing the survey an Informed Consent or Patient Data Release will need to be signed by the caregiver. The caregiver survey will be completed prior to the implant procedure and again at 6 months post-implant. The same caregiver must complete the pre and post implant surveys of the same patient.

For subjects enrolled during Phase II collection of diagnostic assessment data will be complete 6 months after last enrollment for the geography/country. At that time, any subjects without a diagnosis will be exited from the study. Collection of implant data will be complete 6 months after the last Phase II diagnosis for the respective geography/country. Any subjects not implanted by the end of the 6 months will be exited from the study. The Geography/country study timeline (Figure 2) depicts the geography/country timeline.

Figure 2: Geography/country study timeline



4.4 Minimization of Bias

Potential sources of bias in this study may result from the Hawthorne effect, selection of study centers, selection of subjects, treatment of subjects, and evaluation of study data. The following methods have been incorporated into the study to minimize potential bias.

- Center selection criteria, documented under separate cover, will need to be met prior to participation in IMPROVE Brady
- Study center characteristics will be collected at activation on possible differences that may effect the primary endpoints
- Centers will be used as their own control
- Subjects will be screened to confirm eligibility for enrollment with defined inclusion/exclusion criteria prior to enrollment
- Subject demographics will be collected at baseline on possible differences that may effect the primary endpoints
- It is anticipated that the distribution of subjects with various co-morbidities will vary by study centers. To minimize potential bias, all sites will be encouraged to enroll at least 10 subjects in each study Phase and enrollment at a site cannot exceed 20% of the sample size for the geography/country to ensure a more even distribution of data
- All study Clinicians will be required to follow the Clinical Investigation Plan
- All study clinicians and Medtronic personnel will be trained on their respective aspects of the clinical investigation plan using standardized training materials.

5 STUDY PROCEDURES

All local and regional regulatory requirements will be fulfilled prior to center activation and enrollment of subjects into the study. Each study site must have written documentation of site and investigator readiness, including (but not limited to):

- Medical Ethics Committee (MEC), Institutional Review Board (IRB) or Head of the Medical Institution written approval of the current version of the Clinical Investigation Plan and Patient Informed consent/Patient Data

Release OR written documentation from the investigator stating approval is not required OR a written waiver from the MEC/IRB must be on file with the sponsor

- When (MEC)/IRB or Head of the Medical Institution written approval is submitted to Medtronic the following needs to be included:
  - The approval letter must contain enough information to identify the version/date of the documents approved or it must be retrievable from the submission letter.
  - Approval letter must be accompanied by a roster or written documentation that center staff participating in the study did not participate in the approval process

- Competent Authority approval or notification (if required)
- Investigator Curriculum Vitae on file with the sponsor (signed and dated as required per geography/country)
- Signed/dated Clinical Trial Agreement on file with the sponsor
- Signed/dated documentation of training of required personnel

All clinical investigators managing the subjects must be qualified practitioners that will be involved in the diagnosis and/or treatment of subjects with SND. All implanting physicians must be experienced in the handling of market released pacemakers from the Medtronic family of devices. All participating Clinicians will complete study training regarding the Informed Consent Process (if applicable), case report forms and Clinical Investigation Plan.

Medtronic will inform the investigator in writing when all requirements have been fulfilled for center activation.

The following study equipment may be useful to have available at each center to support study activities:

- Electrocardiography machine
- Echocardiography machine
- Holter monitor, Event Monitor or Reveal
- Ergometer or treadmill.

5.1 Informed Consent/Patient Data Release Process

Patient Informed Consent(PIC)/Patient Data Release (PDR) is defined as legally effective, documented confirmation of a subject's (or their legally authorized representative or guardian) voluntary agreement to participate in a particular clinical investigation after information has been given to the subject on all aspects of the clinical investigation that are relevant to the subject's decision to participate.

A PDR can only be used when ethics committee approval of the study is not needed or when local laws allow.

Prior to enrolling patients, each investigational center's Medical Ethics Committee (MEC), Institutional Review Board (IRB) or Head of the Medical Institution must, if required by local laws and regulations, approve the Clinical Investigation Plan (CIP) and Patient Informed Consent/Patient Data Release (PIC/PDR). If MEC/IRB approval is not required by local laws and regulations then written documentation from the investigator stating this or a waiver from the MEC/IRB must be sent to Medtronic. Any changes to the PIC/PDR consent must be approved by Medtronic and the MEC/IRB or Head of the Medical Institution reviewing the application before being used to consent a prospective study subject. The document(s) should be controlled (i.e. versioned and/or dated) to ensure it is clear which version(s) were approved by the MEC/IRB or Head of the Medical Institution.

Prior to initiation of any study-specific procedures, subjects (or their legally authorized representative or guardian) must sign and date the data protection authorization and/or other privacy language where required by law and the MEC/IRB or Head of Medical Institution and Medtronic approved Patient Informed Consent/Patient Data Release. A copy of the PIC/PDR form or a signed copy where required by law, will be given to all subjects (or their legally authorized representative or guardian) in a language he/she is able to read and understand.

The process of obtaining patient informed consent shall:

- Avoid coercion and undue influence of subjects to participate
- Answer all questions to the subject's satisfaction
- Not waive or appear to waive subject's legal rights
- Use language that is non-technical and understandable to the subject
- Provide ample time for the subject to consider participation
- Include a dated signature of the subject acknowledging that their participation in the study is voluntary
- Include a dated signature by the clinical investigator or authorized designee (if required)

If the PIC/PDR is obtained the same day the subject begins participating in study-related procedures, it should be documented in the subject's case history that consent was obtained prior to participation in any study-related procedures.

In the event the subject cannot read and/or write, witnessed (impartial third party) informed consent will be allowed, provided detailed documentation of the process is recorded in the subject's case history, the witness was present during the entire discussion and the witness signs and dates the PIC/PDR to attest that the information was accurately explained, and clearly understood by the patient and

that consent was freely given. The original or a copy of the signed PIC/PDR must be filed in the hospital/clinical chart or with the subject's study documents. A copy of the signed PIC/PDR and data protection authorization/or other privacy language where required by law must be provided to the subject.

The PIC/PDR consent form and data protection authorization and/or other privacy language where required by law must be available for monitoring and auditing. Any Medtronic Field personnel who supports the study must be able to review the subject's signed and dated consent form and verify it's completeness prior to proceeding with study related activities. In the event the Medtronic Field personnel identify a consent as being incomplete, the study activities will not be allowed to occur until the consent of the subject can be adequately and appropriately obtained.

5.2 Data Collection

Table 1 depicts the data collection requirements for the study.

Table 1: Data Collection and Study Procedure Requirements at Subject Visits

Study Procedure	Enrollment/Baseline	Diagnostic Assessment	Implant	Scheduled Follow Up
Informed Consent/Medical Release	X			
Inclusion/Exclusion	X			
Demographics	X			
Medical History	X			
Symptoms	X			
Vitals (HR, BP)	X			
Cardiovascular Medications	X	X	X	
Referral information	X	X	X	
Diagnostic tests/results	X (if applicable)	X		
Blood labs		X		
Final Diagnosis		X		
Device Indication		X		
Pt Education Utilized		X		
Treatment Decision		X		
System Information			X	
Device Programming			X	
Save to disk∞			X	
Patient Survey*			X	X
Caregiver Survey†			X	X
Death	As they occur			
Reason for Exit				
Study Deviation				

∞ A pre-discharge save to disk needs to be submitted to Medtronic, if available

* The patient survey is only completed for those patients implanted with a market released pacemaker from the Medtronic family of devices.

† The caregiver survey is only completed by consenting caregivers of subjects implanted with a pacemaker from the Medtronic family of market released devices.

5.3 Enrollment/Baseline Procedures

The investigator or designated study coordinator will evaluate patients for inclusion and exclusion criteria. Patients who meet these criteria may be invited to participate in the study. Each study subject or legal representative must sign an informed consent/Patient Data Release prior to any study procedures taking place.

Non-Implanting Physician/Site: Enrollment is anticipated to occur prior to a final diagnosis of the patient being known, however, the patient may be enrolled at any time the IMPROVE Brady inclusion/exclusion criteria are met.

Implanting Physician/Site: If the patient was enrolled in IMPROVE Brady by a referral physician/center and then referred to an implanting physician/center, also participating in the IMPROVE Brady study, an additional study consent does not need to be obtained. If the patient was not previously enrolled in the study then the patient may be enrolled at any time the IMPROVE Brady inclusion/exclusion criteria are met.

When a subject signs and dates the patient consent form/Patient Data Release, he/she is considered a subject enrolled in the study. The date the subject signed the consent form must be reported in the CRF.

The Baseline assessment will be utilized to collect subject demographic data, cardiovascular medical history, symptoms, vital signs, cardiovascular medication use and referral information.

5.4 Diagnostic Assessment Visit(s)

A diagnostic assessment is any post enrollment visit to the study center for continued diagnostic assessment or management. During these visits information about utilization of diagnostic tests, results and cardiovascular medication use will be collected. Information about the final diagnosis and treatment decision will also be collected during the diagnostic assessment visit. Within each geography/country, collection of the diagnostic assessment visit data will be complete:

- When the subject meets study exit criteria
- 6 months after the last Phase I enrollment for Phase I subjects
- 6 months and after the last Phase II enrollment for Phase II subjects.

The study protocol does not dictate when the Diagnostic Assessment(s) is/are to occur.

Any patient meeting an SND indication with a treatment plan that includes being implanted with an IPG device must have blood drawn to assess for untreated hypothyroidism (TSH & T4 exceeding normal limits) and anemia (HGB<10), if it

was not already done during the diagnostic assessment as part of the site's standard of care.

5.5 Implant Visit

The implant visit is when the IPG is implanted in the study subject and will only occur for those subjects meeting the ACC/AHA/HRS and ESC pacing indications. The implant will be performed according to the hospital's standard implant practice. IMPROVE Brady does not have device programming requirements. Information about the procedure, the device, and how the device was programmed will be collected. A pre-discharge save-to-disk with a final interrogation will also be collected and submitted to Medtronic, if available.

(Phase II only)
At the implant visit the study subjects being implanted with a market released pacemaker from the Medtronic family of devices will complete a patient survey prior to implant to assess their quality of life and functional status. During this visit the subject's caregiver will be asked to complete a Caregiver survey after signing a PIC/PDR. The purpose of the caregiver survey is to assess how providing care to the patient impacts the caregiver.

5.6 Scheduled Follow-up Visit (Phase II only)

The scheduled 6 months post-implant follow up visit is required for subjects that received a market released pacemaker from the Medtronic family of devices and their participating caregiver. During this visit the subject with the IPG will complete the patient survey and the caregiver will complete a caregiver survey. The caregiver completing the survey must be the same caregiver that completed the pre-implant caregiver survey.

5.7 Study Exit

Subjects may be exited from the study for any of the following situations, including but not limited to:

- Subject does not meet an indication for pacing therapy
- Subject meets an indication for pacing but not a SND indication for pacing therapy
- Subject has met a SND indication for pacing therapy and did not receive a market released pacemaker from the Medtronic family of devices
- Subject has met a SND indication for pacing therapy but will not be receiving pacing therapy
- Subject has completed the final scheduled follow-up visit.

- Geography/country completion of Phase I follow-up
- Study Closure
- Subject lost to follow-up
- Subject death
- Subject did not meet inclusion/exclusion criteria
- Subject chooses to withdraw (e.g., consent withdrawal, relocation to another geographic location)
- Investigator deems withdrawal necessary (e.g., medically justified, failure of subject to maintain adequate study compliance)

5.8 Lost to Follow-Up

In the case that the subject is determined to be lost to follow-up, regulations set forth by the governing IRB/MEC (where applicable) will be followed.

5.9 Subject Follow-up after Withdrawal

Upon withdrawal from the study, no further study data will be collected or study visits will occur for the subject.

5.10 Medications

There are no medications that are required for this study. All cardiovascular medications and cardiovascular herbal treatments will be collected. The only medications that are excluded from use during this study are investigational medications.

6 STUDY DEVIATIONS

A study deviation is defined as an event within a study that did not occur according to the Clinical Investigation Plan or the Clinical Trial Agreement.

Prior approval by the Medtronic study manager is expected in situations where the investigator anticipates, contemplates, or makes a conscious decision to deviate. Prior approval is not required when a deviation is necessary to protect the life or physical wellbeing of a subject in an emergency or in unforeseen situations beyond the investigator's control (*e.g.* subject failure to attend scheduled follow-up visits, inadvertent loss of data due to computer malfunction, inability to perform required procedures due to subject illness, etc.).

For medically justifiable conditions which preempt a subject's ability to complete a study-required procedure, it may be permitted to complete only one deviation Case

Report Form which will apply to all visits going forward. This may also apply for other unforeseen situations (e.g. the subject permanently refuses to complete a study required procedure and the data will not contribute to the primary end point analysis, etc.). However, prior approval from Medtronic is required for such situations.

All study deviations must be reported on the Case Report Form regardless of whether medically justifiable, pre-approved by Medtronic, an inadvertent occurrence, or taken to protect the subject in an emergency. The deviation must be recorded with an explanation for the deviation and corrective/ preventative action(s).

In the event the deviation involves a failure to obtain a subject's consent, or is made to protect the life or physical wellbeing of a subject in an emergency, the deviation must be reported to the MEC/IRB (where applicable) as well as Medtronic within five (5) working days. Reporting of all other study deviations should comply with MEC/IRB policies and/or local laws and must be reported to Medtronic as soon as possible upon the center becoming aware of the deviation. Reporting of deviations must comply with IRB/ MEC policies, local laws, and or regulatory agency requirements. Refer to Investigator Reports (Table 2) for geography/country-specific deviation reporting requirements and timeframes for reporting to Medtronic and/or regulatory bodies.

Medtronic is responsible for analyzing deviations, assessing their significance, and identifying any additional corrective and/or preventive actions (e.g. amend the Clinical Investigation Plan, conduct additional training, terminate the investigation, etc.). Repetitive or serious investigator compliance issues may represent a need to initiate a corrective action plan with the investigator and site, and in some cases, necessitate freezing enrollment until the problem is resolved or ultimately terminating the investigator's participation in the study. Medtronic will provide center-specific reports to investigators summarizing information on deviations that occurred at the investigational site on a periodic basis.

7 ADVERSE EVENTS

The collection of adverse event data is not required to meet the objective(s) of this clinical trial. The products used in the clinical trial are market approved and used within the current Indications for use as indicated in the product labeling. However, it is the responsibility of the Investigator to abide by any adverse event reporting requirements stipulated by local laws and regulations and the site's Investigational Review Board (IRB) or Medical Ethics Committee (MEC).

User (Investigator) reporting of events to regulatory authorities related to market approved products may be required.

7.1 Vigilance Reporting

It is the responsibility of the investigator to report all product complaints and malfunctions immediately via the regular channels for CE marked products.

The reporting of product complaints and malfunctions of these CE-labeled devices is not part of the clinical study and should be done by the investigator.

8 SUBJECT DEATH

8.1 Data Collection

Subject deaths will be documented on the Study Exit form. The date of death and classification of cardiovascular relatedness, if known, will also be documented. It is the responsibility of the Investigator to abide by any death reporting requirements stipulated by local laws and regulations and the site's Investigational Review Board (IRB) or Medical Ethics Committee (MEC).

User (Investigator) reporting of deaths to regulatory authorities related to market approved products may be required.

9 RISK ANALYSIS

All implantable systems (pacemaker and lead(s)) utilized in this study are market released and are used according to medical, technical and ethical standards without any change to the approved use of the system. The safety and clinical performance of the market released systems have been demonstrated through previous pre-clinical testing and clinical studies in similar populations, but not necessarily the same population as this study. The risks are described in the informed consent.

The blood draw procedure that is performed as a protocol requirement is not associated with significant risk, and the procedure is carried out in many clinics as standard practice.

9.1 Potential Benefits

There are no direct benefits to the patient for participating in IMPROVE Brady. However, information gained from the study will contribute to the body of knowledge regarding diagnosis and treatment of patients with SND and may help improve the quality of care for these patients.

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

10.1 Planned Study Closure

Study Closure is a process initiated by distribution of an initial study closure letter. 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 study closure process is complete upon distribution of the Final Report or after final payments, whichever occurs last. IRB/MEC re-approvals are required until the overall study closure process is complete.

10.2 Early Termination OR Suspension

Early Termination of the Study is the closure of a clinical study that occurs prior to meeting defined endpoints. This is possible for the whole study, a geography/country or a single center.

Study Suspension is a temporary postponement of study activities related to enrollment. This is possible for the whole study, a geography/country or a single center.

Criteria

Study Termination or Suspension

Possible reasons for considering study suspension or early termination of the study may include:

- None of the study subjects in the geography/country have been implanted with an indicated IPG at the completion of Phase I
- SND indicated subjects are ≤ 5% of subjects enrolled in the geography/country and/or implanted subjects is ≤ 5% of indicated subjects in the geography/country by the end of Phase I
- Enrollment is slower than anticipated
- Observed/suspected performance of the market released pacemaker from the Medtronic family of devices used in the study is different from the product's design intent.
- Decision by Medtronic or regulatory body (where the study is operating under regulatory body authority)

Investigator/Center Termination or Suspension

Possible reasons for clinical investigator or center termination or suspension include but are not limited to:

- Failure to obtain initial IRB/MEC/Head of Medical Institution approval or annual renewal of the study (where applicable)
- Consistent non-compliance to the clinical investigation (e.g. failure to adhere to inclusion/exclusion criteria, failure to follow subjects per scheduled follow-ups, etc.)
- Lack of enrollment
- Noncompliance to regulations and the terms of the Clinical Trial Agreement (e.g. failure to submit data in a timely manner, failure to follow-up on data queries and monitoring findings in a timely manner, etc.)
- IRB/MEC suspension of the center
- Fraud or fraudulent misconduct is discovered (as defined by local law and regulations)
- Investigator request (e.g. no longer able to support the study)

Procedures

If Medtronic terminates or prematurely suspends the study:
Medtronic will promptly inform the clinical investigators of the termination or suspension and the reasons and inform the regulatory authority(ies) (where required per regulatory requirements).

In the case of study termination or suspension for reasons other than a temporary IRB/MEC approval lapse, the investigator will promptly inform the IRB/MEC.

- In the case of study termination, the investigator must inform the subjects and may inform the personal physician of the subjects to ensure appropriate care and follow-up is provided.
- In the case of a study suspension, subjects already enrolled should continue to be followed out of consideration of their safety, rights and welfare.

If the investigator terminates or suspends the study without prior agreement of Medtronic:

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

If the IRB/MEC terminates or suspends its approval of the study:

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

11 STATISTICAL METHODS AND DATA ANALYSIS

Medtronic statisticians will conduct all statistical analysis. The sample size package PASS 2008 was used for sample size evaluation. In this study, it is hypothesized 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 sinus node dysfunction (SND). The two primary endpoints are the impact of the intervention on the diagnosis of subjects

with SND and whether SND indicated subjects receive IPG therapy. In current practice, both of these proportions are unknown for a set of patients 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 rates and binomial proportions. The second principle of the analysis is that sample size calculations for Phase II (intervention phase) of the study design will depend on the outcomes observed in Phase I (control phase) 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 1:2 collection ratio will also allow for more information to contribute to secondary objectives 3 and 4. The third principle of the analysis is that both the statistical methods and the Phase II sample size calculations will be geography/country specific because the study outcomes are expected to vary by geography/country.

11.1 Primary Objective(s)

Primary Objective #1
Evaluate the impact of the intervention on the diagnosis of SND.

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.

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 separately within geography/country as well as overall.

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 a 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.

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 SND and that 15 (10%) of SND subjects opted for IPG therapy. 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.

Primary Objective #2

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

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.

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 implants typically occur more quickly than the 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 separately within geography/country as well as overall. 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.

B. Determination of Patients/Data for Analysis

The number of 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.

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 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.

11.2 Secondary Objectives

Secondary Objective #1

Describe the diagnosis and treatment of phase I subjects.

Endpoint Definition

The proportion of subjects receiving an SND diagnosis and the number of diagnosis that result in indicated therapy at pre-specified time points and the number of subjects diagnosed and implanted per person-year

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.

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 a 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 a 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.

Secondary Objective #2

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

Endpoint Definition

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

Secondary Objective #3

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

Endpoint Definition

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

Analysis Methods

A. Statistical Methodology

For Secondary Objectives 2 and 3 above, the following statistical analysis is proposed. A stratified log-rank test of two Kaplan-Meier curves will determine if there is a significant difference in the time to endpoint before and after intervention. The stratification will occur by geography/country and also by site. Stratified 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 between the diagnosis and implant and further will examine number of visits separated by Phase, geography/country, type of enrolling physician, and possibly other baseline characteristics.

B. Determination of Patients/Data for Analysis

The subjects to include in the analysis of secondary objectives 2 and 3 are the same as specified for primary objectives 1 and 2 respectively.

Secondary Objective #4

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

Endpoint Definition

Compare the difference in caregiver burden from pre-implant to 6 months post-implant

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.

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.

Secondary Objective #5

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

Endpoint Definition

Compare the difference in QOL and functional status between pre-implant and 6 months post-implant.

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.

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]

[redacted]

12 DATA AND QUALITY MANAGEMENT

Data will be collected using an electronic data management system for clinical trials. CRF data will be stored in a secure, password-protected database which will be backed up nightly. Data will be reviewed using programmed and manual data checks. Data queries will be made available to centers for resolution. Study management reports may be generated to monitor data quality and study progress. At the end of the study, the data will be frozen and will be retained indefinitely by Medtronic.

Procedures in the CIP require source documentation. In some cases, items on the CRFs may be considered source as long as there is evidence of the visit in the subject's record. Even when the CRF may be considered as source, an alternate method of source documentation is always strongly encouraged.

Save-to-disk data collected prior to discharge from the hospital will be sent to Medtronic, if available. Upon receipt, device data will be maintained with databases and retrieved for analysis and reporting.

The sponsor or a regulatory authority may audit the study center to evaluate the conduct of the study. The Clinical Investigator must immediately notify Medtronic when it learns that a regulatory authority will be auditing the site. The clinical investigator(s)/institution(s) shall allow trial related monitoring, audits, Ethics Board review, and regulatory inspection(s) by providing direct access to source data/documents.

13 WARRANTY/ INSURANCE INFORMATION

13.1 Warranty

Warranty information is provided in the product packaging for the commercially released system and additional copies are available upon request.

13.2 Insurance (CEE)

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

13.3 Insurance (India)

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

13.4 Insurance (Latin America)

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

13.5 Insurance (MEA)

The Medtronic Mediterranean SAL is a wholly owned subsidiary of Medtronic Inc., which as the parent company of such entity maintains appropriate clinical study liability insurance coverage as required under applicable laws and regulations and will comply with applicable law and custom concerning specific insurance coverage. If required, a Clinical Trial Insurance statement/certificate will be provided to the MEC/IRB.

13.6 Insurance (MEA)

The Medtronic Africa (Pty) Ltd.is a wholly owned subsidiary of Medtronic Inc., which as the parent company of such entity maintains appropriate clinical study liability insurance coverage as required under applicable laws and regulations and will comply with applicable law and custom concerning specific insurance coverage. If required, a Clinical Trial Insurance statement/certificate will be provided to the MEC/IRB.

14 MONITORING

It is the responsibility of Medtronic to ensure proper monitoring of the study per regulations. Appropriately trained Medtronic personnel or delegates appointed by Medtronic will perform study monitoring at the study center in order to ensure that the study is conducted in accordance with the CIP the Clinical Trial Agreement (CTA), and applicable regulatory requirements. Medtronic must therefore be allowed access to the subjects' clinic and hospital records when so requested as per the Subject Informed Consent/Patient Data Release Consent, and CTA.

14.1 Monitoring Visits

Frequency of monitoring visits will occur based on subject enrollment, duration of the study, study compliance, findings from previous monitoring visits and any suspected inconsistency in data that requires investigation. Regulatory documents (e.g., IRB/MEC approval letters and CTAs, etc.) will be reviewed at a representative number of study centers. The number of centers and amount of

subject data monitored against source documentation is determined by type of study and timing of data cutoff for study deadlines.

Monitoring visits will be conducted periodically to assess site study progress, the investigator's adherence to the CIP, regulatory compliance including but not limited to IRB/MEC approval and review of the study, maintenance of records and reports, and review of source documents against subject CRFs. Monitors facilitate site regulatory and study compliance by identifying findings of non-compliance and communicating those findings along with recommendations for preventative/corrective actions to site personnel. Communication with the site personnel occurs during the visit and following the visit via a written follow-up letter. Monitors may work with study personnel to determine appropriate corrective action recommendations and to identify trends within the study or at a particular center.

15 REQUIRED RECORDS AND REPORTS

15.1 Investigator Records

The investigator is responsible for the preparation and retention of the records cited below. It is recommended that measures be taken to prevent accidental or early destruction of study related materials. All of the below records, with the exception of case history records and case report forms, should be kept in the Investigator Site File (i.e., the study binder provided to the investigator) or Subject Study Binder. CRFs may be maintained and signed electronically within the electronic data capture system during the trial. The following records are subject to inspection and must be retained for a period of two years (or longer as local law or hospital administration requires) after the date on which the investigation is terminated.

- All correspondence between the IRB/MEC, sponsor, monitor,
- Subject's case history records, including:
  - Signed and dated informed consent form/patient data release
  - Medical history
  - Baseline, diagnostic assessment(s), implant data, and scheduled follow-up
  - Documentation of the dates and rationale for any deviation from the protocol
- Signed and dated CRFs.
- All approved versions of the Clinical Investigation Plan, Patient Informed Consents/Patient Data Releases
- Lists of sites, investigators and IRB/MECs
- Signed and dated Clinical Trial Agreement.
- Investigators current curriculum vitae (signed and dated, if required).
- Delegated task list.

- IRB/MEC approval documentation or a written waiver. Written information that the investigator or other study staff, when member of the IRB/MEC, did not participate in the approval process (where applicable); IRB/MEC Roster (when applicable).
- Study training records for site staff.
- Regulatory Authority Approval (if applicable)
- Insurance certificates (where applicable).
- Any other records that local regulatory agencies require to be maintained.
- Final Study Report including the statistical analysis.

15.2 Investigator Reports

The investigator is responsible for the preparation (review and signature) and submission to the sponsor of all case report forms and any deviations from the clinical investigation plan. If any action is taken by an IRB/MEC with respect to this clinical study, copies of all pertinent documentation must be forwarded to Medtronic in a timely manner. Reports are subject to inspection and to the retention requirements as described above for investigator records.

The investigator shall prepare and submit in a complete, accurate and timely manner the reports listed in this section.

Table 2: Investigator Reports Applicable for all Geographies per Medtronic Requirements

Report	Submit To	Description/Constraints
Withdrawal of IRB/MEC approval	Sponsor	The investigator must report a withdrawal of approval by the reviewing IRB/MEC of the investigator's part of the investigation within 5 working days.
Progress Report	Sponsor and IRB/MEC	Provide if required by local law or IRB/MEC
Study Deviations	Sponsor and IRB/MEC	Any deviation from the clinical investigation plan shall be recorded together with the explanation of the deviation. Notice of deviations from the CIP to protect the life or physical well being of a subject in an emergency shall be given as soon as possible, but no later than 5 working days after the emergency occurred. Except in such emergency, prior approval is required for changes in the plan or deviations.
Final Report	IRBs/MECs Relevant Authorities	This report must be submitted within 3 months of study completion or termination.

15.3 Sponsor Records

Medtronic shall maintain the following accurate, complete, and current records:

- All essential correspondence which pertains to the investigation
- Signed Investigator Trial Agreements, and current investigator curriculum vitae (signed and dated, if required) , and delegated task list
- All signed and dated case report forms submitted by investigator, samples of informed consents, and other information provided to the subjects
- Copies of all IRB/MEC approval letters, IRB/MEC rosters and relevant IRB/MEC correspondence
- Names of the institutions, investigators and IRB/MEC's in which the clinical investigation will be conducted
- Correspondence with authorities as required by national legislation
- Insurance certificates, if applicable
- Names/contact addresses of monitors
- Statistical analyses and underlying supporting data
- Final report of the clinical investigation
- All approved versions of the Clinical Investigation Plan, PIC/PDR and study related reports
- Study training records for site personnel and Medtronic personnel involved in the study
- Any other records that local regulatory agencies require to be maintained.

15.4 Sponsor Reports

Medtronic shall prepare and submit the following complete, accurate, and timely reports listed in the tables below (by geography/country). In addition to the reports listed below, Medtronic shall, upon request of reviewing IRB/MEC, or regulatory agency, provide accurate, complete and current information about any aspect of the investigation.

Table 3: Sponsor Reports for Europe

Report	Submit To	Description
Withdrawal of IRB/MEC approval	Investigators Head of Institution IRB/MEC and relevant authorities	Investigators, IRBs/MECs will be notified only if required by local laws or by the IRB/MEC.
Progress Reports	IRB/MEC	This will be submitted to the IRB/MEC only if required by the IRB/MEC.
Study deviation	Investigators	Site specific study deviations will be submitted to investigators quarterly.

Table 4: Sponsor Reports for Hong Kong

Report	Submit To	Description
Study deviation	Investigators	Ensure that all deviations from the Clinical Investigation Plan are reviewed with the appropriate clinical investigator(s), are reported on the case report forms and the final report of the clinical investigation. Site specific study deviations will be submitted to investigators quarterly.

Medtronic records and reports will be stored in locked file cabinets at Medtronic during the course of the study. Electronic versions of the reports will be kept on a password-protected document management system. After closure of the study, all records and reports will be archived indefinitely.

Appendix A: Patient Informed Consent and Patient Data Release

At the time of IMPROVE Brady Clinical Investigation Plan Version 1 completion, the Patient Informed Consent and Patient Data Release form, that comply with local laws and regulations of the participating geographies/countries were still being developed. A Patient Informed Consent and Patient Data Release Form will be distributed under separate cover.

Appendix B: Case Report Forms

At the time of IMPROVE Brady Clinical Investigation Plan Version 1 completion, case report forms were still being developed. Case Report Forms will be distributed under separate cover when available.

Appendix C: Preliminary Publication Plan

Publications addressing the IMPROVE Brady data will be handled according to Cardiac Rhythm Disease Management Standard Operating Procedures and as indicated in the Clinical Trial Agreement.

Publication Committee

The IMPROVE Brady Advisory Committee will manage publications utilizing data from this study with the goal of publishing results. The Advisory Committee will develop the final Publication Plan as a separate document.

The Publication Committee's role is to manage elements addressed in the publication plan as outlined in this appendix, develop the final Publication Plan under separate cover, execute the Publication Plan, oversee the publication of primary, secondary and ancillary study results, review and prioritize publication proposals, provide input on publication content, and determine authorship. In addition, the committee will apply and reinforce the authorship guidelines set forth in the Publication Plan. Membership in the Publication Committee does not guarantee authorship. The committee will meet at regular intervals.

Management of Primary, Secondary and Ancillary Publications

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

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

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

Requests for publications utilizing subset data (e.g., site) beyond the overall results will be evaluated for scientific validity and the ability of Medtronic to provide resources. The Advisory Committee must approve publication of ancillary requests and will ensure that requests do not present conflicts with other proposals and are not duplicative.

Criteria for Determining Authorship

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

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

- Substantial contribution to conception and design, or acquisition of data, or analysis and interpretation of data
- Drafting the article or revising it critically for important intellectual content
- Final approval of the version to be published

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

All investigators not listed as co-authors will be acknowledged as the "Medtronic IMPROVE Brady Clinical Study Investigators" and will be individually listed according to the guidelines of the applicable scientific journal. Any other contributors will be acknowledged by name and their specific contribution indicated.

Transparency

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

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

Appendix D: Participating Investigators and Institutions

At the time of IMPROVE Brady Clinical Investigation Plan Version 1 completion, center confirmation was not finalized. A complete list of participating investigators and institutions where study activities will be conducted will be distributed under a separate cover when available.

Appendix E: IRB/MEC List

At the time of IMPROVE Brady Clinical Investigation Plan Version 1 completion, center information was not finalized. Therefore a complete list of participating IRB/MECs and the Chairperson(s) will be distributed under separate cover when available.

Appendix F: Study Overview

Study purpose

The purpose of this global, prospective, multi-center, post-market study is to characterize the current management of patients presenting with possible sinus node dysfunction (SND) and to assess practice-specific process improvement intervention consisting of education, critical care pathways and documentation tools that advocate and reinforce the use of evidence-based therapies intended to improve adherence to consensus treatment guidelines and the quality of care for SND patients.

Study scope and design

The study may be conducted in 9 geographies/countries; with approximately 10 study centers per geography or country. Approximately 1,650 subjects per geography/country, or up to 14,850 subjects worldwide, will be enrolled in the study. There are two phase to the study. Enrollment for Phase I is anticipated to occur for approximately 12 months but will continue until 550 patients have been enrolled for the geography/country. Enrollment during Phase II is anticipated to occur for approximately 18 months or until approximately 1100 patients per geography/country have been enrolled. Centers that enroll faster than others will be allowed to enroll up to 20% of the sample size, maximum of 330 subjects per site, for each geography/country.

Phase I of the study serves as the control period, during which physicians will assess and treat subjects per their site's standard care practice. For subjects enrolled during Phase I, information will be collected regarding what was done to diagnose a patient and, if applicable, information regarding the device that was implanted. All Phase I patients will be exited from the study and not allowed to partake in Phase II of the study.

At the completion of Phase I, the Principal Investigator and co-investigators will complete an educational workshop and provided access to the IMPROVE Brady toolkit. The Principal Investigator and his/her colleagues are encouraged to use the toolkit to create a practice specific process improvement intervention regarding the diagnosis and treatment plan for patients. The educational workshop and toolkit is the intervention being examined, in the study. The IMPROVE Brady toolkit may include, but not limited to, diagnostic algorithm(s), patient video and tools for investigators to educate their patients about their disease state, available therapy options, and benefits and risks associated with the therapy options. Information collected in Phase II will be identical to Phase I regarding what was done to diagnose a patient and, if applicable, information regarding the device that was implanted.

CLINICAL STUDY OBJECTIVES

Primary objectives

1. Evaluate the impact of the intervention on the diagnosis of SND
2. Evaluate the impact of the intervention on SND subjects that receive an indicated IPG device

Secondary objectives

1. The key secondary objectives with pre-specified hypotheses to be tested include:
2. Describe the diagnosis and treatment of Phase I subjects

3. Evaluate the change in time to diagnosis of SND before and after intervention
4. Evaluate the change in the time to receiving an indicated IPG device for SND subjects before and after intervention
5. Evaluate the caregiver burden between pre-implant and 6 months post-implant
6. Evaluate change in Quality of Life (QOL) and functional status between pre-implant
7. and 6 months post-implant

Main Inclusion / exclusion criteria (not an exhaustive list)

Inclusion Criteria:

- Patient is at least 18 years of age
- Patient's heart rate meets at least **one** of the following:
    - Patient has a sinus rate ≤50 **OR** a junctional escape rhythm no faster than 50
    - Patient has a history of exercise intolerance
- Patient complains of general fatigue, shortness of breath, shortness of breath with exertion, syncope, light headed dizziness, palpitations, lethargy, dyspnea **OR** malaise within the last 30 days that are not related to other discovered causes (such as untreated hypothyroidism or anemia).

Exclusion Criteria:

- Patient has type II 2nd degree AV block, High degree AV block (2:1, 3:1, 4:1 etc.) or 3rd degree AV block
- Patient has recent history of blood loss
- Patient has a medical history leading to suspicion of neurological disorder
- Patient has a history of Chronic Atrial Fibrillation

Study Duration

The expected study duration per geography/country, from first enrollment in Phase I to last follow-up in Phase II, is approximately 4.5 years per geography/country.

Study Devices

Any market released pacemaker from the Medtronic family of devices and any market released lead may be used in this study

Study Sponsor and Management

The study is being sponsored and managed by Medtronic, Inc.

Appendix G: Bibliography

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