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Brady MX

Clinical Investigation Plan

Version 1

31 MARCH 2016

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CONTACT INFORMATION

Medtronic contact information will be provided under separate cover.

ADVISORY COMMITTEE

Medtronic, Mexico will assemble an independent scientific advisory committee comprised of local health care professionals to consult on this initiative.

1. INTRODUCTION

1.1. Study Purpose

Medtronic, is sponsoring a quality improvement study called Brady MX.
It is hypothesized that lack of awareness of treatment and diagnostic pathways results in lower number of referrals to implanters of IPGs

- Education and process improvement initiatives can improve the diagnosis and increase appropriate therapy applications for SND
- The quality improvement methods to be studied will have general applicability which can be utilized beyond the Brady MX study.

1.2. Study Scope

The study may be conducted in up to10 sites under oversight by the “Secretaria de Salud” in Mexico. The study will be conducted in two phases, with Phase I serving as control subjects and Phase II measuring the impact of the intervention. Up to 500 subjects will be enrolled in the study with at least 210 enrolled per phase. An enrollment target of 45 subjects per center in total 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 up to 42 subjects within each phase of the study.

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 from first enrollment to last follow-up, is approximately 26 months.

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]. Mexico there are 25 Brady implants per million (documented in Seguro Popular). 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].

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

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

The aim of Brady MX is to improve adoption of consensus treatment guidelines in Mexico 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.

4. **METHODOLOGY**

The Brady MX study is a prospective, sequential, post market study with an educational phase and 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 treatment guidelines will improve the quality of care for patients with sinus node dysfunction (SND). The study will be conducted in two phases, with Phase I serving as control subjects and Phase II measuring the impact of the intervention.

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 500 Mexican subjects. with at least 210 subjects enrolled per study phase. Once enrolled, Phase I subjects should be followed for approximately 6 months and Phase II subjects should be followed for approximately 6 months. Brady MX is anticipated to be completed in mid-2018.
Subject data will be collected at enrollment/baseline, diagnostic assessment visits and implant visit. Data will continue to be collected until one of the exit criteria has been met. Brady MX does not mandate specific requirements regarding any other procedures, subject visits to the clinic, clinical treatment of subjects or device programming. Clinical data will be collected using electronic case report forms.

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

4.1. 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 receiving a referral for an indicated IPG device

Secondary Objective

The secondary objectives to be measured include:

1. Evaluate the impact of the intervention on whether SND subjects undergo an IPG implant

Ancillary Objectives

1. Characterize the patient population that declines indicated IPG therapy
2. Characterize the usage and impact of interventional tools (e.g., diagnostic algorithm(s), patient education tools) on the management of SND
3. Evaluate device pacing mode of subjects receiving indicated IPG device before and after intervention
4. Characterize the impact of the intervention on screening strategies and the impact on enrollment.

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:

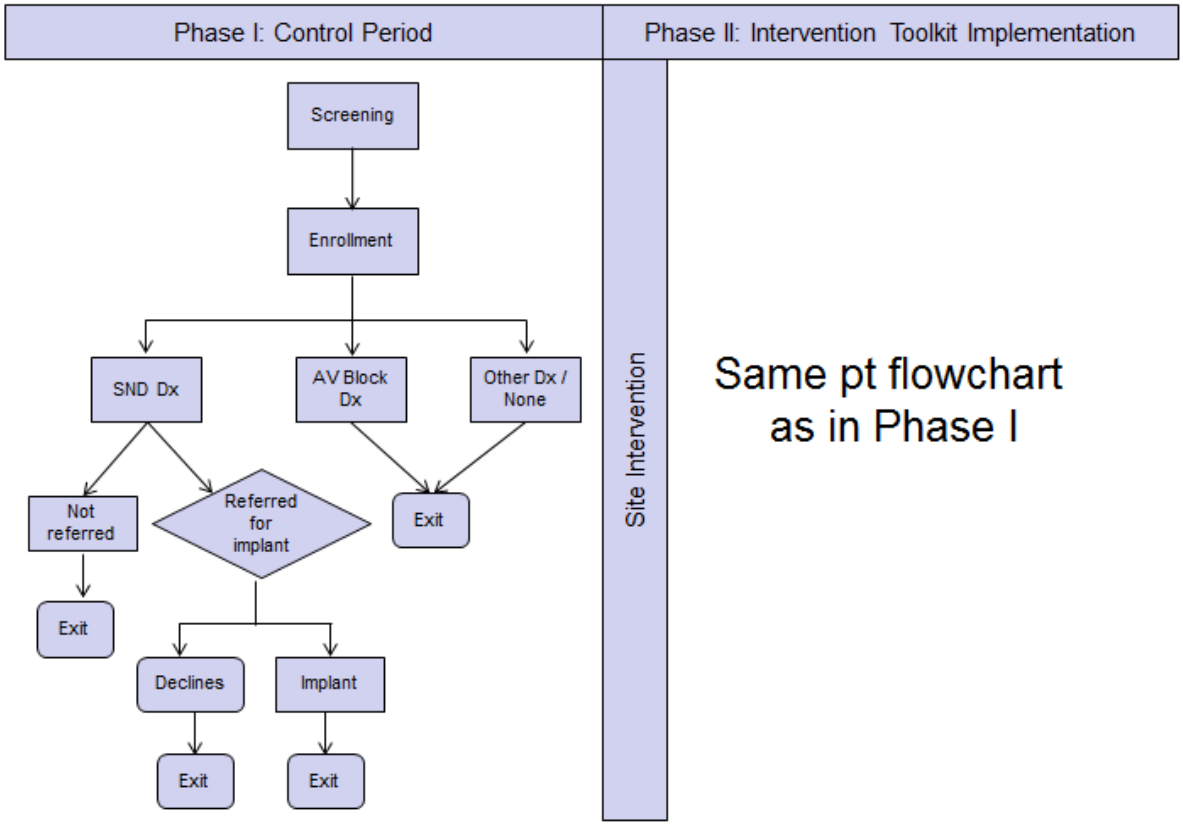
- Patient has recent history of blood loss
- Patient has a medical history leading to suspicion of neurological disorder
- Patient has a history of Chronic Atrial Fibrillation
- Patient is enrolled or planning to participate in a concurrent drug and/or device study at any time during the course of this 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 for Brady MX

Figure 1: IMPROVE Brady Study Design



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 6 months but will continue until a minimum of 210 subjects have been enrolled. For subjects enrolled during Phase I, collection of diagnostic assessment and implant data will be complete 6 months after the last enrollment. At that time, all Phase I subjects will be exited

Phase II:
The objective of the Brady MX 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 Brady MX toolkit. In addition, the Principal Investigator and his/her colleagues are encouraged to adapt tools from the Brady MX 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 6 months but will continue until a minimum of 210 subjects have been enrolled.

The Brady MX 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.

For subjects enrolled during Phase II collection of diagnostic assessment data will be complete 6 months after last enrollment. At that time, any subjects without a diagnosis will be exited from the study.

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 Brady MX. Study center characteristics will be collected at activation on possible differences that may affect the primary endpoints. Centers will be used as their own control
- Subjects will be screened to confirm eligibility with the help of screening logs, for enrollment with defined inclusion/exclusion criteria prior to enrollment
- Subject demographics will be collected at baseline on possible differences that may affect 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 5 subjects in each study Phase and enrollment at a site cannot exceed 42 subjects per phase 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 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), or Head of the Medical Institution written approval of the current version of the Clinical Investigation Plan and Patient Informed consent/Patient Data Release (what is applicable depending on the site)

When MEC 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

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. 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 Insertable Cardiac Monitor
- 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), or Head of the Medical Institution must approve the Clinical Investigation Plan
(CIP) and Patient Informed Consent/Patient Data Release (PIC/PDR). Any changes to the PIC/PDR consent must be approved by Medtronic and the MEC 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 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 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
Informed Consent/ Medical release	X		
Inclusion / Exclusion	X		
Demographics	X		
Medical History	X		
Symptoms	X		
Vitals (HR, BP)	X		
Cardiovascular Medications	X	X	X
Diagnostic tests/ results	X if applicable	X	
Final Diagnosis		X	
Device Indication		X	
System information			X
Pt Education tool used (Phase II only)		X	
Treatment decision		X	
Death	As they occur		
Reason for exit			

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.

Enrollment is anticipated to occur prior to a final diagnosis of the patient being known, however, the patient may be enrolled at any time after the Brady MX 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 and cardiovascular medication use.

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. 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 after the last Phase II enrollment for Phase II subjects
- Patient education tools have been reviewed with the patient by the investigator (Phase II only)

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

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 for sinus node dysfunction.
The implant will be performed according to the hospital's standard implant practice. Brady MX does not have device programming requirements. Information about the device and lead configuration, as well as serial number will only be collected for Medtronic and Vitatron devices.

5.6. 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 but will not be receiving pacing therapy
- Subject diagnosis meets an SND indication for IPG Therapy and a non-Medtronic/Vitatron device was implanted.
- Completion of study follow-up with no diagnosis made
- Study Closure
- Subject lost to follow-up, patient doesn't come back after baseline for diagnosis test decision
- 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)

5.7. **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.

5.8. **Medications**

There are no medications that are required for this study. All cardiovascular medications will be collected.

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.

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 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.

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, or a single center. Study Suspension is a temporary postponement of study activities related to enrollment. This is possible for the whole study 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 have been implanted with an indicated IPG at the completion of Phase I
- Enrollment is slower than anticipated

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 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.)
- 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 MEC approval lapse, the investigator will promptly inform the 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 MEC (where applicable).

If the 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 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 or designees 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 a referral for an IPG therapy. In current practice, both of these proportions are unknown but have been estimated for a set of patients meeting the study inclusion criteria. The sample size calculations will use exact confidence intervals and tests to compare rates and binomial proportions.

11.1. Primary Objective(s)

Primary Objective #1

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

Hypothesis

The primary objective will be tested with the following hypothesis:

H_0: $p_{1t} = p_{2t}$

H_A: $p_{1t} \neq p_{2t}$

where p_{1t} is the proportion of patients with SND in Phase I and p_{2t} is the proportion of patients with SND in Phase II at time point t.

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 = 6, or t is a multiple of 6 representing 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 binomial exact 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 hospital. 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 site as well as overall.

B. Determination of Patients/Data for Analysis
All subjects that are enrolled in the study and that meet study inclusion/exclusion criteria 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, 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* 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 subjects with bradycardia is currently unknown. The power calculations conservatively assume that the SND diagnosis will be 10% at six months of follow-up, or equivalently an SND incidence of 0.2 diagnoses per person-year. If 200 subjects are collected each in Phase I and in Phase II, assuming a type I error of 0.05 and power of 0.80, a binomial exact test will detect an increase in SND diagnosis of at least 10%. For example, the study will find a statistically significant difference between a Phase I SND percentage of 10% at 6 months and a Phase II SND percentage of 20% at 6 months. If the proportion of SND diagnoses is smaller than 10%, there will be more power to detect significant differences in the diagnosis proportion. It is expected that the study attrition rate may be 5% of the study population. To account for attrition, the sample size for Phase I will be a minimum of 210 subjects and for Phase II will be a minimum of 210 subjects.

Primary Objective #2
Evaluate the impact of the intervention on SND subjects receiving a referral for an indicated IPG device.

Hypothesis
The primary objective will be tested with the following hypothesis:

H_0: $p_{1t} = p_{2t}$

H_A: $p_{1t} \neq p_{2t}$

where p_{1t} is the proportion of patients referred for an IPG in Phase I and p_{2t} is the proportion of patients in Phase II at time point *t*.

Endpoint Definition
The absolute change in the proportion of subjects receiving therapy referral for an indicated IPG 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

Statistical Methodology

To compare the proportion of SND subjects that receive a referral for indicated therapy pre-intervention (Phase I) to the proportion post-intervention (Phase II), a binomial exact
test will determine statistical significance. The proportion of subjects diagnosed will be evaluated at multiple time points because the time from diagnosis to implant is expected to vary by hospital. Shorter time intervals will be used to evaluate the proportion of referrals 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.

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 referral 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.

11.2. Secondary Objective

Secondary Objective #1

Evaluate the impact of the intervention on whether SND subjects undergo an IPG implant

Hypothesis

The secondary objective will be tested with the following hypothesis:

H_0: $p_{1t} = p_{2t}$

H_A: $p_{1t} \neq p_{2t}$

where p_{1t} is the proportion of patients with an IPG in Phase I and p_{2t} is the proportion of patients with an IPG in Phase II at time point t.

Endpoint Definition

The absolute change in the proportion of SND 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 SND subjects that receive indicated therapy pre-intervention (Phase I) to the proportion post-intervention (Phase II), a binomial exact test will determine statistical significance. The proportion of subjects diagnosed will be evaluated at multiple time points because the time from diagnosis to implant is expected to vary by site. 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 binomial 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.

11.3. Ancillary Objectives

Ancillary Objective #1
Characterize the patient population that declines indicated IPG therapy.
Endpoint Definition
Decision to receive/decline therapy & why or why not

Analysis Methods
A. Statistical Methodology
Descriptive statistics will be used to describe the number of subjects that receive or decline an indicated therapy split by the reasons subjects provide for their decision.

B. Determination of Patients/Data for Analysis
Subjects in either study phase who receive a diagnosis of SND will be characterized. The subjects will be asked for their reasons to either receive or decline indicated therapy.

Ancillary Objective #2
Characterize the usage and impact of interventional tools (e.g., diagnostic algorithm(s), patient education tools) on the management of SND.

Endpoint Definition
Use of diagnostic tools; use of patient education materials, use of diagnostic algorithm(s), use of other tools

Analysis Methods

A. Statistical Methodology

Descriptive statistics will be used to describe the frequency of usage of interventional tools that assist in the diagnosis and management of SND.

B. Determination of Patients/Data for Analysis

Subjects in Phase II will be characterized. For each subject, the education tools provided to the subject and the interventional tools used by the patient's physicians that are applicable will be recorded.

Ancillary Objective #3
Evaluate device pacing mode of subjects receiving indicated IPG device before and after intervention

Endpoint Definition
Change in pacing mode set at time of implant

Analysis Methods
Statistical Methodology
Descriptive statistics will be used to describe the pacing mode implemented by implanting physicians.

Determination of Patients/Data for Analysis
Subjects in either study phase who receive indicated therapy for SND will be characterized. The device pacing mode set by the implanting physician will be recorded on the Implant CRF at the time of implant.

Ancillary Objective #4
Characterize the impact of the intervention on screening strategies and the impact on enrollment.

Endpoint Definition

Change in the proportion of subjects enrolled out of those screened by site

Analysis Methods

A. Statistical Methodology

Descriptive statistics will be used to describe the proportion of subjects enrolled out of those screened per site.

B. Determination of Patients/Data for Analysis

All subjects screened and enrolled in each study phase.

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 (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.

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

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 of MEC members (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.

15.1. 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.

Appendix A: Patient Informed Consent and Patient Data Release

At the time of Brady MX Clinical Investigation Plan Version 1 completion, the Patient Informed Consent and Patient Data Release form, that comply with local laws and regulations of Mexico 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 Brady MX 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 Brady MX data will be handled according to Cardiac Rhythm Heart Failure Management Standard Operating Procedures and as indicated in the Clinical Trial Agreement.

Publication Committee

The Brady MX 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 Brady MX 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 in Mexico when required by local law
- 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 Brady MX 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 Brady MX 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: Bibliography

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. Am Heart J, 2007;154:12-38.

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

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