Reference:
SJM-CIP-10073

BRADYCARE II

Advanced BRADYCARdia Device Feature Utilization and Clinical OutcomEs II

Clinical Investigation Plan (CIP)

28 May 2015

Sponsor [redacted]

PRINICPAL INVESTIGATOR SIGNATURE PAGE

Advanced BRADYCARdia Device Feature Utilization and Clinical OutcomEs II

Version A

Reference #: SJM-CIP-10073

I have read and agree to adhere to the clinical investigational plan and all regulatory requirements applicable in conducting this clinical study.

Principal Investigator

Printed name: _____

Signature: _____

Date: _____

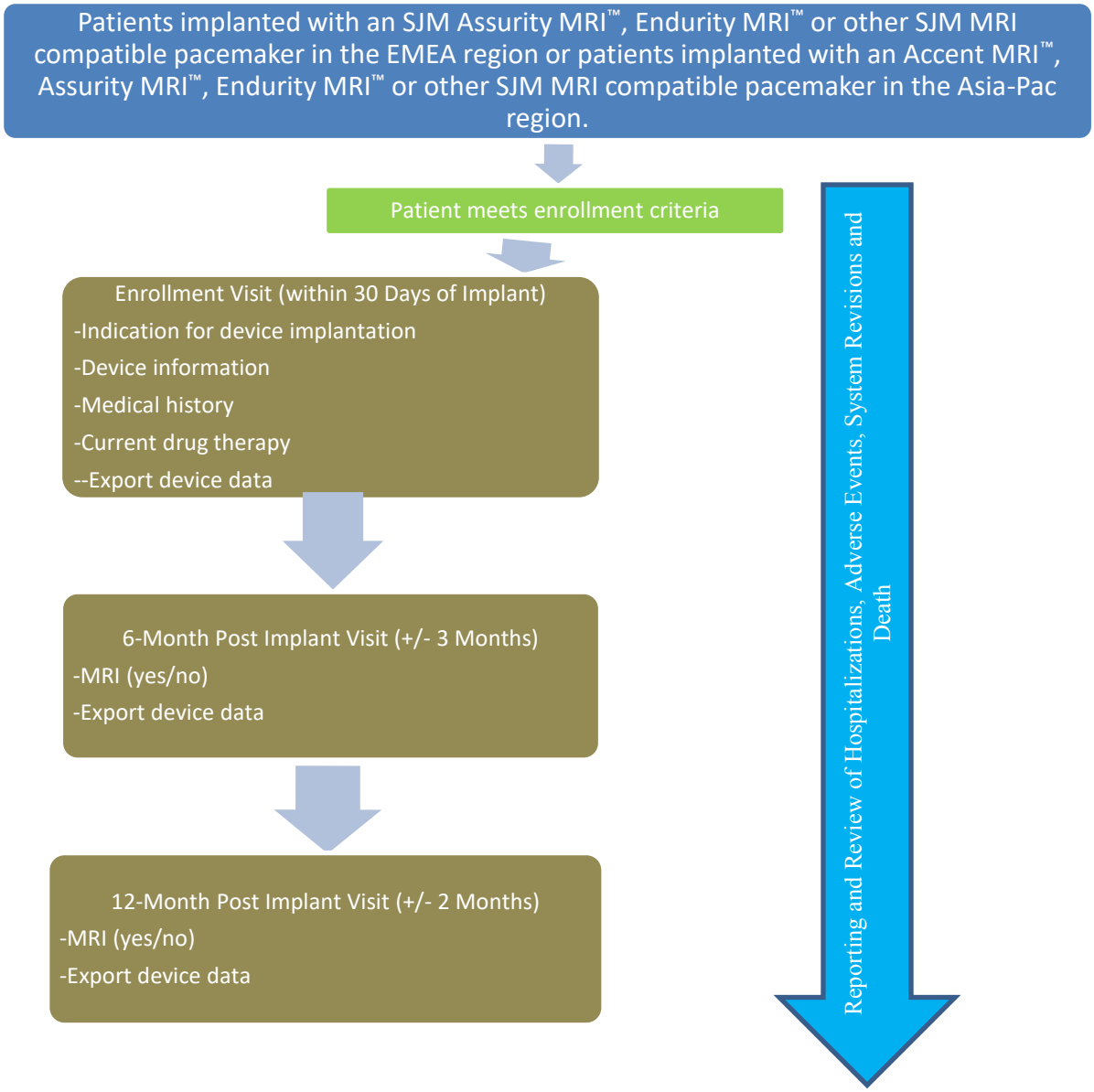
Table of Contents

1.0 SYNOPSIS

Title:	Advanced Bradycardia Device Feature Utilization and Clinical Outcomes II
Acronym:	BRADYCARE II
Purpose:	To characterize the utilization of diagnostic capabilities in SJM pacemakers to manage patients with a standard bradycardia pacing indication
Objectives:	The primary objective of the study is to characterize: • Complication rates in the general pacemaker patient population The secondary objectives of the study are to characterize: • Impact of the usage of advanced features in pacemaker on the clinical outcomes • MRI scanning capabilities and rates in pacemaker patients by country
Outcome Measures:	The primary outcome measure is: • Complication rate at 1 year post implant in general pacemaker population The secondary outcome measures are: • Effect of the usage of advanced features in pacemaker on clinical outcomes • Number and proportion of MRI scans received in pacemaker patients by country
Design:	The study is a prospective, non-randomized, multi-center observational study designed to evaluate the diagnostic capabilities, indications, MRI scanning capabilities and clinical outcomes of patients implanted with SJM pacemakers. The total duration of the study is expected to be approximately 30 months. The clinical study will be conducted in up to 160 centers across Europe, Middle East, Africa, (EMEA region) and Asia, Australia and New Zealand (Asia-Pac region). Up to 2016 subjects will be enrolled in this study. Subjects will be followed for 1 year after pacemaker implant.
Devices used:	SJM Assurity MRI™, Endurity MRI™ or other SJM MRI compatible pacemakers in EMEA region and the Asia-Pac region will use an SJM Accent MRI™, Assurity MRI™, Endurity MRI™ or other SJM MRI compatible pacemakers.

Study Population:	A patient becomes a subject once he/she has been fully informed about the study, has agreed to participate, signed & dated the consent. Patients who have been implanted with an SJM Assurity MRI™, Endurity MRI™ or other SJM MRI compatible pacemakers in the EMEA region within 30 days or patients implanted with an Accent MRI™, Assurity MRI™, Endurity MRI™ or other SJM MRI compatible pacemakers in the Asia-Pac region within 30 days.
Inclusion/Exclusion Criteria:	Inclusion Criteria • Patients who have been implanted with an SJM Assurity MRI™, Endurity MRI™ or other SJM MRI compatible pacemakers in the EMEA region within 30 days or patients implanted with an Accent MRI™, Assurity MRI™, Endurity MRI™ or other SJM MRI compatible pacemakers in the Asia-Pac region within 30 days. • Patient is geographically stable and willing to comply with the required follow-up schedule. • Patient is not pregnant or planning to become pregnant during the course of the study. • Patient is > 18 years of age. Exclusion Criteria • Patient's life expectancy is less than 1 year.
Data Collection:	Enrollment (within 30 days of implant) Device indication, Device information, Medical history, Current drug therapy, Export device data. 6-Month Post Implant Visit (±3 months) MRI (yes/no), Export device data. 12-Month Post Implant Visit (±2 months) MRI (yes/no), Export device data. Unscheduled Office Visits MRI (yes/no), Export device data (if available), Hospitalizations.

1.1 Study Flow Chart



1.2 Study Contacts

[redacted]

2.0 BACKGROUND AND JUSTIFICATION FOR CLINICAL STUDY

Pacemaker technology is constantly evolving. In the past 10 years, numerous advancements have been made in pacemaker therapy, diagnostics and connectivity.[1, 2] These advancements include automated capture, automated sensing, patient alert functions, algorithms minimizing ventricular pacing, automatic mode switching in response to atrial tachyarrhythmia, rate responsive pacing, advanced diagnostic features, remote monitoring and radiofrequency (RF) technology. However, little information is available on how these new features are being utilized by physicians in the real world, especially in countries outside the USA, and how these features impact patient outcomes.[3-8]

Many patients who receive pacemakers will go through natural changes in their disease state and lifestyle that may warrant changes in the way their pacemaker is programmed. St. Jude Medical pacemakers have the ability to identify clinical arrhythmias and provide a wide variety of programming options to address changing clinical status.

This observational study is designed to gain a better understanding of how diagnostic capabilities in the Accent MRI™, Assurity MRI™, Endurity MRI™, or other St. Jude Medical MRI compatible pacemakers are being utilized to manage patients. Pacemaker information and health status will be collected for all patients enrolled in this study. The insight obtained from the device and clinical data collected in this study could lead to potential improvements in device parameter nominal settings. Furthermore, through this study, new insights may be obtained about the progression of heart disease in bradycardia patients and how the flexibility of programming and diagnostic capabilities can benefit the changing clinical status of these patients.

The Advanced Bradycardia Device Feature Utilization and Clinical Outcomes II (BRADYCARE II) study is sponsored by St. Jude Medical (hereinafter referred to as SJM) and will include only market approved products.

3.0 RISKS AND BENEFITS OF THE CLINICAL STUDY

The risks associated with the use of an MRI compatible pacemaker are anticipated to be comparable to those associated with the use of other currently available pacemakers. Subjects participating in this study are indicated for a pacemaker system as part of their standard medical management and are subject to the risks associated with these devices.

3.1 Description of Subject Population

The study population includes those subjects who meet a standard bradycardia pacing indication, are implanted with an SJM Assurity MRI™, Endurity MRI™ pacemaker or similar model in the EMEA region and patients implanted with an SJM Accent MRI, Assurity MRI, Endurity MRI or similar model in the Asia-Pac region, and meet inclusion/exclusion criteria. For the SJM BRADYCARE II study, it is the sponsor's intention that the enrolled subject population be as representative as possible of the eligible population. Physician investigators are strongly encouraged to evaluate all consecutive eligible subjects for participation in the study and, if inclusion and exclusion criteria are met, to approach all eligible subjects. The minimum enrollment requirement for completing this study is 2016 subjects.
The study will be conducted at up to 160 centers across countries in Europe, Middle East, Africa (EMEA region) and Asia, Australia and New Zealand (Asia-Pac region). Centers will be selected for participation in the study based on their ability to screen and enroll eligible subjects, and perform the required study procedures. SJM will attempt to have a diverse group of centers participating in the study including academic and non-academic institutions. A maximum of 200 of the total enrollment can be included per center.

3.2 Anticipated Clinical Benefits

The information gathered in this study will add to the understanding of treatment options for subjects with slow heart rates who require MRI scans. SJM expects subjects implanted with an SJM Brady MRI pacemaker system to receive the same benefit as subjects implanted with other SJM pacemaker systems.

4.0 STUDY DESIGN

4.1 Purpose

The purpose of this observational study is to characterize the utilization of diagnostic capabilities in SJM pacemakers to manage patients with a standard bradycardia pacing indication. Subjects will be followed for 1 year (12 months). It is estimated this study will last approximately 2.5 years (30 months) inclusive of the enrollment period.

4.2 Study Design and Scope

The study is a prospective, non-randomized, multi-center observational study designed to evaluate the diagnostic capabilities, indications, MRI scanning capabilities and clinical outcomes of patients implanted with an MRI compatible SJM pacemaker with a standard bradycardia pacing indication. Any patient that receives an Assurity MRI, Endurity MRI pacemaker (or

newer version) in the EMEA region or any patient that receives an Accent MRI, Assurity MRI, Endurity MRI or similar SJM MRI compatible device in the Asia-Pac region is eligible for enrollment in the study if they meet the inclusion/exclusion criteria.
Subjects will be followed for 12-months after pacemaker implant. Data will be collected at enrollment (within 30 days of device implant), 6 and 12-months post-implant and during any unscheduled follow-up visit. Remote follow-up using Merlin@home® and Merlin.net® is allowed for the 6-month visit as per the site's standard of care. However, subjects must have an in-office follow-up visit at 12-months post pacemaker implant. During the follow-up visits, arrhythmic episode diagnoses, device data, drug therapy, stored electrograms and if an MRI was done will be collected. All clinical events such as hospitalizations, emergency room visits, system revisions and external cardioversions will also be collected. All study data, including device data and stored electrograms will be sent to SJM via the electronic data capture (EDC) system.

This study will be offered to all subjects who are implanted with an SJM Brady MRI system in the EMEA and Asia-Pac region, therefore, the study population is expected to reflect the population of patients implanted with an SJM Brady MRI system in the EMEA and Asia-Pac region.

4.3 Number of Subjects Required to be Included in the Study

Up to 2016 subjects will be enrolled in this study. No more than 200 enrollments (10% of the total study enrollment) will be allowed per center without prior SJM approval.

4.4 Estimated Time Needed to Enroll this Subject Population

The study may continue up to 2.5 years (30 months), dependent on the rate of enrollment.

4.5 Objectives

4.5.1 Objectives

The primary objective of the study is to characterize:

- complication rates in the general pacemaker patient population

The secondary objectives of the study are to characterize:

- Impact of usage of advanced features in pacemaker on the clinical outcomes
- MRI scanning capabilities and rates in pacemaker patients by country

4.5.2 Outcome Measures

The primary outcome measure is:

- Complication rate at 1 year post implant in general pacemaker population

The secondary outcome measures are:

- Effect of the usage of advanced features in pacemaker on the clinical outcomes
- Number and proportion of MRI scans received in pacemaker patients by country

4.6 Inclusion and Exclusion Criteria

A subject, who meets all of the inclusion criteria, and none of the exclusion criteria, is eligible to participate in this study.
All subjects enrolled in the clinical study (including those withdrawn from the clinical study or lost to follow-up) will be accounted for and documented, assigning an identification code linked to their names, alternative identification or contact information.
This log will be kept up to date throughout the clinical study by the principal investigator or his/her authorized designee. To ensure subject privacy and confidentiality of data, this log must be maintained throughout the clinical study at the clinical site.
To participate in this clinical study, the subject must meet **all** of the following inclusion criteria:

4.6.1 Inclusion Criteria

- Patients who have been implanted with an SJM Assurity MRI™, Endurity MRI™ or other SJM MRI compatible pacemakers in the EMEA region within 30 days or patients implanted with an Accent MRI™, Assurity MRI™, Endurity MRI™ or other SJM MRI compatible pacemakers in the Asia-Pac region within 30 days.
- Patient is geographically stable and willing to comply with the required follow-up schedule.
- Patient is not pregnant or planning to become pregnant.
- Patient is > 18 years of age.

Subjects are not eligible for clinical study participation if they meet the following exclusion criteria:

4.6.2 Exclusion Criteria

- Patient's life expectancy is less than 1 year.

4.7 Subject Population

The study population consists of subjects who have been implanted with a SJM bradycardia pacemaker system.

4.7.1 Subject Screening

All subjects presenting at the investigational site should be screened by a member of the investigational team previously trained on the CIP and delegated to do so.

Subjects who do not meet the inclusion/exclusion criteria will not be eligible to participate in this study.

Subjects meeting the inclusion/exclusion criteria will be fully informed about the study and asked to participate in the study. If the subject agrees to participate, a duly signed and dated subject Informed Consent will be obtained.

4.7.2 Point of Enrollment

Subjects are considered enrolled in the study from the moment the subject has provided written Patient Informed Consent. (Refer to section 4.8 for the Informed Consent Process).

4.8 Informed Consent Process

4.8.1 General Process

Prior to enrolling in the clinical study and conducting study-specific procedures, all subjects will be consented, as required by applicable regulations. The consent form must be signed and dated by the subject and by the person obtaining the consent.

The principal investigator or his/her authorized designee will conduct the Informed Consent Process. This process will include a verbal discussion with the subject on all aspects of the clinical study relevant to the subject's decision to participate in the clinical study.

The subject shall be provided with the informed consent form that is written in a language that is understandable to the subject and has been approved by the center's Ethics Committee. Failure to obtain informed consent from a subject prior to study enrollment should be reported to St. Jude Medical within 5 working days and to the reviewing center's Ethics Committee consistent with the center's Ethics Committee reporting requirements.

5.0 DEVICE

5.1 Device Description

In this observational study, subjects are already implanted with an approved St. Jude Medical Brady MRI pacemaker including Accent MRI™, Assurity MRI™, Endurity MRI™ or other SJM MRI compatible pacemaker.

The MRI pacemaker has new hardware and firmware to prevent unintended stimulation due to electromagnetic fields created by the MRI scanner. The new hardware and firmware include:

- Reduction in feed-through capacitance to mitigate gradient-induced stimulation
- Addition of a band-stop filter (MR filter assembly) to limit the ingress of MRI-specific frequencies which otherwise could result in RF rectification and/or other interference.

The device shape and size is modified to accommodate the MRI filter assembly.

The intended purpose of a SJM Brady MRI System, instructions for use, storage and handling instructions, preparation for use and precautions can be found in the instructions for use for each component (IFUs). Use of a SJM Brady MRI System should follow a standard bradycardia pacing indication (also provided in the IFU).

The SJM Brady MRI System has been market released and may be used by any physician experienced with implanting standard pacemakers and leads. No special training is needed to use the device. All medical and surgical procedures will be followed as instructed in the IFU.

Table 1: Description of Proposed Devices

Device Component	Model/Type	Investigational or Market Released
Pacemakers	Accent MRI™ (PM1124, PM1224, PM2124, PM2224)	Market Released
	Assurity MRI™ (PM1272, PM2272)	Market Released
	Endurity MRI™ (PM1172, PM2172)	Market Released
	Endurity MRI™ Conditional (PM1162, PM2162)	Market Released
	Endurity Core (PM1140, PM2140, PM1152, PM2152)	Market Released

5.2 Device Accountability (if applicable)

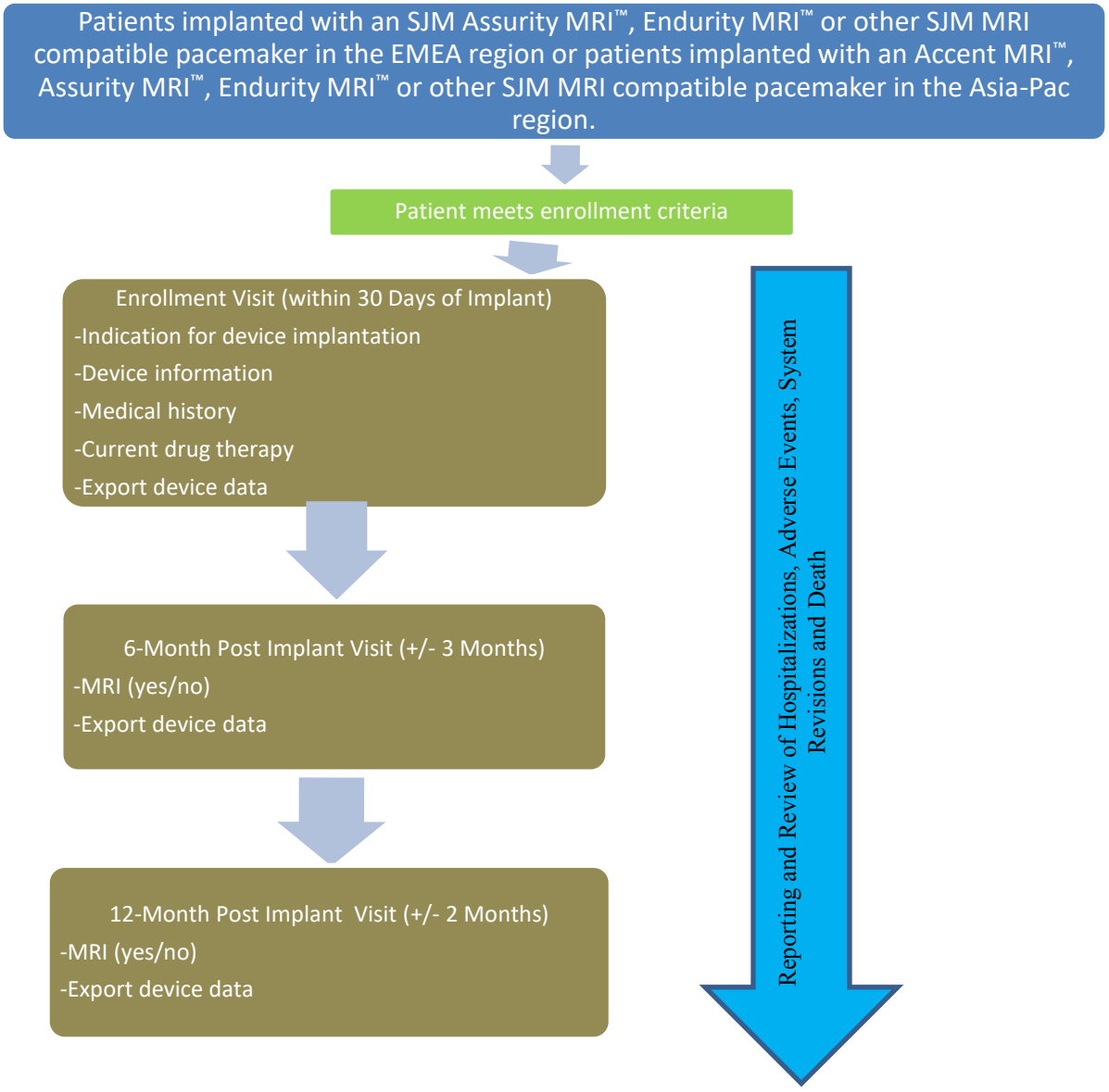
Device accountability is not required for this study.

5.3 Device Handling & Storage

St. Jude Medical requires all products be stored, according to the IFU.

6.0 PROCEDURES

6.1 Study Flow Chart



6.2 Procedures

The clinical study will be conducted in accordance with the CIP. All parties participating in the conduct of the clinical study will be qualified by education, training, or experience to perform their tasks and this training will be documented appropriately.

The clinical study will not commence until St. Jude Medical receives written approval from the Ethics Committee and relevant regulatory authorities as applicable and all required documents have been collected from the site(s).

Table 2: List of all Study Specific Activities/Procedures

Visit / Study Activity	Enrollment (within 30 days of implant)*	6-Month[a] (+/- 3 Months)	12-Month (+/- 2 Months)	Unscheduled Office Visit
Informed Consent Process	X			
Demographics	X			
Medical History	X			
Implant Indication	X			
System Information	X			
Drug Therapy	X			
Device Interrogation	X	X	X	(X)
Check if an MRI done since the last visit (Yes/No)	X	X	X	X
Adverse Event	(X)	(X)	(X)	(X)
System Revision		(X)	(X)	(X)
Product Out of Service		(X)	(X)	(X)
Deviation	(X)	(X)	(X)	(X)
Withdrawal		(X)	(X)	(X)
Hospitalization	(X)	(X)	(X)	(X)
Death		(X)	(X)	(X)

*Enrollment may occur same day as implant
(a) The subject who has a remote 6-month follow-up using Merlin.net® must be contacted by phone.
(X) If applicable

6.3 Enrollment Visit

The following enrollment activities are performed after the subject has been screened and must occur before any study procedure/visit.

- The principal investigator or delegated study personnel are responsible for screening all potential subjects to determine subject eligibility for the study.

- Record enrollment information (name of the study, date of consent and inclusion/exclusion information) in the hospital records and complete and submit the Enrollment and Medical History form in a timely manner (recommended within 5 days).
- Notification of enrollment to the Sponsor will take place only when the Sponsor receives the Enrollment form.

NOTE: As soon as the subject signs the Patient Informed Consent, adverse events need to be reported according to the guidelines mentioned in Section 8.2.

If a subject does not meet all inclusion criteria or meets the exclusion criteria, the subject cannot participate in the study and cannot be enrolled.

Subject data including gender, age, cardiac disease history, cardiac drug therapy, arrhythmia history, smoking history, system information and indication for pacemaker implant will be collected.

Interrogate the device and obtain the following device measurements:
- RA and RV bipolar capture thresholds (if applicable)
- P- and R-wave sensing amplitudes (if applicable)
- RA and RV lead pacing impedance (if applicable)

Upload device session records including all stored IEGMs using the SJM EDC Portal device data upload utility.

Below is the required data that must be collected:
- Enrollment Form
- Medical History Form
- Cardiac Drug Therapy
- Cardiac History
- System Information
- Device Interrogation
- Adverse Event(s) (if applicable)
- Hospitalization (if applicable)

Subjects who meet the inclusion/exclusion requirements, sign an Ethics Committee approved informed consent, and have been implanted with a SJM Brady MRI pacemaker system will be considered for enrollment into the study. If a subject does not meet all inclusion criteria or meets the exclusion criteria, the subject cannot participate in the study and cannot be enrolled. The enrollment date for subjects in the study will be the date when the protocol defined enrollment procedures are completed. Refer to Section 4.7.2 for specific points of enrollment.

6.4 Scheduled Follow-up Visits – 6-Month (+/- 3 Mon) and 12-Month (+/- 2 Mon) Post Implant

Enrolled subjects will be seen at 6-Months (+/- 3 Months) and 12-Months (+/- 2 Months) post pacemaker implant. During these visits, the following evaluations and procedures will be performed:
- Follow Up Form

- Device Interrogation
- System Revision Form (if applicable)
- Product Out of Service Form (if applicable)
- Adverse Event Form(if applicable)
- Deviation Form (if applicable)
- Hospitalization Form (if applicable)
- Withdrawal Form (if applicable)
- Death Form (if applicable)

Submit the completed forms and upload device session records including all IEGMs using the SJM EDC Portal device data upload utility.

For a remote 6-Month follow-up visit: Prior to obtaining the first remote follow-up the site must ensure that the Merlin.net® PCN option to clear all diagnostics and EGMs is enabled. The site must also ensure the session record export option is enabled. A phone interview must be completed in order to collect the required data (information about adverse events, MRI or hospitalizations since enrolling).

6.5 Unscheduled Visits

An Unscheduled Visit is defined as any visit where an active study subject returns to the participating study site for medical care outside of a specified study visit. Examples of unscheduled visits may include subjects returning to the office for an adverse event, wound check and/or device programming change.

The visit should be documented by completing the Unscheduled Visit Form and any other applicable forms (Adverse Event, System Revision, Product Out of Service, Deviation, Hospitalization, Withdrawal and Death Form).

Submit the completed forms and upload device session records (if applicable) including all IEGMs using the SJM EDC Portal device data upload utility.

Following an Unscheduled visit, the subject should be seen for the next scheduled study visit within window.

6.6 Subject Study Completion

When the subject's participation in the clinical study has been completed, the subject will return to the medical care as per physician's recommendation.

6.7 Any Known or Foreseeable Factors that May Compromise the Outcome of the Clinical Study or the Interpretation of the Results

The purpose of this study is to characterize the utilization of diagnostic capabilities in SJM pacemakers to manage patients with a standard bradycardia pacing indication. This study will be offered to all subjects who are implanted with an SJM Brady MRI system in the EMEA and Asia-Pac region. There are no foreseeable factors that may compromise the outcome of this study.

The study is not expected to have higher than normal rates of attrition. Follow up compliance will be closely monitored to ensure these rates do not rise higher than expected.

6.8 Criteria and Procedures for Subject Withdrawal or Discontinuation

Subjects must be informed about their right to withdraw from the study at any time and for any reason without sanction, penalty or loss of benefits to which the subject is otherwise entitled and withdrawal from the study will not jeopardize their future medical care or relationship with the Investigator. Subjects will be asked to specify the reason for the termination, but have the right not to answer.

The Investigator may decide to withdraw a subject from the study at any time with reasonable rationale. The subject's future care will not be influenced by a decision, voluntary or otherwise, to withdraw from the study. All reasonable efforts should be made to retain the subject in the clinical study until completion of the study.

Reasons for subject's withdrawal include, but are not limited to:

- Subject refuses to continue participating in the study
- Subject does not meet the inclusion/exclusion criteria and does not require additional follow-up for safety reasons
- Subject is deceased (Complete Death Form)
- Subject's non-compliance
- Subject's participation is terminated by the PI or Investigator, although the subject consented, since participation is no longer medically appropriate
- Subject is 'lost to follow up': Subject does not adhere to the scheduled follow up visits but has not explicitly requested to be withdrawn from the clinical study. Site personnel should at all times make all reasonable efforts to locate and communicate with the subject in order to achieve subject compliance to the scheduled follow up visits:
    1. A subject will be considered 'Lost to Follow Up' after a minimum of two phone calls of a physician or delegate at the investigational site to the subject or contact. These two phone calls need to be documented in the subject's hospital records.
    2. If these attempts are unsuccessful, a certified letter should be sent to the subject's last known address or general practitioner (GP) and a copy of this letter should be maintained in the subject's hospital records.

Note: If a subject misses one or more of the scheduled follow up visits (inclusive of the assigned visit windows), this will be considered as a missed visit requiring submission of a Deviation Form. The subject may return for subsequent visits and will not be excluded from the study.

If a subject withdraws from the clinical study, the site will record the subject's reasons for withdrawal on a Withdrawal CRF.

When subject withdrawal from the clinical study is due to an adverse event the subject will be followed by their study doctor per standard of care outside of the study until the adverse event is resolved or the

PI determines that the subject's condition is stable. The status of the subject's condition should be documented at the time of withdrawal.

7.0 COMPLIANCE TO CIP

7.1 Statements of Compliance

The study will be performed in accordance with the most current versions of the World Medical Association (WMA) Declaration of Helsinki, ISO14155 and any regional and/or national regulations and will be compliant to this International Standard and any regional and national regulations, as appropriate.

The Investigator will not start enrolling subjects or requesting informed consent from any subject prior to obtaining Ethics Committee approval and authorization from the Sponsor in writing for the study.

In case additional requirements are imposed by the Ethics Committee, those requirements will be followed, if appropriate. If any action is taken by an Ethics Committee, and regulatory requirements with respect to the study, that information will be forwarded to St. Jude Medical.

As Sponsor, St. Jude Medical has taken up general liability insurance in accordance with the requirements of the applicable local laws. Appropriate country representative will be utilized to understand the requirements for the type of insurance that will be provided for subjects, such information will be incorporated into the informed consent, as applicable.

If required, additional subject coverage or a study specific insurance will be provided by the Sponsor as well.

7.2 Adherence to the Clinical Investigation Plan

A deviation is defined as an event where the clinical investigator, site personnel, Sponsor or Sponsor representative did not conduct the clinical study according to the Clinical Investigational Plan, Ethics Committee requirements or the Investigator Agreement. The Investigator is not allowed to deviate from the CIP, except as specified under emergency circumstances.

In some cases, failure to comply with the CIP may be considered failure to protect the rights, safety and well-being of subjects, since the non-compliance exposes subjects to unreasonable risks. For example, failure to adhere to the inclusion/exclusion criteria: these criteria are specifically defined by the Sponsor to exclude subjects for whom the device is not beneficial and the use involves unreasonable risks. This may be considered failure to protect the rights, safety and well-being of the enrolled subject. Similarly, failure to perform safety assessments intended to detect adverse events may be considered failure to protect the rights, safety and well-being of the enrolled subject. Investigators should seek minimization of such risks by adhering to the CIP.

Simultaneously, in the event that adhering to the CIP might expose the subject to unreasonable risks, the Investigator is also required to protect the rights, safety and well-being of the subject by intentionally deviating from the requirements of the CIP, so that subjects are not exposed to unreasonable risks.

It is the responsibility of the Investigator to provide adequate medical care to a subject enrolled in a study.

Regulations require that the PI maintain accurate, complete, and current records, including documents showing the date of and reason for every deviation from the Clinical Investigational Plan. Relevant information for each deviation will be documented on a Deviation Form. The site will submit the form to St. Jude Medical.

Regulations require Investigators obtain approval from St. Jude Medical and the Ethics Committee [as required] before initiating changes in or deviations from the CIP, except when necessary to protect the life or physical well-being of a subject in an emergency.

Prior approval must be requested when the PI anticipates, contemplates, or makes a conscious decision to depart from the CIP, except when unforeseen circumstances are beyond the Investigator's control (e.g. a subject who fails to attend a scheduled follow-up visit, a subject is too ill to perform a CIP-required test, etc.). All deviations, including those beyond the Investigator's control, must be reported on a Deviation Form.

To obtain approval, the Principal Investigator may call or email and discuss the potential deviation with St. Jude Medical or designee prior to initiating any changes.

All deviations must be reported to appropriate regulatory authorities in specified timelines (if appropriate).

7.3 Repeated and Serious Non-Compliance

In the event of repeated non-compliance or a one-time serious non-compliance, as determined by the Sponsor, a Clinical Research Associate or clinical representative will attempt to secure compliance by one or more of the following actions:

- Visiting the Investigator
- Contacting the Investigator by telephone
- Contacting the Investigator in writing
- Retraining of the Investigator

If an Investigator is found to be repeatedly non-compliant with the signed agreement, the CIP or any other conditions of the clinical study, the Sponsor will either secure compliance or, at its sole discretion, terminate the Investigator's participation in the clinical study.

8.0 ADVERSE EVENTS

8.1 Definitions

8.1.1 Medical Device

Any instrument, apparatus, implement, machine, appliance, implant, software, material or other similar or related article:

- Intended by the manufacturer to be used, alone or in combination, for human beings for one or more of the specific purpose(s) of
  - Diagnosis, prevention, monitoring, treatments or alleviation of disease,
  - Diagnosis, monitoring, treatment, alleviation of, or compensation for, an injury,
  - Investigation, replacement, modification, or support of the anatomy or of a physiological process,
  - Supporting or sustaining life,
  - Control of conception,
  - Disinfection of medical devices and
- Which does not achieve its primary intended action in or on the human body by pharmacological, immunological or metabolic means, but which may be assisted in its intended function by such means.

8.1.2 Adverse Event (AE)

Any untoward medical occurrence, unintended disease or injury, or untoward clinical signs (including abnormal laboratory findings) in subjects, users or other persons, whether or not related to the investigational medical device under study.

This definition includes events related to the investigational medical device or the comparator.
This definition includes events related to the procedures involved.

8.1.3 Serious Adverse Event (SAE)

An adverse event that led to:

- Death
- A serious deterioration in the health of the subject, that either resulted in:
  - A life-threatening illness or injury OR
  - A permanent impairment to a body structure or a body function OR
  - An in-patient or prolonged hospitalization OR
  - A medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body OR
  - A malignant tumor
- Fetal distress, fetal death or a congenital abnormality or birth defect

A planned hospitalization for a pre-existing condition, or a procedure required by the CIP is not considered a serious adverse event.

8.1.4 Adverse Device Effect (ADE)

An adverse event related to the use of an investigational medical device.

This definition includes adverse events resulting from insufficient or inadequate instructions for use, deployment, implantation, installation, or operation, or any malfunction of the investigational medical device.

This definition includes any event resulting from use error or from intentional misuse of the investigational medical device.

8.1.5 Serious Adverse Device Effect (SADE)

Adverse device effect that has resulted in any of the consequences characteristic of a serious adverse event.

8.1.6 Anticipated Serious Adverse Device Effect (ASADE)

A serious adverse device effect, which by its nature, incidence, severity or outcome has been previously identified in the risk analysis report.

8.2 Procedure for Assessing, Recording and Reporting Adverse Events, Adverse Device Effects, Serious Adverse Events and Serious Adverse Device Effects:

Safety surveillance within this study and the safety reporting both performed by the Investigator, starts as soon as the subject is enrolled in this study (date of signature of the informed consent). The Investigators who agree to participate in this observational study shall be instructed to report all adverse events on enrolled patients starting from the date of implant.
The safety surveillance and the safety reporting will continue until the last follow-up visit has been performed, the subject is deceased, the subject/investigator concludes his participation into the study or the subject/investigator withdraws the subject from the study.

Adverse event data including deaths will be collected throughout the clinical study and will be reported to the Sponsor on a dedicated case report form or through the EDC system. The Investigator will record all adverse events on the appropriate case report forms.

Records relating to the subject's subsequent medical course must be maintained and submitted (as applicable) to the Sponsor until the event has subsided or, in case of permanent impairment, until the event stabilizes and the overall clinical outcome has been ascertained. Adverse events will be monitored until they are adequately resolved. The status of the subject's condition should be documented at each visit.

Reportable adverse events to the Sponsor are considered:

- Adverse Device Effects (ADEs) which include device and/or procedure related events. All ADEs will be collected from the time of device implant.
- Serious Adverse Events (whether or not the event is considered device and/or procedure related). All SAEs will be collected from the time of device implant.

All above events will be reported to the Sponsor, as soon as possible, but no later than 72 hours of first learning of the event. In case of EDC failure, notify the Sponsor via AdverseEvent@sjm.com.

Additional information may be requested, when required, by the Sponsor in order to support the reporting of AEs to regulatory authorities.

The Sponsor will ensure that all events are reported to the relevant authorities as per regulations.

The Investigator must notify the EC, if appropriate, in accordance with national and local laws and regulations, of the AEs reported to the Sponsor.

8.3 Device Deficiency

A Device Deficiency is defined as an inadequacy of a medical device with respect to its identity, quality, durability, reliability, safety or performance. Device deficiencies include malfunctions, use errors and inadequate labeling.
Device deficiencies are not collected in this study.

If the device deficiency involves an adverse event category as described in the protocol, the Investigator shall notify the Sponsor by completing the adverse event or death case report form as applicable and must provide the Sponsor with all necessary documentation needed.

If the device deficiency does not involve a reportable adverse event per protocol, the Investigator should notify the SJM Product Surveillance Department by emailing the information about the device deficiency to the local country office or to: SYcomplaints@sjm.com or call 1-800-722-3774 as soon as possible after becoming aware of the device deficiency. Please contact the local SJM representative to coordinate product returns as applicable.

8.4 List of Anticipated Adverse Events

The following are potential complications associated with the use of any pacing system:

- Arrhythmia
- Heart block
- Thrombosis
- Threshold elevation
- Valve damage
- Pneumothorax
- Myopotential sensing
- Vessel damage
- Air embolism
- Body rejection phenomena
- Cardiac perforation
- Cardiac tamponade
- Formation of fibrotic tissue; local tissue reaction
- Inability to interrogate or program a device because of programmer malfunction
- Infection
- Interruption of desired device function due to electrical interference

- Loss of normal desired pacing and/or sensing due to lead displacement
- Body reaction at electrode interface, or
- Lead malfunction (fracture or damage to insulation)
- Loss of normal device function due to battery failure or component malfunction
- Device migration
- Pocket erosion
- Hematoma
- Pectoral muscle stimulation
- Phrenic nerve or diaphragmatic stimulation

The following, in addition to the above, are potential complications associated with the use of rate-modulated pacing systems:

- Inappropriate, rapid pacing rates due to sensor failure or to the detection of signals other than patient activity
- Loss of activity-response due to sensor failure
- Palpitations with high-rate pacing

8.5 Subject Death

8.5.1 Procedure for Recording and Reporting Subject Death

Should a death event occur, the Investigator is required to record death information in the hospital records, immediately document the information on the Death Form and submit it to SJM. All subject deaths are to be documented and reported to the Sponsor within 72 hours after becoming aware of the event.

An Adverse Event Form should be completed in addition to the Death Form **only if there was an adverse event that led directly to the patient's death**. Otherwise, if there is no AE associated with the death, the completion of a Death Form is sufficient.

By completing the Death Form in the EDC system, the Sponsor will be automatically notified.

The subject's death means an early conclusion of the subject's participation in the study. Therefore, beside completion of a Death Form, the Investigator is required to complete the Withdrawal Form.

The Investigator must notify the Ethics Committee, if appropriate, in accordance with their reporting requirements.

9.0 DATA MANAGEMENT

Overall, the Sponsor will be responsible for the data handling.

The Sponsor and/or its affiliates will be responsible for compiling and submitting all required reports to governmental agencies.

Data will be analyzed by the Sponsor and may be transferred to the Sponsor's locations outside of Europe and/or any other worldwide regulatory authority in support of a market-approval application.

SJM respects and protects personally identifiable information that we collect or maintain. As part of our commitment, SJM is certified to the U.S. - European Union Framework and U.S. – Swiss Safe Harbor Framework Agreements regarding human resources and subject clinical trial personal information. The privacy of each subject and confidentiality of his/her information will be preserved in reports and when publishing any data. Confidentiality of data will be observed by all parties involved at all times throughout the clinical study. All data will be secured against unauthorized access.

The Principal Investigator or institution will provide direct access to source data during and after the clinical study for monitoring, audits, Ethics Committee review and regulatory authority inspections. As required, the Principal Investigator or institution will obtain permission for direct access to source documents from the subject, hospital administration and national regulatory authorities before starting the clinical study.

9.1 Data Management Plan

A detailed Data Management Plan will be established to ensure consistency of the data. This document will include procedures used for data review, database cleaning, and issuing and resolving data queries. If appropriate, the DMP may be updated throughout the study duration. All revisions will be tracked and document controlled.

CRF data will be captured in a validated electronic database management system hosted by St. Jude Medical.

Only authorized site personnel will be permitted to enter the CRF data through the electronic data capture (EDC) system deployed by SJM. An electronic audit trail will be used to track any subsequent changes of the entered data.

9.2 Document and Data Control

9.2.1 Traceability of Documents and Data

The Investigator will ensure accuracy, completeness, legibility and timeliness of the data reported to the sponsor on the CRFs and in all required reports.

9.2.2 Recording Data

Source documents will be created and maintained by the investigational site team throughout the clinical study. The data reported on the CRFs will be derived from, and be consistent with, these source documents, and any discrepancies will be explained in writing.

CRF data will be captured in a validated electronic database management Oracle Clinical system hosted by SJM.

All sites will enter data through electronic data capture (EDC). Only authorized site personnel will be permitted to enter the data through the electronic data capture (EDC) system deployed by SJM. An electronic audit trail will be used to track subsequent changes of the entered data.

10.0 MONITORING

Centralized monitoring may occur through routine internal data review. This monitoring is designed to identify missing and inconsistent data, data outliers, and potential protocol deviations that may be indicative of site non-compliance.

11.0 REGULATORY INSPECTIONS

The Investigator and/or delegate should contact St. Jude Medical immediately upon notification of a governmental agency inspection at the site. A clinical monitor or designee will assist the Investigator and/or delegate in preparing for the audit.

An Investigator who has authority to grant access will permit authorized governmental agency employees, at reasonable times and in reasonable manner, to enter and inspect any establishment where devices are held (including any establishment where devices are used or where records or results are kept).

An Investigator, or any person acting on behalf of such a person with respect to the study, will permit authorized governmental agency employees, at reasonable times and in reasonable manner, to inspect and copy all records relating to the study.

An Investigator will permit authorized governmental agency employees to inspect and copy records that identify subjects, upon notice that governmental agency has reason to suspect that adequate informed consent was not obtained, or that reports required to be submitted by the Investigator, to the Sponsor or EC have not been submitted or are incomplete, inaccurate, false or misleading.

12.0 STATISTICAL CONSIDERATIONS

12.1 Statistical Design, Hypotheses, Method and Analytical Procedures

This is a post market, prospective, non-randomized observational study.

The primary endpoint will be summarized as counts and proportion of patients who experience complications. The 95% Binomial confidence interval for the complication rate at 1 year post implant will be reported as well.

Other data will be presented using appropriate summary statistics. All continuous data will be summarized using descriptive statistics, such as the number of non-missing data, mean ± standard deviation, median and range (minimum – maximum). Categorical data will be tabulated with counts and its percentage.

12.2 Sample Size

The sample size calculation is based on the study design and primary objective of this study. The literature[9] shows a complication rate of 12.2% at 1 year. Assuming the complication rate at one-year post implant is 12.2%, in order to obtain a confidence interval width of 3.1%, at least 1713 subjects will be required. Assuming a 15% attrition rate at one year, a total recruitment of 2016 subjects is needed.

12.3 Pass/Fail Criteria to be Applied to the Results of the Clinical Study

This study is intended to characterize complication rates in the general pacemaker patient population. Therefore, Pass/Fail criteria do not apply to this study.

12.4 The Provision for an Interim Analysis, when Applicable

There are no pre-specified interim analyses planned for this study.

12.5 Criteria for the Termination of the Clinical Study on Statistical Grounds

There are no pre-specified criteria for terminating the clinical investigation on statistical grounds.

12.6 Procedures for Reporting any Deviation(s) From the Original Statistical Plan

Any deviations from the statistical analysis plan will be documented.

12.7 The Specification of Subgroups for Analysis

Stratified reporting/analysis will be performed by countries/ regions (EMEA/Asia-Pac).

12.8 Procedures that Take into Account All the Data

All subjects who have signed a Patient Informed Consent (PIC) will be considered enrolled in the study, hence are eligible for the primary analysis. Primary analysis population will include those subjects that have signed a PIC form, and have the CIP defined pacemaker implanted.

12.9 The Treatment of Missing, Unused or Spurious Data, Including Drop-Outs and Withdrawals

No imputation technique will be used, unless specified in the guidelines of the questionnaire data.

12.10 In Multi-Center Studies, the Minimum and Maximum Number of Subjects to be Included for each Center

This study is expected to enroll 2016 subjects in approximately 160 centers in the EMEA region and Asia-Pac region. It is desirable to have a balance of the subjects across participating centers; therefore, the maximum number of subjects to be included at each enrolling center is 200. Every effort will be made to promote recruitment; however, a low level of participation in the study could still occur, so the minimum number of subjects to be included at enrolling centers is one.

13.0 DOCUMENT RETENTION

The principal investigator (PI) will maintain all clinical study documents from prior, during and (as specified) after the clinical study on file at the site for a minimum of 15 years after the termination of this study, or longer as per local laws, or when it is no longer needed to support a marketing application, whichever is later.

The PI must contact the Sponsor prior to destroying or archiving off-site any records and reports pertaining to this study to ensure that they no longer need to be retained on-site.

All original subject files must be stored for the longest possible time permitted by the regulations at the hospital, research institute, or practice in question. If archiving can no longer be maintained at the site, the Investigator will notify the Sponsor.
All data and documents will be made available on request of the relevant authorities in case of an audit.

The Sponsor will archive and retain all essential clinical study documents from prior, during and (as specified) after the clinical study as per requirements.

14.0 AMENDMENTS TO CLINICAL INVESTIGATIONAL PLAN

Study related documents such as the CIP, CRFs, Informed Consent form and other subject information, or other clinical study documents will be amended as needed throughout the clinical study. The version number and date of amendments will be documented.

The amendments to the CIP and the subject's Informed Consent will be notified to, or approved by, the Ethics Committee and regulatory authorities, if required. Any amendment affecting study subjects requires that the subject be informed of the changes and a new consent be signed and dated by the Investigator and subject at the subject's next follow up visit.

15.0 STUDY COMMITTEES

15.1 STEERING COMMITTEE (SC)

The Steering Committee may be used to advise the Sponsor during a clinical study, such as in the development of the study CIP, during the conduct of the study, during data analysis and/or presentation/publication of the study results. Membership may include a Clinical Coordination Investigator (CCI) or site Investigators for the study under review.

16.0 INVESTIGATION SUSPENSION OR TERMINATION

16.1 Premature Termination of the Whole Clinical Study or of the Clinical Study in One or More Investigational Sites.

The Sponsor reserves the right to stop the study at any stage, with appropriate written notice to the Investigator.

Possible reasons for early termination of the study by the Sponsor, either at local, national or international level, may include, but are not limited to:

- The device / therapy fails to perform as intended
- Sponsor's decision
- Request from Regulatory bodies
- Request of Ethics Committee(s)
- Concern for subject safety and welfare
- Failure to secure subject Informed Consent prior to any investigational activity
- Repeated non-compliance with this CIP or the Clinical Trial Agreement
- Inability to successfully implement this CIP
- Violation of the Declaration of Helsinki 2008 (refer to Appendix C)
- Violation of applicable national or local laws and regulations
- Falsification of data, or any other breach of ethics or scientific principles

The study will be terminated according to applicable regulations.

The Investigator may also discontinue participation in the clinical study with appropriate written notice to the Sponsor.

Should either of these events occur, the Investigator will return all documents to the Sponsor; provide a written statement as to why the premature termination has taken place and notify the Ethics Committee and/or the Competent Authority (if applicable). Follow-up for all enrolled subjects will be as per CIP requirements.

A Principal Investigator, Ethics Committee or regulatory authority may suspend or prematurely terminate participation in a clinical study at the investigational sites for which they are responsible.

If suspicion of an unacceptable risk to subjects arises during the clinical study or when so instructed by the Ethics Committee or regulatory authority, St. Jude Medical may suspend the clinical study as appropriate while the risk is assessed. St. Jude Medical will terminate the clinical study if an unacceptable risk is confirmed.

St. Jude Medical will consider terminating or suspending the participation of a particular investigational site or Investigator in the clinical study if monitoring or auditing identifies serious or repeated deviations on the part of an Investigator.

If suspension or premature termination occurs, the terminating party will justify its decision in writing and promptly inform the other parties with whom they are in direct communication. The Principal Investigator and St. Jude Medical will keep each other informed of any communication received from Ethics Committee or regulatory authority.

If for any reason St. Jude Medical suspends or prematurely terminates the study at an individual investigational site, St. Jude Medical will inform the responsible regulatory authority, as appropriate, and ensure that the Ethics Committee are notified, either by the Principal Investigator or by St. Jude Medical. If the suspension or premature termination was in the interest of safety, St. Jude Medical will inform all other Principal Investigators.

If suspension or premature termination occurs, St. Jude Medical will remain responsible for providing resources to fulfill the obligations from the CIP and existing agreements for following up the subjects enrolled in the clinical study, and the Principal Investigator or authorized designee will promptly inform the enrolled subjects at his/her investigational site, if appropriate.

16.2 Resuming the Study after Temporary Suspension

When St. Jude Medical concludes an analysis of the reasons for the suspension, implements the necessary corrective actions, and decides to lift the temporary suspension, St. Jude Medical will inform the Principal Investigators, EC, or regulatory authority, where appropriate, of the rationale, providing them with the relevant data supporting this decision.

Concurrence will be obtained before the clinical study resumes from the Ethics Committee or regulatory authority where appropriate.

If subjects have been informed of the suspension, the Principal Investigator or authorized designee will inform them of the reasons for resumption.

16.3 Study Conclusion

The study will be concluded when:

- All sites are closed AND
- The Final Report generated by St. Jude Medical has been provided to sites or St. Jude Medical has provided formal documentation of study closure

17.0 PUBLICATION POLICY

The results of the clinical study will be submitted, whether positive or negative for publication.

A 'Publication Agreement' will be signed between the Principal Investigator and the Sponsor either as a separate Publication Agreement or within the Clinical Trial Agreement.

18.0 BIBLIOGRAPHY

(1) Luebke DL. Advances in pacemaker technology. *Crit Care Nurse* 2001 June;21(3):20-4.
(2) Neuzner J, Schwarz T, Sperzel J. Pacemaker automaticity. *Am J Cardiol* 2000 November 2;86(9A):104K-10K.
(3) Alings M, Vorstenbosch JM, Reeve H. Automaticity: design of a registry to assess long-term acceptance and clinical impact of Automatic Algorithms in Insignia pacemakers. *Europace* 2009 March;11(3):370-3.
(4) DAS MK, Dandamudi G, Steiner HA. Modern pacemakers: hope or hype? *Pacing Clin Electrophysiol* 2009 September;32(9):1207-21.
(5) Kalahasty G, Ellenbogen K. The role of pacemakers in the management of patients with atrial fibrillation. *Cardiol Clin* 2009 February;27(1):137-50, ix.
(6) Kuhne M, Schaer B, Kaufmann C et al. A randomized trial comparing two different approaches of pacemaker selection. *Europace* 2007 December;9(12):1185-90.
(7) Lloyd MS, El Chami MF, Langberg JJ. Pacing features that mimic malfunction: a review of current programmable and automated device functions that cause confusion in the clinical setting. *J Cardiovasc Electrophysiol* 2009 April;20(4):453-60.
(8) Mandava A, Mittal S. Clinical significance of pacemaker-detected atrial high-rate episodes. *Curr Opin Cardiol* 2008 January;23(1):60-4.
(9) Pakarinen S, Oikarinen L, Toivonen L. Short-term implantation-related complications of cardiac rhythm management device therapy: a retrospective single-centre 1-year survey. *Europace* 2010;12: 103-108.

APPENDIX A: ABBREVIATIONS

Select or add abbreviations used

Abbreviation	Term
ADE	Adverse Device Effect
AE	Adverse Event
ANZ	Australia – New Zealand
ASADE	Anticipated Serious Adverse Device Effect
CA	Competent Authority
CCI	Clinical Coordination Investigator
CEC	Clinical Events Committee
CIP	Clinical Investigational Plan
CRF	Case Report Form
CPRB	Clinical Project Review Board
DD	Device Deficiency
DMP	Data Management Plan
DSMB	Data Safety Monitoring Board
EC	Ethics Committee
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
EMEA	Europe, Middle East, Africa
GP	General Practitioner
IB	Investigator Brochure
ICMJE	International Committee of Medical Journal Editors
IRB	Institutional Review Board
ISB	Investigator Site Binder
ISO	International Organization for Standardization
MP	Monitoring Plan
NA	Not Applicable
PI	Principal Investigator
POA	Power of Attorney
RDC	Remote Data Capture
SADE	Serious Adverse Device Effect
SAE	Serious Adverse Event
SC	Steering Committee
SJM	St. Jude Medical
WMA	World Medical Association

APPENDIX B: CIP REVISION HISTORY

Revision History				
Amendment Number	Version	Date	Rationale	Details
Not Applicable	A	28MAY2015	First release of CIP	NA

Appendix C: Declaration of Helsinki

The most current version of the document will be followed.

Appendix D: List of Clinical Investigation Sites and Ethics Committee

A list of Clinical Investigational sites and Ethics Committee will be kept under a separate cover and is available upon request.

Appendix E: Sample Informed Consent

The study specific informed consent template will be provided under separate cover.

Appendix F: Case Report Forms

Case Report Forms will be kept under separate cover.