Reference:
SJM-CIP-10051

MediGuide Registry

Clinical Investigation Plan (CIP)

Sponsor	St. Jude Medical, Inc. 15900 Valley View Court Sylmar, CA 91342 U.S.A Tel: 818-493-2609 Fax: 818-364-5814
Clinical Coordinating Investigator	Dr. Bernard Thibault/Professor of Medicine Montreal Heart Institute Department of Cardiology 5000 Belanger Street Montreal Canada Tel: +1 514-376-3330
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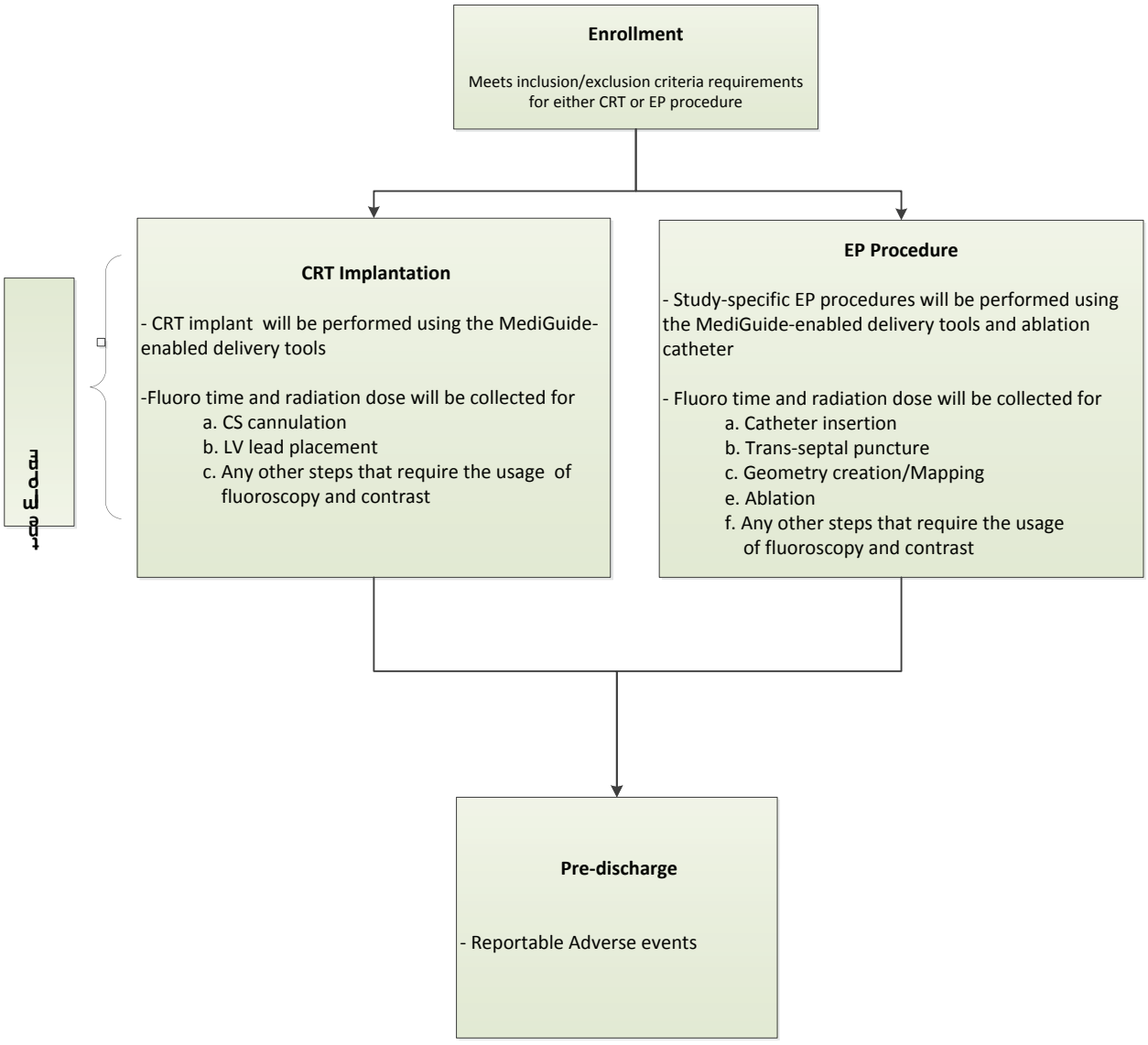
1.0 SYNOPSIS

Title:	MediGuide Registry
Acronym:	None
Purpose:	The goal of this registry/observational study is to collect data on the clinical utility of MediGuide™ system in CRT implantation and EP procedures
Objectives:	The intent of this worldwide registry/observational study is to understand the utility of the MediGuide™ technology in real world clinical practice during CRT implantation and study-specific-EP procedures. The study should provide an understanding of the effect of MediGuide™ technology on: • The amount of fluoroscopy time and the radiation exposure • Total procedure time • Peri-procedural clinical event rate Additionally, this study will address the following • Identification of procedural challenges which may aid in developing future MediGuide tools • Evaluation of newly available MediGuide tools during the study • Correlation between MediGuide operator experience and the radiation exposure amount and time
Design:	This is a worldwide, multicenter, non-randomized registry/observational study. The study will enroll up to 1000 patients from up to 65 centers undergoing either CRT implantation or an EP procedure. The study will enroll a minimum of 250 patients for each group. Patients who are undergoing either procedure at study centers equipped with MediGuide™ technology utilizing market approved MediGuide™-enabled tools will be eligible to participate in this study. This study may continue for up to 3 years, depending on the rate of enrollment.
Devices Used:	Market-approved MediGuide™-enabled tools and software
Study Population	CRT Group All patients from participating sites who are indicated for a CRT-D/P device implant, including an upgrade with a new LV lead implant and are implanted with St. Jude Medical pulse generators and willing to provide

	written Informed Consent can be enrolled in this study. Patients can be implanted with non-St. Jude Medical leads EP Group All patients from participating sites who are indicated for an atrial fibrillation, atrial flutter or VT ablation procedure for which market approved MediGuide™-enabled ablation catheter is available and willing to provide written Informed Consent can be enrolled in this study.
Data Collection	Data collection schedule • CRT patients: Data will be collected for patients undergoing CRT implantation at implant and pre-discharge . • EP procedures: Data will be collected for patients undergoing an EP procedure at the time of the procedure and pre-discharge.

1.1 Study Flow Chart



1.2 Study Contacts

Study Director:

Kristin Ruffner
One Lillehei Plaza
St. Paul, MN 55417
Tel: 651-756-6717
Email: kruffner@sjm.com

Study Manager:

John Gill
15900 Valley View Court
Sylmar, CA 91342
U.S.A
Tel: 818-493-2609
Email: jgill@sjm.com

2.0 BACKGROUND AND JUSTIFICATION FOR CLINICAL STUDY

The number of fluoroscopically-guided minimally invasive diagnostic and therapeutic procedures has greatly increased in recent years.[1] However, the potential injuries from the associated radiation exposure are often underestimated. The radiation dose for some interventional procedures may be several orders of magnitude greater than that for simple radiographic studies.[2, 3] Once the dose exceeds a certain limit, the injury becomes progressively more severe with increasing dose, although the true severity of major injuries will only become apparent weeks to months after the procedure.[4] Very high doses usually produce some symptoms within 24 hours of the procedure. Furthermore, it is known that even sub-threshold exposure to radiation under recommended occupational limits has been shown to increase the chance of life-time cancer.[5] The core principle governing the use of ionizing radiation is ALARA (as low as reasonably achievable) and according to this principle there is no magnitude of radiation exposure that is known to be completely safe.[6, 7] This principle confers a responsibility on all physicians to minimize the radiation injury hazard to their patients, to their staff, and to themselves.

St. Jude Medical ((hereinafter referred to as SJM) has developed a novel 3D electromagnetic navigation system (MediGuide™) that is capable of non-fluoroscopic navigation of sensor-enabled tools in the x-ray environment. By projecting the tool's position and orientation onto the pre-recorded fluoroscopic images, the system allows for tracking of tools within pre-recorded x-ray loops while compensating for primary and secondary organ motion, thus reducing x-ray exposure during diagnostic and therapeutic cardiac procedures for which MediGuide™-enabled tools are available.

Previous single-center studies have shown that the application of the MediGuide™ technology can lead to a significant reduction in fluoroscopy burden during ablations of atrial flutter, SVT, and atrial fibrillation.[8-12] In a recent single-center registry,[13] the MediGuide™ navigation system was used for over 600 cases of ablations for atrial flutter, atrial fibrillation and ventricular tachycardia and implantation of cardiac resynchronization therapy (CRT) devices. In these cases, the median fluoroscopy time was not only reduced compared to the traditional fluoroscopy time but the complication rate was lower than previously-published data. It was also observed by the same group that the total fluoroscopy time and the exposure to radiation was reduced further as the operator gained more experience in working with MediGuide™ system and tools.[14] However, these studies were all conducted at a single center and the radiation reduction benefit, complication rate, and operator proficiency across clinics at different geographies are unknown.

The MediGuide registry is sponsored by SJM. The goal of this study is to collect data on the clinical utility of MediGuide™ system in CRT implantation and study-specific EP procedures.

3.0 RISKS AND BENEFITS OF THE CLINICAL STUDY

The risks involved with this study are similar to those associated with MediGuide™ enabled implantation of commercially available CRT systems and MediGuide™ enabled ablation procedures with commercially available ablation tools. There are no additional risks to the patients enrolled in this study.

3.1 Description of subject population

Approximately 1000 patients undergoing CRT implant or study-specific EP procedures at study centers equipped with MediGuide™ technology utilizing market approved MediGuide™-enabled tools will participate in this study.

3.2 Anticipated clinical benefits

Patients participating in this study may be exposed to less radiation due to the reduced fluoroscopy use when using the MediGuide™ system.

3.3 Potential reportable adverse events

Anticipated adverse events
Adult respiratory distress syndrome (ARSD)
Air embolism
Allergic reactions to contrast media (agents)
Anemia
Anesthesia reaction
Arrest (cardio)
Arrest (respiratory)
Arrhythmias
AV fistula
Bleeding (non-hematoma)
Cardiac Perforation
Cardiac Tamponade
Cardiac thromboembolism
Cerebrovascular accident/attack
Chest pain/discomfort
Complete AV block
Component damage to ICD or PM
Coronary artery spasm
Coronary artery thrombosis
Coronary sinus dissection

Coronary sinus perforation
Death
Decompensated Heart Failure
Diaphragmatic paralysis
Elevated pacing thresholds
Endocarditis
Erosion/extrusion
Exacerbation of pre-existing atrial fibrillation
Gastroparesis
Hematoma
Hemothorax
High DFTs
Infection
Lead dislodgement or lead migration
Lead fracture
Lead insulation damage
Loss of capture
Loss of sensing
Left atrial esophageal fistula
Myocardial Infarction
New or worsened angina
Oversensing
Oversensing resulting in therapy
Pacemaker mediated tachycardia (PMT)
Pectoral stimulation
Pericardial effusion
Pericarditits
Phrenic nerve injury
Phrenic nerve/diaphragmatic stimulation
Pneumothorax
Premature battery depletion

Prolonged detection of redetection time
Pulse generator malfunction
Pseudoaneurysm
Pulmonary edema
Pulmonary embolism
Pulmonary vein stenosis
Shock/Hypotension
Stroke
Syncope unknown etiology
Therapy for non-ventricular rhythm
Thromboembolism
Thrombosis
Transient ischemic attack (TIA)
Undersensing
Valvular damage
Vascular access complications
Vasovagal reactions
Ventricular arrhythmia

4.0 STUDY DESIGN

4.1 Purpose

The intent of this worldwide registry/observational study is to understand the utility of the MediGuide™ technology in real world clinical practice during CRT implantation and study-specific-EP procedures. The study should provide an understanding of the effect of MediGuide™ technology on:

- The amount of fluoroscopy time and the radiation exposure
- Total procedure time
- Peri-procedural clinical event rate

Additionally, this study will address the following

- Identification of procedural challenges which future MediGuide tools can potentially address
- Evaluation of newly available tools during the study

- Correlation between MediGuide™ operator experience and the radiation exposure amount and time

This study may continue for up to 3 years, depending on the rate of enrollment and follow-up timelines.

4.2 Study Design and Scope

This is a worldwide, multicenter, non-randomized registry/observational study. The study will enroll up to 1000 patients from up to 65 centers undergoing either CRT implantation or an EP procedure. The study will enroll a minimum of 250 patients for each group. Patients who are undergoing either procedure at study sites equipped with MediGuide™ technology utilizing market approved MediGuide™-enabled tools will be eligible to participate in this study.

Data collection schedule

- CRT Group: Data will be collected for patients undergoing CRT implantation at implant and pre-discharge.

- EP Group: Data will be collected for patients undergoing an EP procedure at the time of the procedure and pre-discharge.

4.3 Inclusion and Exclusion Criteria

CRT Group

All patients from participating sites who are indicated for a CRT-D/P device implant, including an upgrade with a new LV lead implant and are implanted with St. Jude Medical pulse generators and willing to provide written Informed Consent can be enrolled in this study. Patients can be implanted with non-St. Jude Medical leads.

EP Group

All patients from participating sites who are indicated for an atrial fibrillation, atrial flutter or VT ablation procedure for which market approved MediGuide™-enabled ablation catheter is available and willing to provide written Informed Consent can be enrolled in this study.

4.4 Subject Population

4.4.1 Subject Screening

All subjects presenting at the study site can be screened by a member of the study 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. In case the subject agrees, a duly signed and dated Patient Informed Consent will be obtained.

4.4.2 Point of Enrollment

Subjects are considered enrolled in the study if the subject has provided written Patient Informed Consent and CRT implant or an EP procedure was attempted.

4.4.3 Description of the IRB/EC specific responsibilities

IRB/EC approval for the study and informed consent will be required prior to beginning the study. A copy of the IRB/EC approval and corresponding informed consent must be forwarded to SJM prior to authorization of the institution to begin the study. Any withdrawal of IRB /EC approval should be reported to SJM within 5 working days of the withdrawal of approval. A list of IRBs/ECs for Institutions participating in the study will be provided upon request.

4.5 Informed Consent Process

4.5.1 General process

Prior to enrolling in the clinical study and conducting study-specific procedures, all subjects will be consented, as required by applicable regulations and the center's IRB/EC. Informed consent must be obtained from each subject prior to any study related procedures. 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 that are 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 IRB/EC. Failure to obtain informed consent from a subject prior to study enrollment should be reported to SJM within 5 working days and to the reviewing center's IRB/EC consistent with the center's IRB/EC reporting requirements.

5.0 DEVICE UNDER INVESTIGATION AND CONTROL/COMPARATORS (IF APPLICABLE)

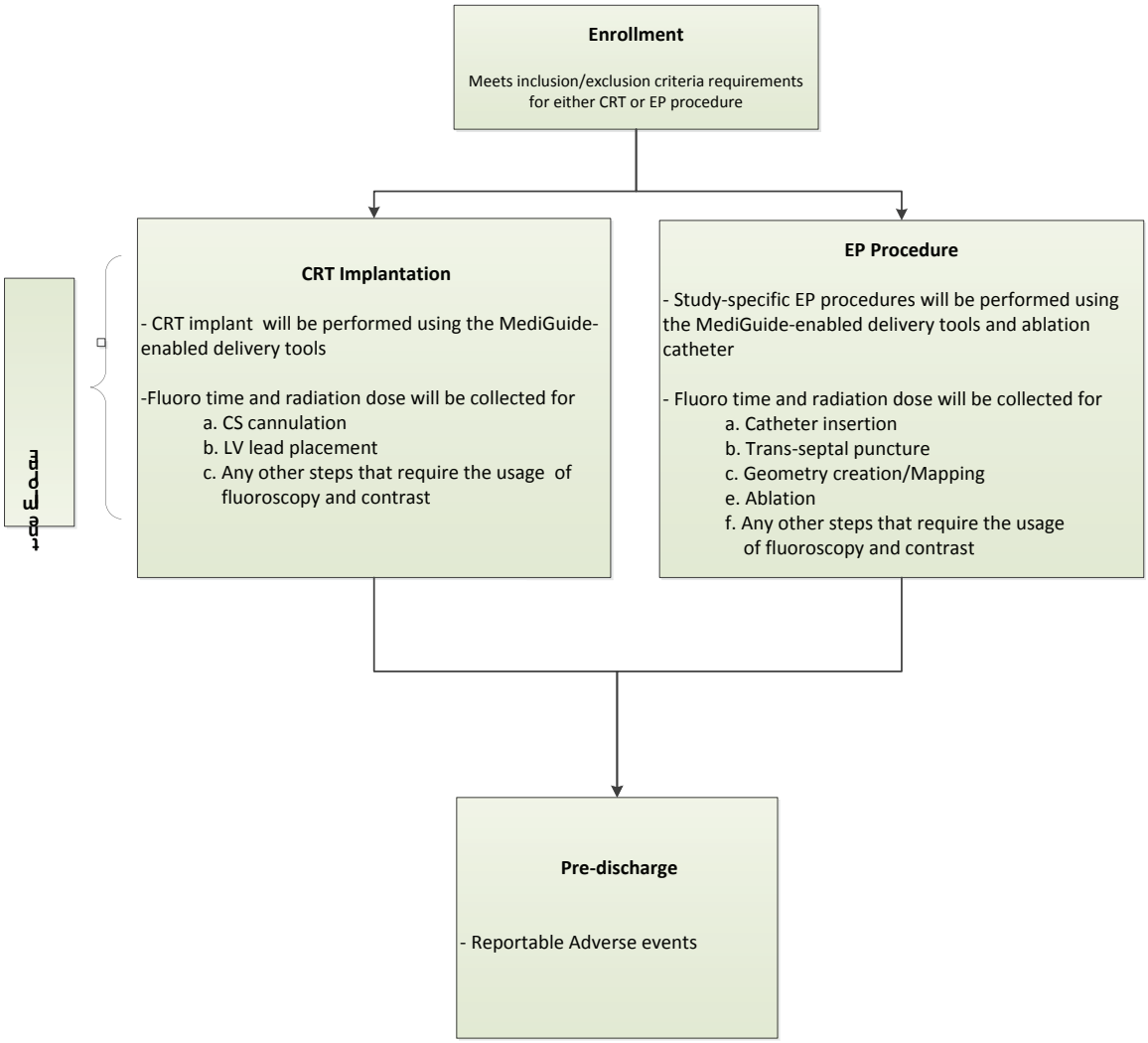
5.1 Device Description

In this study, any market approved MediGuide™-enabled tools and software will be used.

6.0 PROCEDURES

6.1 Study Flow Chart

Figure 2: 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 SJM receives written approval from the IRB/EC and relevant regulatory authorities and all required documents have been collected from the site(s).

Upon site activation, participating clinician's previous experience in performing CRT or EP cases with or without utilizing MediGuide™ enabled tools will be collected via one-time survey.

Table 1: List of all study specific activities/procedures

	CRT Group at Enrollment	EP Group at Enrollment	Discharge
Baseline Demography	X	X	
Medical History	X	X	
Medications	X	X	
12 Lead ECG (most recent)	X		
Echo Measurements (including most recent LVEF)	X	X	
NYHA	X		
Device Session Record	X		
Fluoro Time and Radiation Dose	X	X	
Electrical Lead Measurements for the RA, RV and LV Leads	X		
Reportable Adverse Event/Health Care Utilization	(X)	(X)	(X)
Fluoroscopic Views and Orientation Angles Used	X	X	

(X) if applicable

6.3 Enrollment Visit

During the enrollment process, the following baseline data will be collected for all patients.

Baseline Data (all patients)

- Patient demographics
- Arrhythmia history
- Cardiovascular history (including most recent LVEF)
- Cardiac medications
- NYHA class (CRT patients only)
- 12-lead ECG (most recent for CRT patients only)

Additional procedure related data will be collected specific to the procedure. Definitions for the beginning and ending of procedural steps are also provided.

CRT Group

- Devices implanted, i.e., leads and pulse generator
- MediGuide™ tools used at each step of the procedure if applicable
- MediGuide™ software version used if applicable
- Coronary venous anatomy
- Amount of fluoroscopy time and radiation dose in either cGray·cm^2 or µGray·m^2 during the following steps in the procedure.
    i. CS cannulation: From the moment the operator directs the technique to cannulate CS until the outer catheter is stable in CS
    ii. LV lead placement: From the moment outer catheter is stable in LV until the suture sleeve for LV lead is tied down
    iii. Any other steps that required the usage of fluoroscopy
- Electrical lead measurements for the RA, RV and LV leads
- Device session record

EP Group

- MediGuide™ tools used at each step of the procedure if applicable
- MediGuide™ software version used if applicable
- Mapping software used
- Ablation parameters
- Ablation site
- Amount of fluoroscopy time and radiation dose during the following steps in the procedure
    i. Catheter insertion: Similar to CS cannulation for CRT implant
    ii. Trans-septal puncture: From the moment of introducing trans-septal sheath until the sheath is stably paced in LA and the dilator is removed
    iii. Geometry creation/Mapping: From the beginning of geometry creation until the complete creation of geometry including mapping as determined by an operator
    iv. Ablation: From the beginning of ablation until the last attempt for ablation is made
    v. Any other steps that required the usage of fluoroscopy

Additional Implant/Procedure Related Data (all patients)

- Total procedure: Skin to skin
- Total amount of fluoroscopy time and radiation dose
- Room time: From the moment the patient enters the operation room until the patient exits the operation room
- Number, experience and type of attending personnel
- Fluoroscopic views with orientations and angles
- Types of anesthesia used: conscious sedation vs. general
- Adverse events, if applicable

6.4 Scheduled Follow-ups

6.4.1 Pre-discharge

During the pre-discharge, adverse events will be reported if applicable.

6.5 Description of activities performed by Sponsor Representatives

Trained sponsor personnel may perform certain activities to ensure compliance to the clinical investigational plan and may provide technical expertise.

6.6 Subject study completion

Patient participation in the study is complete upon completion of pre-discharge visit. 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

All foreseeable factors that may compromise the outcome have been taken into account by clinical study design and well defined subject selection criteria.

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 (cause must be documented)
- 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. (This does not apply to missed visits). 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 2 phone calls of a physician or delegate at the investigational site to the subject or contact. These 2 phone calls need to be documented in the subject's hospital records.
  2. If these attempts are unsuccessful, a 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.

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 until resolution of that adverse event or determination 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 IRB/EC approval and Competent Authority approval, if applicable, and authorization from the sponsor in writing for the study.

In case additional requirements are imposed by the IRB/EC or Competent Authority, those requirements will be followed, if appropriate. If any action is taken by an IRB/EC, and regulatory requirements with respect to the study, that information will be forwarded to SJM.

As sponsor, SJM 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, and 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, IRB/EC 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 Case Report Form. The site will submit the CRF to SJM.

Regulations require Investigators obtain approval from SJM and the IRB/EC [as required] before initiating changes in or deviations from the protocol, 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 CRF.

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

The investigator is required to adhere to local regulatory requirements for reporting deviations to IRB/EC. All deviations must be reported to appropriate regulatory authorities in specified timelines (if appropriate).

Investigator will notify SJM and the reviewing IRB/EC within 5 working days of:
- Any deviation to protect the life or physical well-being of a subject in an emergency
- Any failure to obtain informed consent

Investigators or the designee must notify SJM, Inc. as soon as possible and complete the Deviation CRF.

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 or 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 EVENT, ADVERSE DEVICE EFFECT, DEVICE DEFICIENCY

8.1 Definitions

8.1.1 Adverse Event (General Definition)

An adverse event in general is 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 medical device under study.

This definition includes events unrelated to the study medical device, the comparator or procedures involved: adverse event (AE) and serious adverse event (SAE).

It also includes events, which are related to the study medical device, the comparator or the procedures involved: adverse device effect (ADE) and serious adverse device effect (SADE).

Only Serious Adverse Events (SAE), Adverse Device Effects (ADE) and Serious Adverse Device Effects (SADE) will be collected in this study.

8.1.2 Serious Adverse Event (SAE)

Any untoward medical occurrence, which was not related to the study device, procedure or comparator, but resulted in serious injury to a subject or other person. A serious adverse event is one 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 function
- 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.

8.1.3 Adverse Device Effect (ADE)

An adverse event related to the use of a study medical device when the occurrence does not meet the definition of serious.

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

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

8.1.4 Serious Adverse Device Effect (SADE)

An adverse event that happens in a subject or other person, is related to the study device, comparator, or procedure, and has resulted in any of the consequences characteristic of a serious adverse event.

8.2 Procedure for assessing, recording and reporting device deficiencies/complaints, adverse device effects, serious adverse events and serious adverse device effects:

The safety surveillance and the safety reporting, both performed by the investigator, will start as soon as the subject is enrolled in this study (date of signature of the informed consent and an attempted implant/ablation procedure) and will continue until the last study visit has been completed, the subject is deceased, or the subject/investigator withdraws the subject from the study, except as otherwise specified in the CIP.

All reportable adverse event data (as described below) including deaths and device deficiency data (if applicable) 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 reportable adverse events and device deficiencies (if applicable) on the appropriate case report forms.

Reportable adverse events will be monitored until they are adequately resolved. Records related to the subject's subsequent medical course must be maintained and submitted (as applicable) to the Sponsor. The status of the subject's condition will be documented at each visit.

Reportable events to sponsor are considered:

- All Adverse Device Effects (ADEs) (including procedure related events)
- All Serious Adverse Device Effects (SADEs) (including procedure related events)
- All Serious Adverse Events (SAEs)
- All Device Deficiencies (DD) (if applicable), that could have led to a serious adverse device effect
  - if either suitable action had not been taken;
  - if intervention had not been made or
  - if circumstances had been less fortunate

All ADEs, SADEs, SAEs and DD are to be documented and reported to the sponsor within 10 calendar days for US sites and 3 calendar days for sites outside US after becoming aware of the event or per local regulatory timelines.

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

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

For unexpected failure modes or unexpected adverse events, the US site should follow their standard reporting practices for medical device reporting (MDR). As defined in 21 CFR 803, a MDR reportable event (or reportable event) means: An event that device user facilities become aware of that reasonably suggests that a device has or may have caused or contributed to a death or serious injury. A device user facility must report deaths and serious injuries that a device has or may have caused or contributed to, establish and maintain adverse event files, and submit summary annual reports to FDA.

8.3 Subject Death

8.3.1 Procedure for recording and reporting subject death

All patient deaths that occur during this investigation must be reported to St. Jude Medical within 10 days of the center becoming aware of the death for US sites and within 3 calendar days of the center becoming aware of the death for non-US sites. Investigator will complete the Patient Death form. Patient's death is an Early Conclusion of the subject's participation in the study. Therefore, beside completion of a Death CRF, the investigator is required to complete the Termination/Withdrawal form and Product Out of Service CRF.

Patient death may be an outcome of an adverse event. If the death is related to an AE, all the efforts to get AE details should be made by the investigator and an Adverse Event CRF should be completed in addition to the Patient Death CRF. If there are no AEs associated with death, completion of Patient Death CRF will be sufficient.

By completing the electronic Death CRF the sponsor will be automatically notified.
In case of EDC failure, notify Sponsor via AdverseEvent@sjm.com or via Fax (please refer to the Investigator Site Binder, "Sponsor Contact Details" for further details about Fax numbers).

It is the investigator's responsibility to notify the IRB/EC, if appropriate, in accordance with national and local laws and regulations.

Every attempt should be made to explant the pulse generator and/or leads intact. Any explanted devices or leads should be returned to St. Jude Medical for analysis promptly. The reason the pulse generator and/or lead(s) are not being returned to St. Jude Medical must be stated clearly on the Death or Out of Service form.

8.4 Device Deficiency (DD)

A Device Deficiency is defined as an inadequacy of a medical device with respect to its identity, quality, durability, reliability, safety or performance.

DD include malfunctions, use errors and inadequate labeling.

SJM will appropriately document and manage all DDs.

Device deficiencies in SJM market-released products must be reported per SJM product surveillance process. Please notify SJM Tech Service via email at techsvccrm@sjm.com

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.

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.

Data will be submitted through appropriate forms in EDC. Additional source documents will be submitted via EDC, email, fax, etc.

The Principal Investigator or institution will provide direct access to source data during and after the clinical study for monitoring, audits, IRB/EC 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 Oracle Clinical system hosted by SJM. 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 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.

The following data can be recorded directly in the CRFs

- Fluoroscopy time
- Radiation exposure
- Time for steps in the study
- MediGuide™-enabled tools used
- Fluoroscopic views and orientation angles used

The CRFs will be signed and validated by the authorized site personnel.

10.0 MONITORING

Centralized monitoring will 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. On site monitoring may occur at the discretion of the sponsor.

11.0 REGULATORY INSPECTIONS

The investigator and/or delegate should contact SJM 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 IRB/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

In this study, no randomization or cross-over will be used. Analysis of the study objectives will be done using descriptive summary statistics such as the mean, standard deviation, n, and range or a percentage along with the numerator and denominator of that percentage. Ninety-five percent confidence intervals constructed around the estimated means or percentages will also be calculated.

12.2 Sample size

This is a worldwide, multicenter, non-randomized registry/observational study that aims to enroll up to 1000 patients from up to 65 centers undergoing either CRT implantation or an EP procedure. The study will enroll a minimum of 250 patients for each group. This sample size was chosen to provide understanding on the effect of following MediGuide™ technology on.

- The amount of fluoroscopy time and the radiation exposure
- Total procedure time
- Peri-procedural clinical event rate

12.3 In multi-center studies, the minimum and maximum number of subjects to be included for each center

The maximum number of subjects that each center can enroll is 50 patients.

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 until approval from the sponsor 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 Investigator Brochure (IB), Report of Prior Investigations (RPI) CIP, CRFs, Informed Consent form and other subject information, or other clinical study documents will be amended as needed throughout the clinical study, and a justification statement will be included with each amended section of a document. Proposed amendments to the CIP will be agreed upon between the Sponsor and the coordinating investigator (if applicable).

The amendments to the CIP and the subject's Informed Consent will be notified to, or approved by, the IRB/EC and regulatory authorities, if required. The version number and date of amendments will be documented.

The amendment will identify the changes made, the reason for the changes and if it is mandatory or optional to implement the amendment.

Any amendment affecting the subject requires that the subject be re-consented at the subject's next follow up.

Changes to, or formal clarifications of, the CIP will be documented in writing and provided to the investigators. This information will be incorporated when an amendment occurs.

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.

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
- Occurrence of USADE which cannot be prevented in future cases
- 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
- Failure to report unanticipated adverse device effects within 72 hours to SJM and the EC
- 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
- Loss of or unaccounted use of investigational device inventory

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 IRB/EC and/or the Competent Authority (if applicable). Follow-up for all enrolled subjects will be as per CIP requirements.

A Principal Investigator, IRB/EC 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 IRB/EC or regulatory authority, SJM may suspend the clinical study as appropriate while the risk is assessed. SJM will terminate the clinical study if an unacceptable risk is confirmed.

SJM 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 SJM will keep each other informed of any communication received from IRB/EC or regulatory authority.

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

If suspension or premature termination occurs, SJM 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 SJM concludes an analysis of the reasons for the suspension, implements the necessary corrective actions, and decides to lift the temporary suspension, SJM will inform the Principal Investigators, IRB/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 IRB/EC 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 SJM has been provided to sites or SJM has provided formal documentation of study closure

17.0 PUBLICATION POLICY

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.

For more information on publication guidelines, please refer to the International Committee of Medical Journal Editors (ICMJE) on www.icmje.org.

This study will be posted on ClinicalTrials.gov and results will be posted on ClinicalTrials.gov as required.

18.0 BIBLIOGRAPHY

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APPENDIX A: ABBREVIATIONS

Abbreviation	Term

ADE	Adverse Device Effect
AE	Adverse Event
ANZ	Australia – New Zealand
ASADE	Anticipated Serious Adverse Device Effect
AV	Atrioventricular
CA	Competent Authority
CCI	Clinical Coordination Investigator
CIP	Clinical Investigational Plan
CRF	Case Report Form
CRT	Cardiac Resynchronization Therapy
CS	Coronary Sinus
DD	Device Deficiency
DFT	Defibrillation Threshold
DMP	Data Management Plan
EC	Ethics Committee
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
EMEA	Europe, Middle East, Africa
EP	Electrophysiology
GP	General Practitioner
IB	Investigator Brochure
ICD	Implantable Cardioverter Defibrillator
ICMJE	International Committee of Medical Journal Editors
IRB	Institutional Review Board
ISB	Investigator Site Binder
ISO	International Organization for Standardization
LV	Left Ventricle
LVEF	Left Ventricular Ejection Fraction
MP	Monitoring Plan
NA	Not Applicable
NYHA	New York Heart Association
PI	Principal Investigator
PM	Pacemaker
POA	Power of Attorney
RA	Right Atrial
RDC	Remote Data Capture
RV	Right Ventricular
SADE	Serious Adverse Device Effect
SAE	Serious Adverse Event
SC	Steering Committee
SJM	St. Jude Medical
USADE	Unanticipated Serious Adverse Device Effect
VT	Ventricular Tachycardia

APPENDIX B: CIP REVISION HISTORY

Appendix C: Declaration of Helsinki

The most current version of the document will be followed.

Appendix F: List of Clinical Investigation Sites and IRB/EC

A list of Clinical Investigational sites and IRB/EC will be kept under a separate cover and is available upon request.

Appendix G: Informed Consent

Informed consent will be provided under separate cover.