Reference:
SJM-CIP-10149

"MultiPoint Pacing™ Post Market Study (MPP PMS)"

Clinical Investigation Plan (CIP)

Version Number	A
Date	May 24, 2016
Planned Number of Sites and Region(s)	Up to 140 sites worldwide
Clinical Trial Type	The MPP Post-Market Trial is a prospective, multi-center, non-randomized registry/observational study
Sponsor	St. Jude Medical. Inc.

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"MultiPoint Pacing™ Post Market Study (MPP PMS)"

Clinical Investigation Plan (CIP)

Sponsor

St. Jude Medical, Inc.
[redacted]

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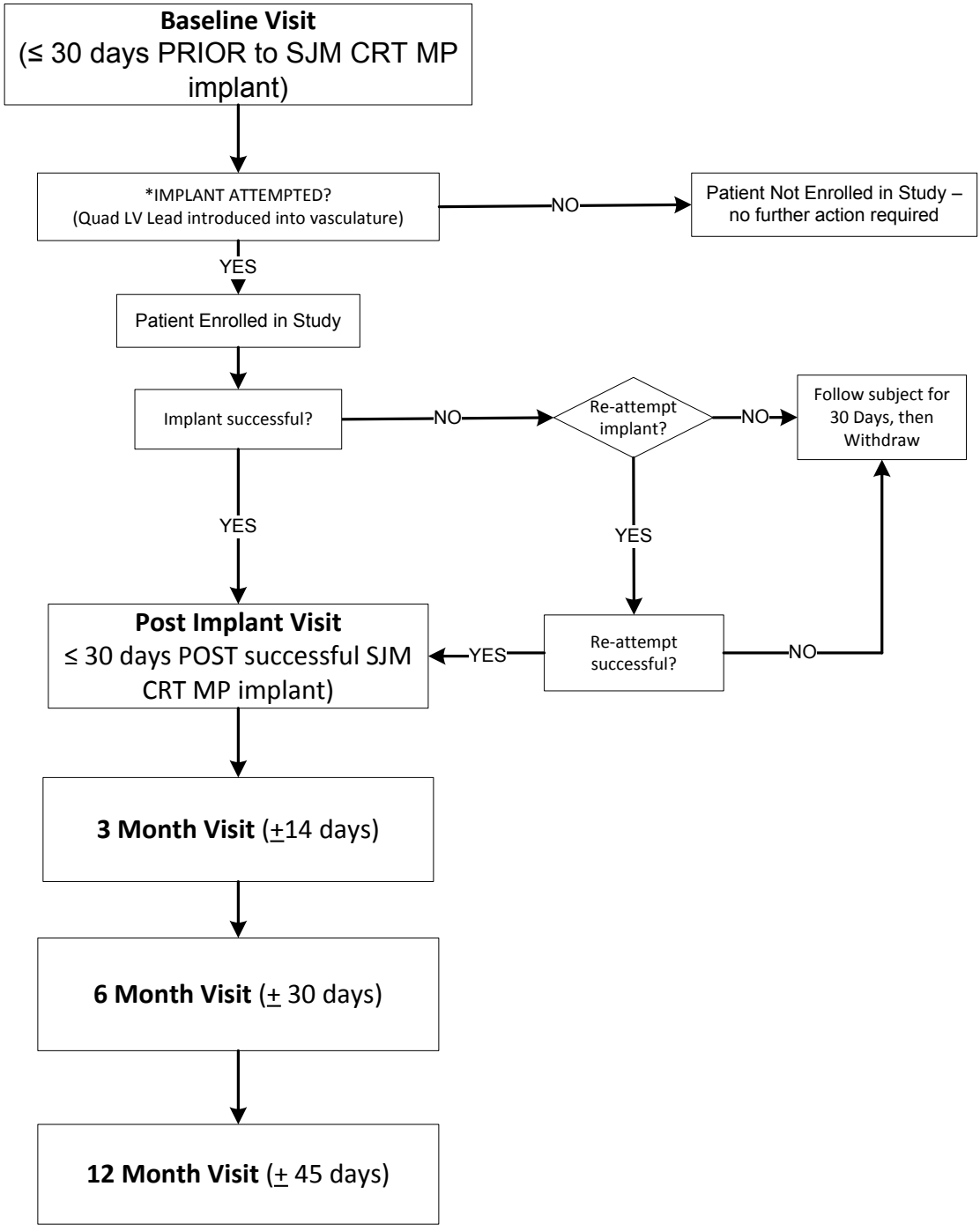
1.0 SYNOPSIS

Title:	MultiPoint™ Pacing (MPP) Post Market Study
Acronym:	MPP PMS
Purpose:	The purpose of this post market study is to characterize real-world use of MPP technology in patients indicated for a cardiac resynchronization therapy (CRT) device.
Objectives:	The primary objective of this post market study is to understand the use of the MPP technology in real-world clinical practice. The study should provide an understanding of the impact of MPP technology on: • Overall CRT response rate measured by Clinical Composite Score (CCS). (A responder is defined as improved or unchanged from baseline and non-responder is defined as worsened from baseline.) • Quality of Life (QOL), left ventricular ejection fraction (LVEF, if available) and left ventricular end systolic volume (LVESV, if available) • Programming timing and workflow • Rates of heart failure (HF) hospitalization events, cardiovascular hospitalizations, and HF 30-day hospitalization rates • Costs associated with HF-related health care utilizations • All-cause mortality
Design:	This is a prospective, multicenter, non-randomized registry/observational study. The study will enroll up to 2,000 patients with successful SJM CRT MP device implant from up to 140 centers undergoing CRT implantation. Any patient who received a market approved SJM Quadra Allure MP, Quadra Assura MP, or newer SJM CRT MP device is eligible for enrollment in the study. MPP programming guidance will be specified in the protocol. Patients will be followed for 12 months after implant. Data will be collected at Baseline (within 30 days prior to implant), Post-Implant (within 30 days following successful CRT device implant), 3, 6, 12 months and during any unscheduled follow-up visit. [redacted]
Devices used:	Market-approved SJM Quadra Allure MP, Quadra Assura MP device, or newer SJM CRT MP device and market-approved SJM Quadripolar LV lead
Study Population	All subjects who meet inclusion criteria, do not meet exclusion criteria, sign an IRB/EC approved informed consent, complete a Baseline visit prior to device implant and have an attempted implant of the SJM Quadra Allure MP, Quadra Assura MP, or newer SJM CRT MP device will be considered

	enrolled in the study.
Inclusion/Exclusion Criteria	Inclusion Criteria *Eligible patients will meet **all** of the following:* • Are scheduled to receive a new CRT implant or an upgrade from an existing ICD/Pacemaker implant (SJM CRT MP device and SJM QUAD Lead) with no prior LV lead placement • Have the ability to provide informed consent for study participation and are willing and able to comply with the prescribed follow-up tests and schedule of evaluations Exclusion Criteria *Patients will be excluded if they meet **any** of the following:* • Are expected to receive a heart transplant during the duration of the study • Have an epicardial ventricular lead system (active or inactive) • Are less than 18 years of age • Are currently participating in a clinical investigation including an active treatment arm and belong to the active arm • Are not expected to complete the study follow-up schedule or duration due to any health condition other than heart failure, such as malignancy, indication for heart transplant or hospice care.
Data Collection	All patients will complete a Baseline visit within 30 days prior to implant. During this visit, inclusion/exclusion criteria evaluation, informed consent, NYHA class, QOL questionnaires (Minnesota Living with Heart Failure – MLWHF and EQ-5D) will be completed. All subjects will undergo SJM CRT MP device implant per standard of care. Device measurements will be collected within 30 days of successful SJM CRT MP device implant during the Post-implant visit. Patients will be followed for 12 months after successful CRT implant. Follow-up data will be collected at 3, 6 and 12 months post implant and during any unscheduled follow-up visits. During the study mandated follow-up visits, arrhythmic episode diagnoses, device data, stored electrograms, LVEF (if available), LVESV (if available), NYHA class, Patient Global Assessment (PGA), and QOL questionnaires (Minnesota Living with Heart Failure – MLWHF and EQ-5D) will be collected. All clinical events for cardiovascular reasons, such as hospitalizations and emergency room visits, 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.

1.1 STUDY FLOW CHART



*The implant procedure is not considered part of the research study.

1.2 STUDY CONTACTS

[redacted]

[redacted]

2.0 BACKGROUND AND JUSTIFICATION FOR CLINICAL STUDY

Heart failure (HF) is a major threat to public health affecting an estimated 5.7 million individuals in the United States. It is estimated that 50% of people diagnosed with HF will die within 5 years.[1] In 2007, the direct and indirect cost for HF in the United States was estimated at $33.2 billion.[2, 3] HF is a varied clinical syndrome with complex pathophysiology, which continues to be defined, and often begins with a primary insult to the myocardium. Patients with HF experience decreased exercise capacity, inability to perform activities of daily living, diminished quality of life and an increased early mortality.

Cardiac resynchronization therapy (CRT) using biventricular (BiV) pacing was developed to restore synchrony in HF patients with delayed ventricular activation, predominantly of the left ventricle (LV). Although a majority of treated patients show a benefit, up to 40% derive no benefit from CRT. In the MIRACLE study, 34% of patients did not demonstrate an improvement in a HF clinical composite score (CCS) that combined all-cause mortality, HF related hospitalization, NYHA class and patient global assessment into an outcome measure.[4] Birnie and Tang summarized various clinical studies that report CRT non-responder rates.[5] Rates of non-response to cardiac resynchronization therapy are often quoted as 20-30% in the listed studies, but the authors suggest the true non-responder rate may be as high as 40-50%. This inconsistent CRT effectiveness may be due to incomplete resynchronization and the presence of intraventricular dyssynchrony.

Although the cause for failed response to CRT is not completely understood, the consensus, supported by growing evidence, is suboptimal LV lead placement accounts for a large percentage of patients who do not respond to CRT. Standard LV lead placement criteria for a stimulation electrode typically focuses on the location of mechanical stability, freedom from phrenic nerve stimulation, reasonable pacing thresholds, or the site of latest electrical activation. However, ischemic cardiomyopathy can cause non-uniform propagation of electrical activity over the myocardium due to scarred myocardial segments and density near the LV stimulation electrode.[6] Thus, a site of latest electrical activation may not always yield the optimal response. In such cases, the ability to pace from more than one left ventricular site may provide benefit.

The St. Jude Medical family of quadripolar leads includes one tip electrode and three ring electrodes. The Quartet™ LV family of leads with the CRT device provides 10 - 14 different pacing vector options (VectSelect™) from the four pacing electrodes on the LV lead. Since this CRT device can provide quadripolar pacing, the device and Quartet™ LV lead will be referred to as the Quadripolar CRT device system in this protocol.

Furthermore, this lead allows pacing from any two of the 10 - 14 available vectors that stimulate the LV in a multi-point fashion (MultiPoint™ pacing or MPP). In addition to the usual interventricular (RV-LV or V-V) timing that is currently available in a traditional CRT devices, MPP further allows timing between two LV lead pacing vectors termed 'LV1-LV2 timing' with programmable delays (5 – 80 ms).

MultiPoint™ pacing (MPP) is a new pacing feature in the Quadripolar CRT system that allows the LV with two pacing vectors compared to one vector in a traditional CRT system. A combination of any two of the 10 – 14 available vectors can be used. Additionally, a delay can be introduced between the two LV pacing vectors.

MPP via one LV lead has the potential to be an alternative to optimize LV lead placement non-invasively, and it is feasible the MPP feature may improve hemodynamics and the response to CRT. Studies showed simultaneously exciting a larger mass or volume of cardiac tissue results in faster depolarization velocity and shorter left ventricular trans-ventricular conduction times.[7, 8] In addition, by capturing a larger volume of cardiac muscle, the site of latest intrinsic activation within the left ventricle may be more likely to be depolarized early, resulting in better synchronization and maximizing cardiac output.

Since MPP delivers two pulses at programmable delays (LV1 and LV2) to two LV sites, the initial volume of excited cardiac tissue is increased. Additionally, by capturing more mass at the initial depolarization, there is a greater likelihood of pacing the site of latest systolic delay. Both of these methods have shown to improve LV function[9-20] and it is believed this additional improvement in LV function may benefit those patients who are otherwise identified as non-responders to conventional BiV pacing.

3.0 STUDY DESIGN

3.1 Purpose

The purpose of this post market study is to characterize real-world use of MPP technology in patients indicated for a CRT device.

3.2 Study Design and Scope

This is a prospective, multicenter, non-randomized registry/observational study. All subjects who meet inclusion criteria, do not meet exclusion criteria, sign an IRB/EC approved informed consent, complete a Baseline visit prior to device implant and have an attempted implant of the SJM Quadra Allure MP, Quadra Assura MP, or newer SJM CRT MP device will be considered enrolled in the study. MPP programming guidelines are provided in Appendix I. Patients will be followed for 12 months after implant. Data will be collected at post-implant (within 30 days of successful CRT device implant), 3, 6, 12 months and during any unscheduled follow-up visit. At 12 months, the responder rate will be evaluated among the following groups:

- MPP Group: MPP ON within 1 month post implant and then continuously programmed ON until 12 months (i.e., MPP ON for months 1-12 continuously)
- Treatment Strategy (BiV/MPP) Group: MPP ON at the 12-month study visit and for at least 3 continuous months prior to 12-month assessment (i.e., BiV ON at some point in months 1-9 and MPP ON for months 10-12)
- BiV Group: MPP OFF at the 12-month study visit and for at least three continuous months prior to 12-month assessment (i.e., BiV ON for months 10-12)
- Other Pacing Group: Other pacing schemes not covered above (Retrospective categorization implemented based on the usage of MPP or BiV for 12 months)

3.2.1 Number of subjects required to be included in the study

The study will enroll up to 2,000 patients with successful SJM CRT MP device implant from up to 140 centers undergoing CRT implantation. Any patient who received a market approved SJM Quadra Allure MP, Quadra Assura MP, or newer SJM CRT MP device is eligible for enrollment in the study.

3.2.2 Estimated time needed to enroll this subject population

[redacted]

3.3 Objectives

The objective of this post-market study is to understand the use of the MPP technology in real-world clinical practice. The study should provide an understanding of the impact of MPP technology on:

- Overall CRT response rate measured by CCS. (A responder is defined as improved or unchanged from baseline and non-responder is defined as worsened from baseline.)
- QOL, LVEF, if available and LVESV, if available
- Programming timing and workflow
- Rates of HF hospitalization events, cardiovascular hospitalizations, and HF 30-day hospitalization rates
- Costs associated with HF-related healthcare utilizations
- All-cause mortality

3.4 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.

3.4.1 Inclusion Criteria

*Eligible patients will meet **all** of the following:*

- Are scheduled to receive a new CRT implant or an upgrade from an existing ICD/Pacemaker implant (SJM CRT MP device and SJM QUAD Lead) with no prior LV lead placement
- Have the ability to provide informed consent for study participation and are willing and able to comply with the prescribed follow-up tests and schedule of evaluations

3.4.2 Exclusion Criteria

*Patients will be excluded if they meet **any** of the following:*

- Are expected to receive a heart transplant during the duration of the study
- Have an epicardial ventricular lead system (Active or Inactive)
- Are less than 18 years of age
- Are currently participating in a clinical investigation including an active treatment arm and belong to the active arm
- Are not expected to complete the study follow-up schedule or duration due to any health condition other than heart failure, such as malignancy, indication for heart transplant or hospice care.

3.5 SUBJECT POPULATION

3.5.1 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 criteria or do meet the exclusion criteria will not be eligible to participate in this study.

3.5.2 Point of Enrollment

All subjects who meet inclusion criteria, do not meet exclusion criteria, sign an IRB/EC approved informed consent, complete a Baseline visit prior to device implant and have an attempted implant of the SJM Quadra Allure MP, Quadra Assura MP, or newer SJM CRT MP device will be considered enrolled in the study.

3.6 INFORMED CONSENT PROCESS

3.6.1 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 relevant to the subject's decision to participate in the clinical study.

The subject shall be provided with the informed consent form written in a language understandable to the subject and approved by the center's IRB/EC. 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 IRB/EC consistent with the center's IRB/EC reporting requirements.

4.0 DEVICE

4.1 Device Description

In this study, the Quartet™ LV family of leads will be implanted with the SJM CRT MP device. The SJM CRT MP devices are supported by the St. Jude Medical Merlin™ Patient Care System (Merlin™ PCS) with software Model 3330 version 21.1.1 rev 1 (or higher).

The Quartet™ family of LV lead is a quadripolar, over–the-wire design that enables implantation using either a stylet or guidewire. The lead has an open lumen and an opening at the lead tip to allow the use of a guidewire. The body of the leads has Optim™ insulation.

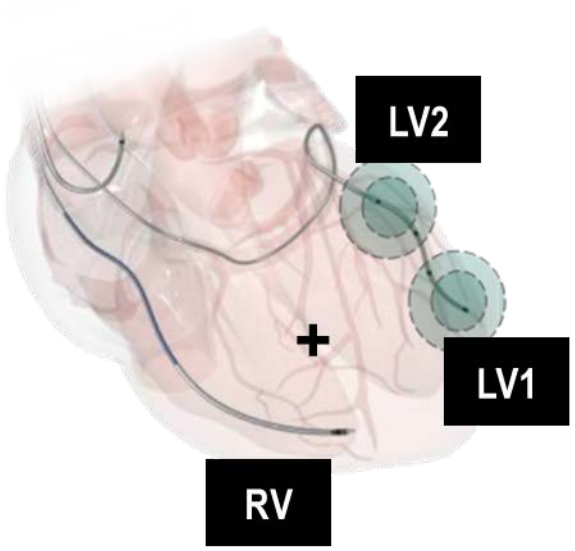
The titanium nitride (TiN) coated platinum/iridium (PtIr) tip electrode on the lead contains a molded ring that elutes steroid. Additionally, the surface of the tip electrode is coated with a thin steroid film to provide immediate steroid release. Three TiN-coated PtIr ring electrodes are located on the lead.

The lead provides pace/sense capability from 4 electrodes (tip and 3 rings):

- Distal Tip (D1)
- Mid 2 (M2)
- Mid 3 (M3)
- Proximal 4 (P4)

The Quartet™ family of LV leads can be programmed with a combination of 10 – 14 possible pacing vectors using the Merlin™ PCS programmer. Vectors are presented as cathode-anode (Figure 1)

Figure 1: SJM CRT MP Device with Quadripolar Technology: LV Lead Vector (10 CRT-D or 14 CRT-P VectSelect Quartet™ Vectors)



Vector	Cathode to Anode
1	D1 → M2
2	D1 → P4
3	D1 → RV Coil
4	M2 → P4
5	M2 → RV Coil
6	M3 → M2
7	M3 → P4
8	M3 → RV Coil
9	P4 → M2
10	P4 → RV Coil
11	D1 → Can
12	M2 → Can
13	M3 → Can
14	P4 → Can

Please note Vector numbering is for protocol use only and is not reflected on the Merlin™ programmer screen.

The user has the option to program the device to MPP in addition to BiV pacing. MPP consists of delivering two sequential LV pulses (LV1 and LV2) in addition to the standard RV pulse as follows:

- RV first: $RV \xrightarrow{D1} LV1 \xrightarrow{D2} LV2$
- LV first: $LV1 \xrightarrow{D1} LV2 \xrightarrow{D2} RV$

LV1 and LV2 configurations can be chosen from any of the 1 – 14 pacing vectors listed in Figure 1 with independent pacing characteristics. Additionally, the timing delay 1 (D1) can be programmed from 5ms to 80ms with 5ms steps and the timing delay 2 (D2) can be programmed from 5ms to 50ms with 5ms steps, respectively.

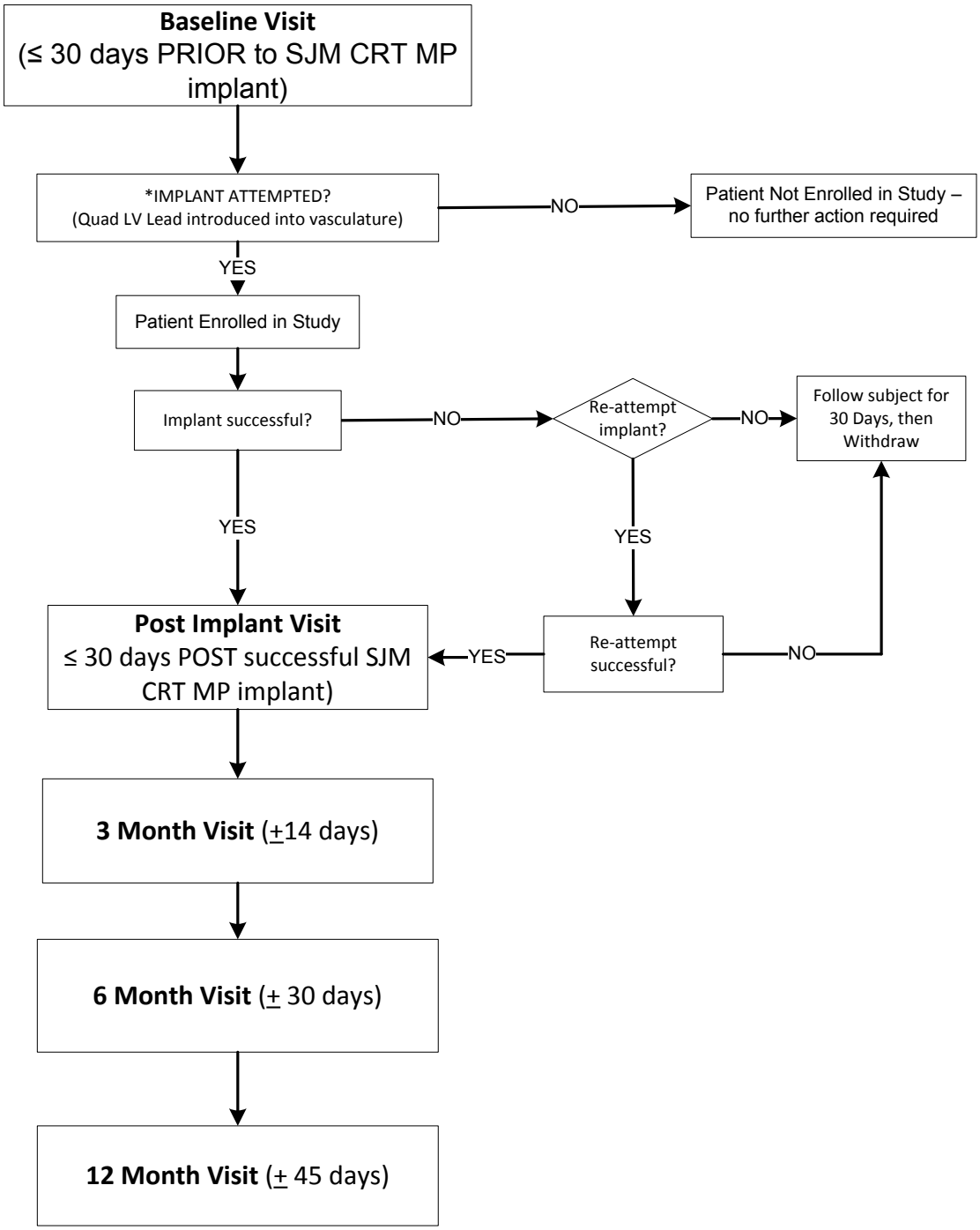
4.2 Device Handling & Storage

Instructions for use, storage and handling instructions, preparation for use and any precautions can be found in the User's Manuals for each of the market-released devices and leads.

5.0 PROCEDURES

5.1 Study Flow Chart

Figure 2: Flow Chart



*The implant procedure is not considered part of the research study.

5.2 Evaluation of responder status

Patients' responder status will be assessed at 3, 6 and 12 months post implant using the CCS. The CCS includes four components: NYHA class, Patient Global Assessment (PGA), HF events, and cardiovascular death.[21]

The NYHA Class assessment and PGA are determined by a designated assessor interviewing patients about their symptoms. Specifically, the PGA will be a single interview question asking the patient to categorize how they feel compared to their previous visits as either:

- Markedly better
- Better
- No change
- Worse
- Markedly worse

At the 3, 6 and 12-month visits, a PGA will be conducted to evaluate how the patient feels compared before having the CRT system implanted.

In this trial, a **HF event** is defined as any one of the following when the subject has symptoms and/or signs consistent with congestive heart failure:

- Hospitalization for HF ≥ 24 hours
- Clinic or hospital visit for HF<24 hours (i.e. outpatient treatment, observational care, ER, Urgent Care and physician's office visit) requiring administration of IV diuretics, inotropes, and/or vasodilators

Finally, **cardiovascular death** is defined as sudden unexpected death; heart failure death; myocardial infarction related death; or 'other' death, such as deaths due to pulmonary embolism, peripheral thromboembolism, stroke, vascular procedure, or other major cardiovascular event.

Using the CCS and decision algorithm described in section 5.2.1 patients are categorized as Improved, Worsened or Unchanged based on the following rules:

- "Improved" – patients demonstrating:
  - At least a one-class improvement in NYHA Class OR improvement by PGA ("better" or "markedly better")

    AND
  - No HF events as described above

    AND
  - No cardiovascular death

- "Worsened" – patients demonstrating:
  - Worsening in NYHA Class OR worsening by PGA ("worse" or "markedly worse")

    OR

- Presence of HF events as described above

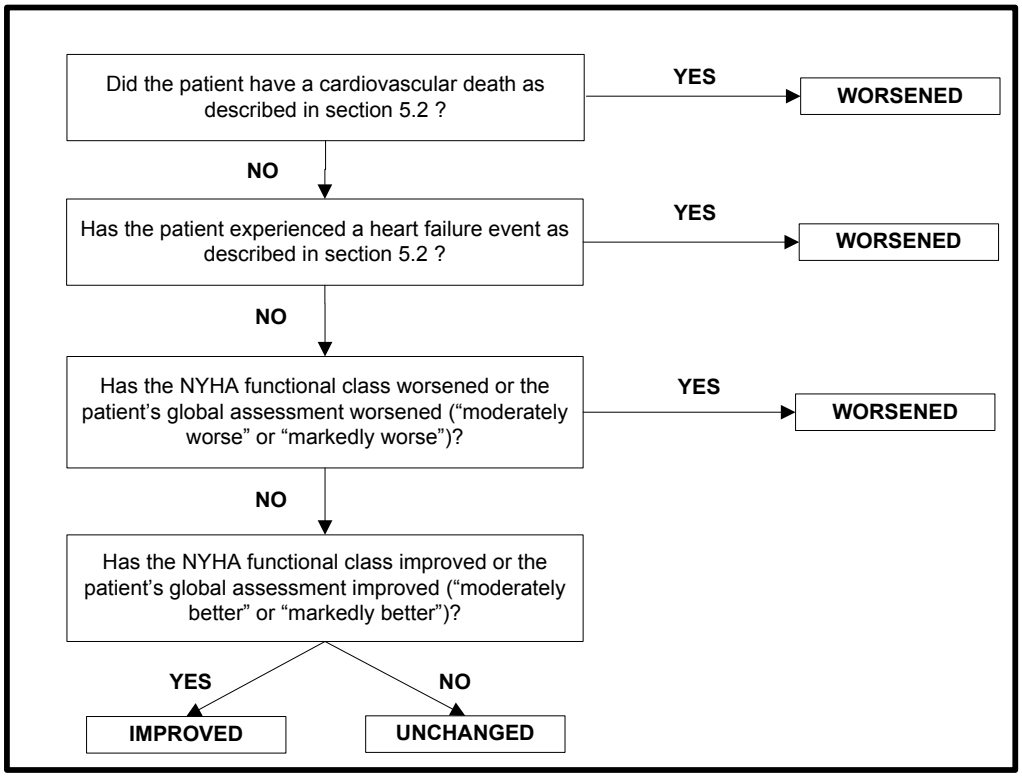
OR

- Cardiovascular death

- "Unchanged" – patients neither "Improved" nor "Worsened".

Patients who are "Improved" or "Unchanged" using the above definition will be grouped together as Responders. Patients classified as "Worsened" will be considered Non-Responders.

5.2.1 Decision algorithm to classify response to CRT treatment



5.3 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 IRB/EC and relevant regulatory authorities and all required documents have been collected from the site(s).

Table 1: List of all study specific activities/procedures

Evaluation	Baseline*	Post-Implant**	3-month Visit	6-month visit	12-month visit
Inclusion/Exclusion Evaluation and Informed Consent	√				
NYHA class	√ §		√	√	√
Patient Global Assessment			√	√	√
MLWHF and EQ-5D questionnaires	√		√	√	√
LVEF (if available) and LVESV (if available)	√		√	√	√
Cardiac Medications List	√				
HF events		√	√	√	√
LV lead capture threshold testing and pacing lead impedance		√ Testing of programmed LV lead vector(s) required	√ Testing of programmed LV lead vector(s) required	√ Testing of programmed LV lead vector(s) required	√ Testing of programmed LV lead vector(s) required
RA, RV capture threshold, signal amplitude and pacing lead impedance testing		√	√	√	√
Device Session Records		√	√	√	√

* Baseline visit should be completed up to 30 days before device implant to be enrolled in the study
** Post-implant visit can occur up to 30 days post successful SJM CRT MP device implant
§ At Baseline visit, NYHA used for device eligibility will be collected on the CRF

5.4 ENROLLMENT

5.4.1 Baseline visit

Patients will undergo screening evaluations as outlined by the inclusion/exclusion criteria. The principal investigator or delegated study personnel are responsible for screening all potential patients to determine eligibility for the study.

All patients will complete a Baseline visit within 30 days prior to implant. During this visit, eligible patients will sign an IRB/EC-approved informed consent form. NYHA class used to

determine device eligibility will be collected on the Case Report Form (CRF). All patients will also complete QOL questionnaires (MLWHF and EQ-5D) at this visit prior to device implant. If a 2D-Echocardiogram was conducted as part of patient's standard of care, LVEF and LVESV values will be collected on the CRF.

Baseline, Medication, MLWHF and EQ-5D questionnaire CRFs will be submitted to St. Jude Medical using the EDC system.

5.4.2 Implant procedures

The implant procedure will be performed according to standard of care and is not considered part of the research study. The User's Manual must be consulted for implantation guidelines, appropriate lead/device connections and general handling information.

All subjects who meet inclusion criteria, do not meet exclusion criteria, sign an IRB/EC-approved informed consent, complete a Baseline visit prior to device implant and have an attempted implant of the SJM Quadra Allure MP, Quadra Assura MP, or newer SJM CRT MP device will be considered enrolled in the study. An implant attempt is defined as insertion of the Quadripolar LV lead into the vasculature for positioning. There are no protocol-specific requirements for the implant procedure and a CRF is not required to be completed within the EDC system.

5.4.3 Unsuccessful Implant

Patients who have an unsuccessful implantation of the SJM Quadripolar CRT MP device system will be followed for a period of 30 days for adverse events and then withdrawn from the study, unless the implant will be re-attempted. All explanted devices and leads should be returned to St. Jude Medical to the address below:

[redacted]

An Out of Service (if applicable) CRF must be completed using the EDC system.

After 30 days, if the patient will not have an implant re-attempted, a Withdrawal CRF and Adverse Event CRF (if applicable) should be completed using the EDC system.

The physician may re-attempt the implantation of the SJM CRT MP device system per their discretion. If the physician chooses to re-attempt the implantation of the SJM Quadripolar CRT MP device system, a System Revision CRF (if applicable), an Adverse Event CRF (if applicable) and Product Out of Service CRF (if applicable) should be completed. All forms should be submitted to St. Jude Medical using the EDC system.

5.4.4 Post-implant visit

In order to be enrolled in the study, patients must meet inclusion criteria, not meet exclusion criteria, sign an IRB/EC-approved informed consent, complete a Baseline visit prior to

device implant, and have an attempted implant of the SJM Quadra Allure MP, Quadra Assura MP, or newer SJM CRT MP device.

All patients who undergo a successful implant of the SJM CRT MP device system will proceed to complete a Post-implant visit. This visit may be completed on the same day as device implant, during pre-discharge, during an in-office wound check or any day following the implant, as long as it is completed within 30 days of successful implant.

During this visit, the following device testing will be conducted:

- RV-LV conduction tests using both RV sense and RV pace configurations

*Note: If patient is pacemaker dependent, conduction tests using RV sense are not required.

For the RA and RV leads:
- Capture threshold testing
- Lead impedance
- Signal amplitude

*Note: If patient is in atrial fibrillation or atrial flutter, RA electrical measurements are not required.

*Note: If patient is in complete heart block or is pacemaker dependent, RV sensing amplitude is not required.

For the LV lead:
The following testing must be performed for the programmed LV lead vector(s)-
- Capture threshold testing
- Lead impedance

The following device session records must be downloaded and sent to St. Jude Medical using the EDC system.
- Initial and Final Programmed Parameters
- Real-Time Measurements and Trends for all implanted leads
- Capture threshold testing results for RA, RV and LV lead
- All “new" stored IEGM(s) since previous session

Once the new IEGM(s) are downloaded and exported, clear all IEGM(s) and diagnostics

Post-Implant Case Report Form (CRF) will be submitted to St. Jude Medical, using the EDC system.

5.5 SCHEDULED FOLLOW-UPS

The schedule of follow-up visits is based on the date of successful SJM CRT MP system implant.

Table 3.0 outlines the time window permitted for each of the study visits.

Table 3: Study Time Interval Windows

3 Months	6 Months	12 Months
± 14 days	± 30 days	± 45 days

All subjects will be followed at 3, 6 and 12 months after the date of successful implant. During each follow-up visit, NYHA class and Patient Global Assessment (PGA) will be completed. Refer to section 5.2. All patients will also complete QOL questionnaires (MLWHF and EQ-5D) during each scheduled follow-up visit. If a 2D-Echocardiogram was conducted as part of the patient's standard of care since the last visit, LVEF and LVESV values will be collected on the Follow-up CRF.

The following device testing will be conducted:

- RV-LV conduction tests using both RV sense and RV pace configurations

*Note: If patient is pacemaker dependent, conduction tests using RV sense are not required.

For the RA and RV leads:

- Capture threshold testing
- Lead impedance
- Signal amplitude

*Note: If patient is in atrial fibrillation or atrial flutter, RA electrical measurements are not required.

*Note: If patient is in complete heart block or is pacemaker dependent, RV sensing amplitude is not required.

For the LV lead:
The following testing must be performed for the programmed LV lead vector(s)-

- Capture threshold testing
- Lead impedance

Final BiV and MPP programming at all visits is per physician's discretion. MPP programming guidelines are provided in Appendix I.

A Follow-up CRF, MLWHF and EQ-5D questionnaires should be completed using the EDC system. If a patient had an inpatient hospital stay, ER visit, observational visit, outpatient visit, urgent care visit, or unscheduled office visit for cardiovascular reasons only since the last visit,

a Health Care Utilization / Hospitalization CRF should be completed. All forms should be submitted to St. Jude Medical using the EDC system.

The following device session records must be downloaded and sent to St. Jude Medical using the EDC system.

- Initial and Final Programmed Parameters
- Real-Time Measurements and Trends for all implanted leads
- Capture threshold testing results for RA, RV and LV lead
- All “new" stored IEGM(s) since previous session

Once the new IEGM(s) are downloaded and exported, clear all IEGM(s) and diagnostics.

5.6 UNSCHEDULED VISITS

An unscheduled visit is defined as a visit between two specified study visits during where device interrogation and reprogramming associated with the Quadripolar LV lead takes place.
Device session records should be downloaded and sent to St. Jude Medical using the EDC system.
A Follow-up CRF, and any other applicable CRF should be completed and submitted to St. Jude Medical using the EDC system.

6.0 CLINICAL EVENTS/ HOSPITALIZATIONS

Any clinical event resulting in an inpatient hospital stay, ER visit, observational visit, outpatient visit, or urgent care visit for cardiovascular reasons must be reported to St. Jude Medical. Detailed source documentation surrounding the clinical event should also be sent to St. Jude Medical using the EDC system. This may include:

- Emergency department notes
- Physician consultation notes
- Medication records and logs
- Admission notes
- Laboratory results and summary details
- Discharge summary
- Operative notes
- Clinician progress notes
- X-ray reports
- Diagnostic test reports

A Health Care Utilization /Hospitalization CRF and Medication CRF (if applicable) should be completed for each clinical event/ hospitalization and submitted along with supporting documentation to St. Jude Medical using the EDC system.

6.1 HEALTH CARE ECONOMIC DATA

To assess potential differences in costs for heart failure-related health care utilizations among the groups described in section 3.2, billing records (i.e., UB-04 and CMS-1500 for centers in the United States) will be collected on a Health Care Utilization/ Hospitalization CRF.

6.2 SUBJECT STUDY COMPLETION

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

6.3 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 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.

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 Protocol Deviation Form. The subject may therefore still 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 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 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, 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 St. Jude Medical.

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 CRF. The site will submit the CRF to St. Jude Medical.

Regulations require Investigators obtain approval from St. Jude Medical 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 CRF.

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).

Investigator will notify St. Jude Medical 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 St. Jude Medical, Inc. as soon as possible and complete the Deviation CRF.

The Investigator is required to adhere to local regulatory requirements for reporting deviations to IRB/EC.

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 RISKS AND BENEFITS OF THE CLINICAL STUDY

The risks associated with the use of the SJM CRT MP device system are anticipated to be comparable to those associated with the use of other currently available CRT devices, and leads. Patients participating in this study are indicated for a CRT system as part of their standard medical management and are subject to the risks associated with these devices (refer to Section 6).

MPP may consume battery voltage faster than conventional BiV pacing. Should MPP not be beneficial to a specific patient, the feature can be disabled, thereby minimizing the effect on battery longevity in that patient.

Patients enrolled in this investigation may benefit as it is expected that the MPP feature will increase the volume of excited cardiac tissue and by capturing more mass at the initial depolarization, there is a greater likelihood of pacing the site of latest systolic delay. Both of these methods have been shown to improve LV function[8, 9] and it is believed that this additional improvement in LV function may benefit those patients who are otherwise identified as non-responders to conventional BiV pacing.

9.0 ADVERSE EVENT, ADVERSE DEVICE EFFECT, DEVICE COMPLAINTS

9.1 DEFINITIONS

9.1.1 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

9.1.2 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.

9.1.3 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.

9.1.4 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 the use error or from intentional misuse of the investigational medical device.

9.1.5 Serious Adverse Device Effect (SADE)

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

9.2 PROCEDURE FOR ASSESSING, RECORDING, AND REPORTING ADVERSE EVENTS, DEVICE COMPLAINTS, 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 attempted implant). The safety surveillance and the safety reporting will continue until the last investigational 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, except as otherwise specified in the CIP.

Potential adverse events associated with the use of for all CRT systems, including the Quadripolar CRT MP device system (device and lead) include but not limited to:

- Allergic reaction to contrast media
- AV nodal reentrant tachycardia
- Bodily rejection phenomena
- Cardiac/coronary sinus dissection
- Cardiac/coronary sinus perforation
- Cardiac tamponade
- Coronary sinus or cardiac vein thrombosis
- Endocarditis
- Excessive bleeding
- Hematoma/seroma
- Induced atrial or ventricular arrhythmias
- Infection
- Lead dislodgement
- Lead/port damage
- Local tissue reaction; formation of fibrotic tissue
- Loss of pacing and/or sensing due to dislodgement or mechanical malfunction of the pacing lead
- Myocardial irritability
- Myopotential sensing
- Pectoral/diaphragmatic/phrenic nerve stimulation
- Pericardial effusion
- Pericardial rub
- Pneumothorax/ hemothorax
- Prolonged exposure to fluoroscopic radiation
- Pulmonary edema
- Renal failure from contrast media used to visualize coronary veins
- Rise in threshold and exit block
- Thrombolytic or air embolism
- Valve damage

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.

The investigator will report the event to the IRB/EC per their reporting requirements.

Reportable events to sponsor are considered:

- All Adverse Device Effects
- All Serious Adverse Effects (whether or not the event is considered device or procedure related)

All above events will be reported to the Sponsor, as soon as possible, but no later than 10 days of first learning of the event.

Observable Adverse Event:
An observable AE is defined as an adverse event related to the implant procedure that is expected to occur for a projected duration in all subjects. Observable AE's are not reportable unless the condition worsens or continues beyond the time frame listed below.

Observable AEs related to the Implant Procedure	
Event	Time Frame post-Implant
Anesthesia related nausea/vomiting	<24 hours
Low-grade fever (<100 degree Fahrenheit fever or < 37.8 degree Celsius	< 48 hours
Percutaneous access pain	< 72 hours
Mild to moderate bruising/ecchymosis at percutaneous access site	< 72 hours
Sleep problems (insomnia)	< 72 hours
Back pain related to laying on the table	< 72 hours

The Sponsor will ensure that all events 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.

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

9.3 SUBJECT DEATH

9.3.1 Procedure for recording and reporting subject death

- All subject deaths are to be documented and reported to the sponsor as soon as possible but no later than 10 days after becoming aware of the event. Notification of death should include a detailed statement of the pertinent events and be signed by the investigator in addition to the appropriate case report forms (Death , Withdrawal, and Product Out of Service CRFs). It is the investigator's responsibility to notify the IRB/EC per the IRB/EC policy. Details of death and the following information, if available, should be provided in a letter to St. Jude Medical by the investigator summarizing the patient's course since enrollment in the study:
  - Date and time of death
  - Place death occurred (e.g. hospital, nursing home, patients home)
  - If death was witnessed
  - Identification of the rhythm at the time of death, if known (include any available documentation)
  - Cause of death
  - Any other circumstances surrounding the death
  - Approximate time interval to death from the initiating event.
  - Autopsy report (if performed)
  - Whether it was device and/or procedure related
  - Whether it was related to the study
  - Device configuration at the time of death

  Provide clinical notes and witness statements. If possible, interrogate the pulse generator. Retrieve and print all episode diagnostics, IEGMs, and programmed parameters. If applicable, the pulse generator should then be programmed OFF.

  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. In the event that the device is not explanted, the above procedure must be followed to retrieve the data. The reason the pulse generator and/or lead(s) are not being returned to St. Jude Medical must be stated clearly on the case report form.

9.4 DEVICE COMPLAINTS

A device complaint is defined as any written, electronic, or oral communication that alleges deficiencies related to the identity, quality, durability, reliability, safety, effectiveness or performance of a device after it is released for distribution.

Device complaints include malfunctions, use errors and inadequate labeling.

Device complaints in St. Jude Medical market-released products must be reported per St. Jude Medical product surveillance process. Please notify SJM Tech Service via email at [redacted].

10.0 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 US and/or any other worldwide regulatory authority in support of a market-approval application.

St. Jude Medical respects and protects personally identifiable information that we collect or maintain. As part of our commitment, St. Jude Medical 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 and additional source documents will be submitted through EDC.

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.

10.1 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 St. Jude Medical. An electronic audit trail will be used to track any subsequent changes of the entered data.

10.2 DOCUMENT AND DATA CONTROL

10.2.1 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.

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

11.0 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.

12.0 STATISTICAL CONSIDERATIONS

The following section describes the statistical methods for the clinical investigation design.

12.1 STATISTICAL DESIGN, HYPOTHESES, METHOD AND ANALYTICAL PROCEDURES

This is a prospective, multicenter, non-randomized registry/observational study. Analysis of the study objectives will be summarized using data collected upon 12-month follow-up visit by the groups defined in section 3.2. The objectives of this study will be summarized as the follows:

- Overall CRT response rate at 12 months will be summarized by percentages with a 95% confidence interval using exact method for binomial distribution.
- QOL, LVEF, and LVESV at baseline, 3, 6, and 12 months will be summarized by means (± standard deviation), median and range.
- Programming timing and workflow between implant and 12 months will be summarized by frequency and percentage for categorical data.
- Rates of heart failure (HF) hospitalization events at 12 months, cardiovascular hospitalizations at 12 months, and HF 30-day hospitalization rates will be summarized using Kaplan-Meier method.
- Costs associated with HF-related health care utilizations at 12 months will be summarized by means (± standard deviation), median and range.
- All-cause mortality at 12 months will be summarized using Kaplan-Meier method.

12.2 SAMPLE SIZE

[redacted]

12.3 MAXIMUM NUMBER OF SUBJECTS TO BE INCLUDED FOR EACH CENTER

The maximum number of subjects that each center can enroll is 300.

13.0 DOCUMENT RETENTION

St. Jude Medical and the Principal Investigators will maintain the clinical study documents as required by St. Jude Medical, Inc. and applicable regulatory requirements. They will take measures to prevent accidental or premature destruction of these documents. The Principal Investigator or St. Jude Medical may transfer custody of records to another person/party and document the transfer at the investigational site or at St. Jude Medical's facility.

These documents must be retained by the investigational site for a period of 2 years after clinical study conclusion and made available for monitoring or auditing by St. Jude Medical's representative or representatives of the FDA and other applicable regulatory agencies. The Principal Investigator must ensure the availability of source documents from which the information on the case report forms was derived.

14.0 AMENDMENTS TO CLINICAL INVESTIGATIONAL PLAN

Study related documents such as 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. The version number and date of amendments will be documented.

The amendments to the CIP and the subject's Informed Consent must be provided to and approved by the IRB/EC when required. Any amendment affecting the subject requires that the subject be informed of the changes and a new consent be signed and dated by the investigator at the subject's next follow up visit. Sites must follow their IRB/EC's policy regarding consenting subjects following a CIP amendment.

15.0 STUDY COMMITTEES

15.1 STEERING COMMITTEE (SC)

The Steering Committee may be used to advise the sponsor during the conduct of the study, during data analysis and/or presentation/publication of the study results. Membership may include 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
- Recommendation from DSMB to Steering committee and Sponsor
- 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 St. Jude Medical 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, 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 IRB/EC 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 IRB/EC 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, 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 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.

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.

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APPENDIX A: ABBREVIATIONS

Select or add abbreviations used

Abbreviation	Term
ADE	Adverse Device Effect
AE	Adverse Event
CA	Competent Authority
CIP	Clinical Investigational Plan
CRF	Case Report Form
DD	Device Deficiency
DMP	Data Management Plan
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
EC	Ethics Committee
ICMJE	International Committee of Medical Journal Editors
IRB	Institutional Review Board
ISB	Investigator Site Binder
MP	Monitoring Plan
NA	Not Applicable
PI	Principal Investigator
RDC	Remote Data Capture
SADE	Serious Adverse Device Effect
SAE	Serious Adverse Event
SC	Steering Committee
SJM	St. Jude Medical

APPENDIX B: CIP REVISION HISTORY

[redacted]				

APPENDIX C: DECLARATION OF HELSINKI

The most current version of the document will be followed.

APPENDIX D: 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.

Clinical Investigational Plan

[redacted]

- [redacted]

[redacted]

Clinical Investigational Plan

[redacted]

Clinical Investigational Plan

[redacted]

Clinical Investigational Plan

[redacted]

Clinical Investigational Plan

[redacted]

Clinical Investigational Plan

[redacted]

[redacted], disclosed

Clinical Investigational Plan

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

APPENDIX F: CASE REPORT FORMS

Case Report Forms will be kept under a separate cover, and are available upon request.

APPENDIX G: MINNESOTA LIVING WITH HEART FAILURE QUESTIONNAIRE

Instructions for use:

1. Patients should respond to the questionnaire prior to other assessments and interactions that may bias responses. You may tell the patient that you would like to get his or her opinion before performing other medical assessments.

2. Ample, uninterrupted time should be provided for the patient to complete the questionnaire.

3. The following instructions should be given to the patient each time the questionnaire is completed.

    a. Read the introductory paragraph at the top of the questionnaire to the patient.

    b. Read the first question to the patient - "Did your heart failure prevent you from living as you wanted during the last month by causing swelling, for example, in your ankles, legs"? Tell the patient, "If you did not have any ankle or leg swelling during the last month you should circle nought after this question to indicate that swelling was not a problem during the last month". Explain to the patient that if he or she did have swelling that was caused by a sprained ankle, or some other cause that was definitely not related to heart failure, he or she should also circle nought. Tell the patient, "If you are not sure why you had the swelling or think it was related to your heart condition, then rate how much the swelling prevented you from doing things you wanted to do and from feeling the way you would like to feel". In other words, how bothersome was the swelling? Show the patient how to use the 1 to 5 scale to indicate how much the swelling affected his or her life during the last month - from very little to very much.

4. Let the patient read and respond to the other questions. The entire questionnaire may be read directly to the patient, being careful not to influence responses by verbal or physical cues.

5. Check to make sure the patient has responded to each question and that there is only one answer clearly marked for each question. If a patient elects not to answer a specific question(s) indicate so on the questionnaire.

6. Score the questionnaire by adding the responses to all 21 questions. In addition, physical (items 2, 3, 4, 5, 6, 7, 12 and 13) and emotional (items 17, 18, 19, 20, and 21) dimensions of the questionnaire have been identified by factor analysis, and may be examined to further characterize the effect of heart failure on a patient's life.

LIVING WITH HEART FAILURE QUESTIONNAIRE

These questions concern how your heart failure (heart condition) has prevented you from living as you wanted during the last month. The items listed below describe different ways some people are affected. If you are sure an item does not apply to you or is not related to your heart failure, then circle 0 (No) and go on to the next item. If an item does apply to you, then circle the number relating to how much it prevented you from living as you wanted.

Did your heart failure prevent you from living as you wanted during the last month by:

		No					Very much
			Very little				
1.	Causing swelling, for example, in your ankles, legs?	0	1	2	3	4	5
2.	Making you sit or lie down to rest during the day?	0	1	2	3	4	5
3.	Making it difficult to walk about or climb stairs?	0	1	2	3	4	5
4.	Making it difficult to work around the house or in the garden?	0	1	2	3	4	5
5.	Making it difficult to go anywhere away from home?	0	1	2	3	4	5
6.	Making it difficult to sleep well at night?	0	1	2	3	4	5
7.	Making it difficult to have relationships or do things with your friends or family?	0	1	2	3	4	5
8.	Making it difficult to work to earn a living?	0	1	2	3	4	5
9.	Making your recreational pastimes, sports or hobbies difficult?	0	1	2	3	4	5
10.	Making your sexual activities difficult?	0	1	2	3	4	5
11.	Making you eat less of the foods you like?	0	1	2	3	4	5
12.	Making you short of breath?	0	1	2	3	4	5
13.	Making you tired, fatigued, or lacking in energy?	0	1	2	3	4	5
14.	Making you stay in hospital?	0	1	2	3	4	5
15.	Costing you money for medical care?	0	1	2	3	4	5
16.	Giving you side effects from medication?	0	1	2	3	4	5
17.	Making you feel you are a burden to your family or friends?	0	1	2	3	4	5
18.	Making you feel a loss of self-control in your life?	0	1	2	3	4	5
19.	Making you worry?	0	1	2	3	4	5
20.	Making it difficult for you to concentrate or remember things?	0	1	2	3	4	5
21.	Making you feel depressed?	0	1	2	3	4	5

APPENDIX H: EQ-5D QUALITY OF LIFE QUESTIONNAIRE

By placing a checkmark in one box in each group below, please indicate which statements best describe your own health state today.

Mobility

I have no problems in walking about ❑
I have some problems in walking about ❑
I am confined to bed ❑

Self-Care

I have no problems with self-care ❑
I have some problems washing or dressing myself ❑
I am unable to wash or dress myself ❑

Usual Activities (*e.g. work, study, housework, family or leisure activities)*

I have no problems with performing my usual activities ❑
I have some problems with performing my usual activities ❑
I am unable to perform my usual activities ❑

Pain/Discomfort

I have no pain or discomfort ❑
I have moderate pain or discomfort ❑
I have extreme pain or discomfort ❑

Anxiety/Depression

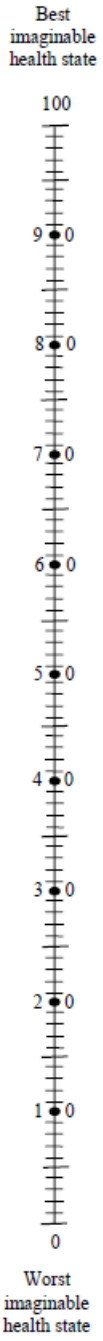
I am not anxious or depressed ❑
I am moderately anxious or depressed ❑
I am extremely anxious or depressed ❑

2

To help people say how good or bad a health state is, we have drawn a scale (rather like a thermometer) on which the best state you can imagine is marked 100 and the worst state you can imagine is marked 0.

We would like you to indicate on this scale how good or bad your own health is today, in your opinion. Please do this by drawing a line from the box below to whichever point on the scale indicates how good or bad your health state is today.

Your own health state today



3

APPENDIX I: MULTIPOINT PACING PROGRAMMING GUIDANCE

This appendix describes the suggested MultiPoint Pacing programming guidance.

MPP consists of delivering two sequential LV pulses (LV1 and LV2) in addition to the standard RV pulse as follows:

- RV first: $RV \xrightarrow{D1} LV1 \xrightarrow{D2} LV2$
- LV first: $LV1 \xrightarrow{D1} LV2 \xrightarrow{D2} RV$

LV1 and LV2 configurations can be chosen from any of the 10 – 14 pacing vectors listed in Table 4.

The timing delay D1 can be programmed from 5ms to 80ms with 5ms step

The timing delay D2 can be programmed from 5ms to 50ms with 5ms step

Table 4: 10 VectSelect™ pacing configurations available in the SJM Quadripolar CRT System. D1 = Distal tip, M2 = middle ring 2, M3 = middle ring 3, P4 = proximal ring, RVC = RV coil

Configuration #	Vector (Cathode – Anode)
1	D1 – M2
2	D1 – P4
3	D1 – RVC
4	M2 – P4
5	M2 – RVC
6	M3 – M2
7	M3 – P4
8	M3 – RVC
9	P4 – M2
10	P4 – RVC
11	D1 - Can
12	M2 - Can
13	M3 - Can
14	P4 - Can

The recommendation for vector selection can be summarized in 2 main points:

- MultiPoint Pacing configuration with the **most separated LV1 and LV2 vectors** (distal and proximal) resulted in better performances (in terms of $LVdP/dt_{max}$ improvement[19], less dyssynchrony[18], contractility[15, 17] and stroke volume[17]) or at least not inferior performances (in terms of AoVTI) compared to BiV simultaneous or other tested programmed delays

- MultiPoint Pacing configurations with **minimum timing delays between RV-LV and between LV1-LV2** resulted in not inferior performances (in terms of $LVdP/dt_{max}$ improvement, stroke volume and AoVTI) compared to BiV Simultaneous or longer programmed delays

Based on the results from Thibault et al[19] and other acute and chronic studies summarized in the 2 points above, the following general MPP programming guidance is recommended:

- MPP vector selection: Program the MPP feature to pace from the most distal and proximal electrode pairs (i.e., choose widest spacing: D1-M3 or D1-P4)
- Timing Delays: use the minimum delays between LV1-LV2 and LV-RV of 5 ms

As guidance, Table 5 lists 37 MPP vector combinations of the several options available for programming.

The investigator can use this guidance to select the appropriate MPP configuration to be programmed.

Within Table 5, the vector combinations are categorized in 6 groups based on cathode electrode selection for LV1 and LV2 pacing configuration. The pacing configurations (LV1 and LV2) can be interchanged.

[redacted]