Abbott	Clinical Investigation Plan Cover Page

NCT Number: NCT02476201
QUARTO III
Quartet Lead and Resynchronization Therapy Options - Assessing the response rate at 6 months in CRT patients implanted with a Quartet™ LV quadripolar lead and the MultiPoint™ Pacing (MPP) feature activated
Study Document No: SJM-CIP-100058
Version A
Date: 21-APR-2015

Sponsor

St. Jude Medical España/ Abbott Medical España
Avenida de Burgos 91
28050 Madrid Spain
Tel: +34 91 917 278 9 45

[redacted]

Reference: CRD_789

QUARTO III

"Quartet Lead and Resynchronization Therapy Options - Assessing the response rate at 6 months in CRT patients implanted with a Quartet™ LV quadripolar lead and the MultiPoint™ Pacing (MPP) feature activated"

"QUARTO III Substudy: Assessing the acute hemodynamic improvement in CRT patients implanted with a Quartet™ LV quadripolar lead and the MultiPoint™ Pacing (MPP) feature activated"

Clinical Investigation Plan (CIP)

Sponsor

St. Jude Medical España
C/ Francisca Delgado 11
Núcleo 3-3º. Arroyo de la Vega
28108 – Alcobendas
Madrid, Spain
Tel: +34 91 458 47 77
Fax: +34 91 344 17 08

Clinical Coordinating Investigator

[redacted]

[redacted]

PRINCIPAL INVESTIGATOR SIGNATURE PAGE

Clinical Investigational Plan Quarto III study

Version A

Reference #: CRD_789

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

Principal Investigator

Printed name: _____

Signature: _____

Date: _____

Principal Investigator

Printed name: _____

Signature: _____

Date: _____

Coordinating Investigator/ National Investigator/ Medical Advisor

SIGNATURE PAGE

Clinical Investigational Plan Quarto III study

Version A

Reference #: CRD_789

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

Coordinating Investigator/Medical Advisor, PI, etc.

Printed name: _____

Signature: _____

Date: _____

Coordinating Investigator/Medical Advisor, PI, etc.

Printed name: _____

Signature: _____

Date: _____

Contents

1.0 SYNOPSIS

Title:	QUArtet lead and Resynchronization Therapy Options III
Acronym:	QUARTO III study
Purpose:	The purpose of the study is to assess prospectively at 6 months the percentage of responder patients implanted with a Cardiac Resynchronization Therapy CRT-D device and a Quartet™ Left Ventricular (LV) quadripolar lead and with the MultiPoint™ Pacing (MPP) feature activated.
Objectives:	To assess prospectively the changes in left ventricular function at 6 months in patients with the MultiPoint™ Pacing (MPP) feature activated.
Endpoints:	Primary Endpoint The primary endpoint of the study is to measure prospectively at 6 months the percentage of responder* patients implanted with a Quartet™ LV quadripolar lead and with the MultiPoint™ Pacing feature activated (using the electrical delay programing approach or anatomical approach) compared with No Pacing at baseline. *A positive CRT response is defined as an improvement of >15 % in Left Ventricular End Systolic Volume (LVESV) at 6 months post-implant, measured by Echocardiography.
	Secondary Endpoints – Reverse LV remodeling, measured as changes in LVESV, Left Ventricular End Diastolic Volume (LVEDV), Left Ventricular End Systolic Diameter (LVESD), Left Ventricular End Diastolic Diameter (LVEDD) and Left Ventricular Ejection Fraction (LVEF) at 6 months with MPP compared to No Pacing at Baseline o Comparison of the above mentioned echo parameters with the patient cohort stratified by etiology (ischemic versus non ischemic patients) – Percentage of super-responders** at 6 months in MPP – Dyssynchrony measured by the strain rate (speckle tracking echocardiography) between the anteroseptal segment and the posterior wall. – LV lead position o Short axis (posterolateral, lateral, anterolateral) o Long axis (apical, midventricular, basal) – New York Heart Association (NYHA) class changes at 6 months

	– All-cause mortality at 6 months – All-cause, cardiovascular and/or heart failure hospitalization rate at 6 months – Combined endpoint of mortality and heart failure hospitalization at 6 months – Combined endpoint of mortality and cardiovascular hospitalization at 6 months. **Super-responder is defined as a patient with a mean absolute LVEF increase of >14% at 6 months post-implant compared with No Pacing at Baseline.
Design:	The investigation is a post-marketing, prospective, multicenter, regional, and non-randomized study. Data will be collected at Enrollment, Baseline, Implant, Unscheduled visits and 6 Month Follow-Up. Patients will exit the study after a completed 6 Month Follow-Up Visit. During the Enrollment visit, the Inclusion/Exclusion criteria will be verified and the Informed Consent Procedure will be performed. Patients will start their participation in the study once they sign the Informed Consent, prior to the CRT-D implantation. During the Baseline visit, demographic data, medical history, and cardiovascular medication will be collected. Echocardiography measurements will be collected following the Echo protocol and will be evaluated by an Echo Core Lab. At Implant procedure, the procedure details will be collected and the MPP feature will be turned ON. During the 6 Month visit, clinical and Echocardiography data will be collected. The Echo Core Lab will analyze the data to assess the percentage of responder and non-responder patients, according to LVESV reduction. The total duration of the study is expected to be approximately [redacted] years with about [redacted] years of enrollment and 6 months of Follow-up for the last patient enrolled. [redacted] Approximately [redacted] subjects will be enrolled in this study.

[redacted]

Devices used:	All subjects will be implanted with a CE-approved St. Jude Medical CRT-D device compatible with MultiPoint™ Pacing feature (models n° [redacted]) or any other St Jude Medical model compatible with the MPP algorithm) and St. Jude Medical quadripolar left ventricular lead [redacted]. Future devices with MPP feature may be added once are market release. All of the devices used in this investigation have received appropriate regulatory certification (are CE marked and market released).
Study Population	Patients meeting all the Inclusion and none of the Exclusion criteria will be fully informed about the investigation and asked to participate in the investigation. In case the patient agrees, a duly signed and dated Patient Informed Consent form will be obtained. A patient becomes a subject once he/she has been fully informed about the study, has agreed to participate, signed & dated the consent.
Inclusion/Exclusion Criteria	<u>Inclusion Criteria</u> – Patient that will be implanted with a CRT-D with the MultiPoint™ Pacing (MPP) feature under the current ESC or ACCF/AHA/HRS Class I or Class IIa indications for CRT-D implant (including upgrades from single or dual chamber ICD or PM). – Patient that will be implanted with a Quartet™ Left Ventricular (LV) quadripolar lead. – In sinus rhythm at baseline visit. – Patients with Left Bundle Branch Block (LBBB) – Must be willing and able to comply with study requirements. – Older than 18 years – Must indicate their understanding of the study and willingness to participate by signing an appropriate informed consent form. <u>Exclusion Criteria</u> – Already has a CRT device implanted. – Myocardial Infarction or unstable angina within 40 days prior the enrollment. – NYHA Class IV – Recent cardiac revascularization (PTCA, Stent or CABG) in the 4 weeks prior to enrollment. – Cerebrovascular Accident (CVA) or Transient Ischemic Attack (TIA) in the 3 months prior the enrollment. – Classification of Status 1 for cardiac transplantation or consideration for transplantation over the next 12 months. – Primary valvular disease requiring surgical intervention. – Atrial Fibrillation (AF):

<table>
<tr><td></td><td>

Persistent AF at the time of enrollment or 30 days prior the enrollment
Permanent AF not treated with AV node ablation within 2 weeks after the CRT-D implant
History or incidence of Paroxysmal or Persistent AF within 30 days prior the enrollment

– Patient for whom suitable Ttransthoracic echocardiographic images for determining the cardiac output (CO) and LV volumes cannot be obtained.
– Undergone a cardiac transplantation or being waiting for it
– Life expectancy < 6 months
– Pregnancy or planning to become pregnant
– Unable to comply with the follow up schedule
– Currently participating in any other clinical investigation.
</td></tr>
<tr><td>Data Collection</td><td>
Data will be collected at Enrollment, Baseline, Implant, Unscheduled visits and 6 Month FU as follows:

Enrollment Baseline — Implant — Unscheduled Visit — 6M FU

The following forms will be used:

<table>
<tr><th></th><th>Baseline visit</th><th>Implant Visit</th><th>Unscheduled</th><th>6 Months</th></tr>
<tr><td>Enrollment Form</td><td>√</td><td>-</td><td>-</td><td>-</td></tr>
<tr><td>Baseline Form</td><td>√</td><td>-</td><td>-</td><td>-</td></tr>
<tr><td>Implant Form</td><td>-</td><td>√</td><td>-</td><td>-</td></tr>
<tr><td>Follow Up Form</td><td>-</td><td>-</td><td>√</td><td>√</td></tr>
<tr><td>Deviation Form</td><td>√§</td><td>√§</td><td>√§</td><td>√§</td></tr>
<tr><td>Adverse Event Form</td><td>√§</td><td>√§</td><td>√§</td><td>√§</td></tr>
<tr><td>Hospitalization form</td><td>√§</td><td>√§</td><td>√§</td><td>√§</td></tr>
<tr><td>System Revision Form</td><td>√§</td><td>√§</td><td>√§</td><td>√§</td></tr>
<tr><td>Withdrawal Form</td><td>√§</td><td>√§</td><td>√§</td><td>√§</td></tr>
<tr><td>Death Form</td><td>√§</td><td>√§</td><td>√§</td><td>√§</td></tr>
</table>
§ If applicable
</td></tr>
</table>

1.1 Substudy synopsis

Substudy Purpose:	The purpose of the substudy is to assess the acute hemodynamic improvement in patients implanted with a CRT-D device and a Quartet™ LV quadripolar lead with the MultiPoint™ Pacing (MPP) feature activated.
Substudy Objectives:	The objective of the substudy is to assess the percentage of patients who achieve a greater hemodynamic response, measured by Cardiac Output (CO), with a MPP/SPP configuration compared to No Pacing.
Substudy Endpoints:	Primary Endpoint The primary endpoint of the substudy is to assess the percentage of patients who achieve the greater CO improvement with a MPP configuration and/or a Single Point Pacing (SPP) configuration versus No Pacing. The CO, based on Velocity Time Integral value (VTI by echocardiography) will be measured within 7 days after implant to evaluate the greater improvement in CO with the following configurations: • MPP Anatomical approach: choose the most anatomically separated vectors according to fluoroscopy images. • MPP Electrical approach: choose the most electrically separated vectors [redacted] • Single Point Pacing (SPP): choose the vectors LV1 and LV2 of the approach with the best CO: o SPP with LV1 o SPP with LV2 Versus • NO pacing
Substudy Design:	The substudy will be conducted in approximately [redacted] centers participating in the Quarto III Study in Spain. The total duration of the substudy is expected to be approximately [redacted] year. Approximately [redacted] subjects will be enrolled in this substudy. During the Substudy visit, within 7 days after the implant, an additional Echocardiography will be performed to a subgroup of [redacted] patients from [redacted] centers. This Echocardiography will not be sent to the Echo Core Lab but evaluated locally at hospital.

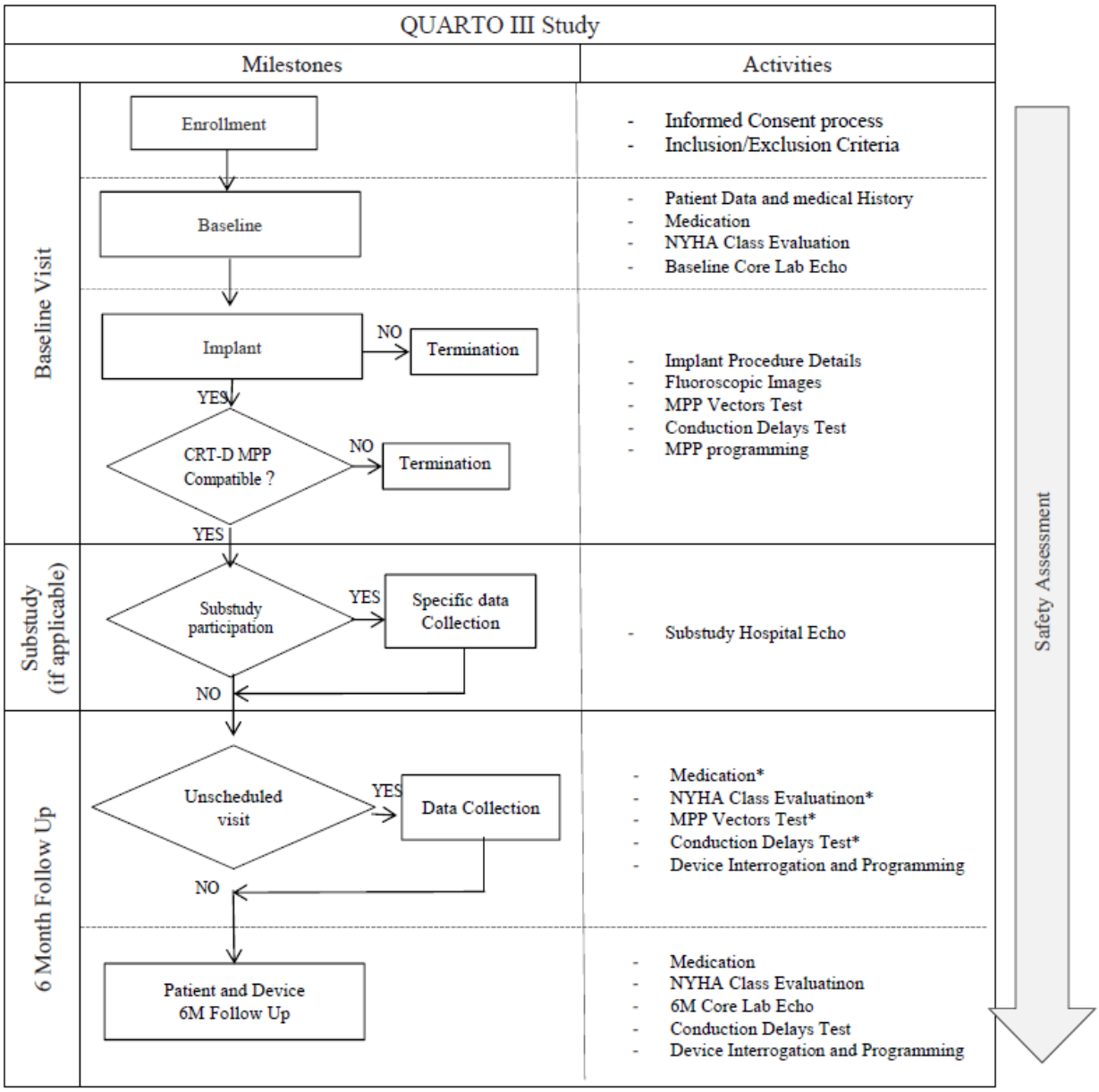
[redacted]

<table>
<tr><td>Substudy Inclusion/Exclusion Criteria</td><td><u>Inclusion Criteria</u>
– Patients enrolled in the Quarto III Study from the centers participating in the substudy will be evaluated.
<u>Exclusion Criteria</u>
– The patient is not in sinus rhythm in the moment of the substudy visit.</td></tr>
<tr><td>Substudy Data Collection</td><td>Data from this hemodynamic measurements will be collected within the first 7 days after the CRT-D Implantation:

Specific Case Report Forms (CRF) will be used for substudy purposes. The following forms will be used:

<table>
<tr><th></th><th>Substudy visit</th></tr>
<tr><td>Substudy Enrollment Form</td><td>√</td></tr>
<tr><td>Substudy Echo Form</td><td>√</td></tr>
<tr><td>Deviation Form</td><td>√§</td></tr>
<tr><td>Adverse Event Form</td><td>√§</td></tr>
<tr><td>Hospitalization form</td><td>√§</td></tr>
<tr><td>Withdrawal Form</td><td>√§</td></tr>
<tr><td>Death Form</td><td>√§</td></tr>
</table>
§ If applicable</td></tr>
</table>

1.2 Study Flow Chart



1.3 Study Contacts

2.0

[redacted]

[redacted]

BACKGROUND AND JUSTIFICATION FOR CLINICAL STUDY

Heart failure (HF) is defined by the European Society of Cardiology (ESC) 2012 guidelines [1] as an abnormality of cardiac structure or function leading to failure of the heart to deliver oxygen at a rate commensurate with the requirements of the metabolizing tissues, despite normal filling pressures (or only at the expense of increased filling pressures) [2]. For the purposes of these guidelines, HF is defined, clinically, as a syndrome in which patients have typical symptoms (e.g. breathlessness, ankle swelling, and fatigue) and signs (e.g. elevated jugular venous pressure, pulmonary crackles, and displaced apex beat) resulting from an abnormality of cardiac structure or function. Many of the symptoms of HF are non-discriminating and, therefore, of limited diagnostic value [3] [4] [5] [6] [7]. Many of the signs of HF result from sodium and water retention and resolve quickly with diuretic therapy, i.e. may be absent in patients receiving such treatment. Demonstration of an underlying cardiac cause is therefore central to the diagnosis of HF. This is usually myocardial disease causing systolic ventricular dysfunction. However, abnormalities of ventricular diastolic function or of the valves, pericardium, endocardium, heart rhythm, and conduction can also cause HF (and more than one abnormality can be present). Over 25% of patients with systolic heart failure have dyssynchronous ventricular contraction [8] that further impairs left ventricular (LV) systolic function, increases energy requirements, and results in progressive heart failure [9].

Heart failure is the most rapidly growing cardiovascular condition in developed countries [10] [11] [12]. It is estimated that in the Western world more than 20 million patients suffer from end-stage HF, so the prevalence of this syndrome is 2-2.5% overall, increasing up to 10% among persons 70 years of age or older [13]. HF is a major threat to public health affecting an estimated 14 million individuals in Europe and it is estimated that 50% of people diagnosed with HF will die within 5 years [1] [11] [14].
Cardiac resynchronization therapy (CRT) devices are designed to synchronize the mechanical activity of the ventricles, as well as that of the atria and ventricles (AV timing). In patients with a low ejection fraction (EF), reduced functional status, and delayed electrical conduction, CRT improves cardiac output (CO) and reduces symptoms [9] without increasing energy consumption [15] [16] [17] [18]. Resultant improvements in LV volumes (reverse remodeling) occur in some, but not all patients [19]. On average, CRT reduces mortality and recurrent admissions in patients with highly symptomatic heart failure, a low ejection fraction (EF), and a wide intrinsic QRS duration [20]. Several landmark clinical trials published in the past few years have provided compelling evidence that CRT can produce significant clinical benefits, including improvements in patients' HF symptoms, quality of life, reduced HF hospitalization, and echocardiographic measures which confer a mortality benefit [21] [22] [23].
Though a majority of treated patients shows a benefit, up to 40% derive no improvement 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 [24]. A summary of non- responder rate from various clinical studies has been performed by Birnie and Tang [25]. Those rates of non-response to cardiac resynchronization therapy are often quoted as 20-30% in the listed studies, but the authors suggest that 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.

All major medical devices companies offer bipolar LV leads that have one ring electrode and one tip electrode that can be positioned via the coronary sinus. This traditional type of bipolar LV lead, when used in combination with right ventricular (RV) lead, may have up to six pacing vectors available to the physician for standard biventricular (BiV) pacing.
St. Jude Medical developed a new family of quadripolar LV leads called Quartet® LV lead. The

the initial volume of excited cardiac tissue is increased. By capturing more mass at the site of 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 [25] 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.

This clinical investigation comes to collect information about the response rate achieve with this new technology compared with the traditional one. A substudy is designed as well to assess the acute hemodynamic improvement achieve with MultiPoint™ Pacing (MPP) feature activated, following the investigational line of some other studies [26] like Quarto I [27] ,

3.0 RISKS AND BENEFITS OF THE CLINICAL STUDY

The risks associated with the use of the Quadripolar CRT 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.

Additional risks associated with MPP compared to conventional BiV pacing are considered to be minimal. There is a theoretical risk that addition of a second LV pacing pulse could have a pro-arrhythmic effect. However, among both preclinical and clinical experience, no arrhythmias have been reported that have been caused by MPP. The risk of reentrant conduction pathways and induced Ventricular Tachycardia (VT) is similar to that caused by standard BiV pacing.

3.1 Description of subject population

Patients meeting the Inclusion/Exclusion criteria will be fully informed about the investigation and asked to participate in the investigation. In case the patient agrees, a duly signed and dated Patient Informed Consent form will be obtained so the patient becomes a subject.

3.2 Anticipated clinical benefits

Patients enrolled in this investigation may benefit as it is expected that the MultiPoint™ Pacing 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 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

3.3 Anticipated adverse events and adverse device effects

Potential complications associated with the implantation of pulse generator system include, but are not limited to:

- Acute hemorrhage/bleeding
- Air emboli
- Arrhythmia acceleration
- Cardiac or venous perforation
- Cardiogenic shock
- Cyst formation
- Erosion
- Exacerbation of heart failure
- Extrusion
- Fibrotic tissue growth
- Fluid accumulation

- Hematoma formation
- Histotoxic reactions
- Infection
- Keloid formation
- Myocardial irritability
- Nerve damage
- Pneumothorax
- Thromboemboli
- Venous occlusion

Other possible adverse effects include mortality due to:

- Component failure
- Device-programmer communication failure
- Lead abrasion
- Lead dislodgment or poor lead placement
- Lead fracture
- Inability to defibrillate
- Inhibited therapy for a ventricular tachycardia
- Interruption of function due to electrical or magnet interference
- Shunting of energy from defibrillation paddles
- System failure due to ionizing radiation

Other possible adverse effects include mortality due to inappropriate delivery of therapy caused by:

- Multiple counting of cardiac events including T-waves, P-waves, or supplemental pacemaker stimuli

Among the psychological effects of the device implantation are imagined pulsing, dependency, fear of inappropriate pulsing and fear of losing pulse capability.

These events are not unique to devices being used within this study and could occur during any device implant outside of the study

Potential complications associated with the use of left ventricular leads are the same as with the use of any lead and include, but it is not limited to:

- Allergic reaction to contrast media
- Body rejection phenomena
- Cardiac/coronary sinus dissection
- Cardiac/coronary sinus perforation
- Cardiac tamponade
- Coronary sinus or cardiac vein thrombosis
- Death
- Endocarditis

- Excessive bleeding
- Hematoma/seroma
- Induced atrial or ventricular arrhythmias
- Infection
- Lead dislodgment
- Local tissue reaction; formation of fibrotic tissue
- Loss of pacing and/or sensing due to dislodgment 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
- Thrombotic or air embolism
- Valve damage

Performance of a coronary sinus venogram is unique to lead placement in the cardiac venous system, and carries risks. Potential complications reported with direct subclavian venipuncture include hemothorax, laceration of the subclavian artery, arteriovenous fistula, neural damage, thoracic duct injury, cannulation of other vessels, massive hemorrhage, and rarely, death.

These events are not unique to study procedures and could occur during any lead implant outside of the study.

3.4 Risks associated with participation in the clinical study

All of the devices used in this investigation have received appropriate regulatory certification (are CE marked and market released).The risks associated with the use of the Quadripolar CRT 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 or substudy are indicated for a CRT system as part of their standard medical management and are subject to the risks associated with these devices.

3.5 Possible interactions with concomitant medical treatments and/or concurrent medical interventions

It is not anticipated any additional interaction with concomitant medical treatments and/or concurrent medical intervention than with a regular CRT-D device treatment. The patients are all candidate to a CRT-D device implant, so any additional risk will be added by the fact of participating in this clinical investigation.

Anyway, the Principal Investigator (PI) from each participant center will evaluate any potential interaction with concomitant medical treatments and/or concurrent medical interventions and will inform the sponsor.

3.6 Steps that will be taken to control or mitigate the risks

This protocol should be followed unless the safety and the availability of the patient do not allow it. Any protocol deviation will be documented accordingly and communicated to the sponsor as soon as possible.

3.7 Risk-to-benefit rationale

The risks associated with the use of the Quadripolar CRT device system are anticipated to be comparable to those associated with the use of other currently available CRT devices, and leads. Patients enrolled in this investigation may benefit from the MultiPoint™ Pacing feature as reported in the literature.Implantation of this system may offer certain advantages as compared to conventional CRT system. The clinical benefits for this new system outweigh the risks and thus provide justification for proceeding with this clinical study.

3.8 Description of history of modifications or recall in relation to safety and clinical performance for device under investigation

Up the date of this protocol, there has not been any history of modifications or recall in relation to safety and clinical performance for the devices in investigation.

4.0 STUDY DESIGN

4.1 Purpose

The purpose of this study is to assess prospectively at 6 months the percentage of responder patients implanted with a CRT-D device and a Quartet™ LV quadripolar lead and with the MultiPoint™ Pacing (MPP) feature activated.

A substudy will be carried on in [redacted] centers with the intention to assess the acute hemodynamic improvement in patients implanted with a CRT-D device and a Quartet™ LV quadripolar lead and with the MultiPoint™ Pacing (MPP) feature activated.

4.2 Study Design and Scope

This is a post-marketing, prospective, non-randomized, multicenter, regional study. Data will be collected at Enrollment, Baseline, Implant and 6 Month Follow-Up. Additionally, approximately [redacted] will participate in a substudy, so additional data will be collected at Substudy Visit within a window of 7 days after the implant.

During the Enrollment visit, the Informed Consent Procedure will be performed and the Inclusion/Exclusion criteria verified. During the Baseline Visit, the Demographic data, Medical History and Cardiac Medication will be collected. Echocardiography measurements during intrinsic rhythm will be collected following the specific study Echocardiography protocol and will be evaluated by an Echo Core Lab. At Implant procedure data and MPP activation evaluation will be collected.

All patients will begin their CRT treatment with the MPP feature turned ON. For those patients who are not able to implant the Quartet™ LV lead or not able to activate the MPP feature, a Termination will be done and their participation in the study will be concluded.

During the Substudy visit, an additional Echocardiography will be performed to [redacted] patients [redacted] centers. This Echocardiography will not be sent/uploaded to the Echo Core Lab but evaluated locally at hospital.

During the 6 Month visit, clinical and Echocardiography data will be collected. The Echo Core Lab will analyze the data to assess the percentage of responder and non-responder patients. The patient's response to CRT will be evaluated according to LVESV reduction. Patients with a LVESV reduction in MPP compared with the data collected at baseline in No pacing of at least 15% will be classified as Responders.

[redacted]

[redacted]

4.2.1 Number of subjects required to be included in the study

[redacted]

4.2.2 Estimated time needed to enroll this subject population

[redacted]

[redacted]

4.3 Objectives

To assess prospectively the changes in left ventricular function at 6 months in patients with the MultiPoint™ Pacing (MPP) feature activated.

4.3.1 Primary Objective

The primary objective of the study is to assess prospectively the percentage of responder patients at 6 months with the MultiPoint™ Pacing (MPP) feature activated.

4.3.2 Secondary Objective

To assess the impact of MPP feature on patient's functional and clinical status.

4.3.3 Substudy Objective

The objective of the substudy is to assess the percentage of patients who achieve a greater hemodynamic response, measured by Cardiac Output, with a MPP configuration or Single Point Pacing (SPP) compared to No Pacing within 7 days after implant.

4.4 Endpoints

4.4.1 Primary Endpoint

The primary endpoint of the study is to measure prospectively at 6 months the percentage of responder patients implanted with a Quartet™ LV quadripolar lead and with the MultiPoint™ Pacing feature activated (using the electrical delay programing approach or anatomical approach) compared with No Pacing at baseline.
A positive CRT response is defined as an improvement of >15 % in Left Ventricular End Systolic Volume (LVESV) at 6 months post-implant, measured by Echocardiography.

4.4.2 Secondary Endpoint

The secondary endpoints of this study are:

- Reverse LV remodeling, measured as changes in LVESV, Left Ventricular End Diastolic Volume (LVEDV), Left Ventricular End Systolic Diameter (LVESD), Left Ventricular End Diastolic Diameter (LVEDD) and Left Ventricular Ejection Fraction (LVEF) at 6 months with MPP compared with no pacing at Baseline
  - Comparison of the above mentioned echo parameters with the patient cohort stratified by etiology (ischemic versus non ischemic patients)
- Percentage of super-responders** at 6 months in MPP
- Dyssynchrony measured by the strain rate (speckle tracking echocardiography) between the anteroseptal segment and the posterior wall (if available)

- LV lead position
  - Short axis (posterolateral, lateral, anterolateral)
  - Long axis (apical, mid-ventricular, basal)
- NYHA class changes at 6 months
- All-cause mortality at 6 months
- All-cause, cardiovascular and/or heart failure hospitalization rate at 6 months
- Combined endpoint of mortality and heart failure hospitalization at 6 months
- Combined endpoint of mortality and cardiovascular hospitalization at 6 months

**Super-responder is defined as a patient with a mean absolute LVEF increase of >14% at 6 months post-implant compared with No Pacing at Baseline.

4.4.3 Substudy Endpoint

The endpoint of the substudy is to assess the percentage of patients who achieve the greater CO improvement with a MPP configuration and/or SPP configuration compared to No Pacing. The CO, based on Velocity Time Integral value (VTI by echocardiography) will be measured within 7 days after implant to evaluate the greater improvement in CO with the following configurations:

- MPP Anatomical approach: choose the most anatomically separated vectors according to fluoroscopy images.
- MPP Electrical approach: choose the most electrically separated vectors according [redacted]
- Single Point Pacing: choose the vectors LV1 and LV2 of the approach with the best CO
  - SPP with LV1
  - SPP with LV2

Versus

- NO pacing

4.5 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. Those patients who agree to participate in the substudy at the selected centers will be candidates for being included in the substudy.

4.5.1 Inclusion Criteria

To participate in this clinical study, the subject must meet all of the following inclusion criteria:

- Patients that will be implanted with a CRT-D with the MultiPoint™ Pacing (MPP) feature under the current ESC or ACCF/AHA/HRS Class I or Class IIa indications for CRT-D implant (including upgrades from single or dual chamber ICD or PM).
- Patient that will be implanted with a Quartet™ Left Ventricular (LV) quadripolar lead.
- In sinus rhythm at baseline visit.
- Patients with Left Bundle Branch Block (LBBB)

- Older than 18 years
- Must be willing and able to comply with study requirements.
- Must indicate their understanding of the study and willingness to participate by signing an appropriate informed consent form.

4.5.2 Exclusion Criteria

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

- Already has a CRT device implanted.
- Myocardial Infraction or unstable angina within 40 days prior the enrollment.
- NYHA Class IV
- Recent cardiac revascularization (PTCA, Stent or CABG) in the 4 weeks prior to enrollment.
- Cerebrovascular Accident (CVA) or Transient Ischemic Attack (TIA) in the 3 months prior the enrollment.
- Classification of Status 1 for cardiac transplantation or consideration for transplantation over the next 12 months.
- Primary valvular disease requiring surgical intervention.
- Atrial Fibrillation (AF):
  - Persistent AF at the time of enrollment or 30 days prior the enrollment.
  - Permanent AF not treated with AV node ablation within 2 weeks after the CRT-D implant
  - History or incidence of Paroxysmal or Persistent AF within 30 days prior the enrollment
- Patient for whom suitable transthorathic echocardiographic images for determining the cardiac output and LV volumes cannot be obtained.
- Undergone a cardiac transplantation or being waiting for it
- Life expectancy < 6 months
- Pregnancy or planning to become pregnant
- Unable to comply with the follow up schedule
- Currently participating in any other clinical investigation.

4.5.3 Substudy Inclusion Criteria

To participate in the substudy the subject must meet the following inclusion criteria:

- Patients enrolled in the Quarto III Study from the centers participating in the substudy.

4.5.4 Substudy Exclusion Criteria

Subjects are not eligible for the substudy if they meet the following exclusion criteria:

- The patient is not in sinus rhythm in the moment of the substudy visit.

4.6 Subject Population

4.6.1 Subject Screening

All subjects presented at the investigational site can be screened by a member of the investigational team previously trained on the CIP and delegated to do so.
Subjects who do not meet the inclusion/exclusion criteria will not be eligible to participate in this study.
Subjects meeting the inclusion/exclusion criteria will be fully informed about the study and asked to participate in the study. In case the subject agrees, a duly signed and dated Patient Informed Consent will be obtained.

Once the eligible subject has signed the Informed Consent and completed the Baseline visit, he/she will advance to the Implant Procedure visit in which the CRT-D device implant and MPP activation tests will be performed. Depending on the result of this test, the subjects will be classified as:

- Implant Failure:

Patients who provided the Informed Consent, meet the Inclusion/Exclusion criteria, but do not receive the CRT-D MPP compatible device or LV lead because of implant failure or physician's decision. These patients' participation into the study will be terminated immediately.

- MPP Activation Failure:

Patients who provided the Informed Consent, meet the Inclusion/Exclusion Criteria, have been implanted with a CRT MPP compatible device but not enough MPP vector combinations are possible to allow the MPP activation or the investigator decided not to program the MPP feature ON. These patient' participation to the study will be terminated immediately.

- Valid subject:

Patients who provided the Informed Consent, meet the Inclusion/Exclusion criteria, have been implanted with a CRT MPP compatible device, have enough MPP vector combinations to allow the MPP activation and the MPP feature is programmed ON. These patients will proceed in the study and constitute the Study Population.

4.6.2 Point of Enrollment

Subjects are considered enrolled in the study from the moment the subject has provided written Patient Informed Consent, prior to the CRT-D implant. (Refer to the following Section for the Informed Consent Process).

4.7 Informed Consent Process

4.7.1 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 Institutional Review Board (IRB)/Ethics Committee (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 St. Jude Medical 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

All subjects will be implanted with a regulatory approved (CE marked and Market released) St. Jude Medical CRT device compatible with MultiPoint™ Pacing feature [redacted] or any other St Jude Medical (SJM) model compatible with the MPP algorithm) and St. Jude Medical quadripolar left ventricular lead [redacted]

During the follow-ups, implanted devices will be checked with [redacted] programmer.

Any commercially available and regulatory approved right atrial and right ventricular leads can be used in this investigation.

All of the devices used in this investigation, have received appropriate regulatory certification and are market released.

[redacted]

[redacted]

[redacted]

[redacted]

5.2 Device Handling & Storage

St. Jude Medical requires all investigational products be stored, according to the labeling, in a secure area to prevent unauthorized access or use. This will prevent non-investigational use of products that are provided for this study.

[redacted]

6.0 PROCEDURES

6.1 Study Flow Chart

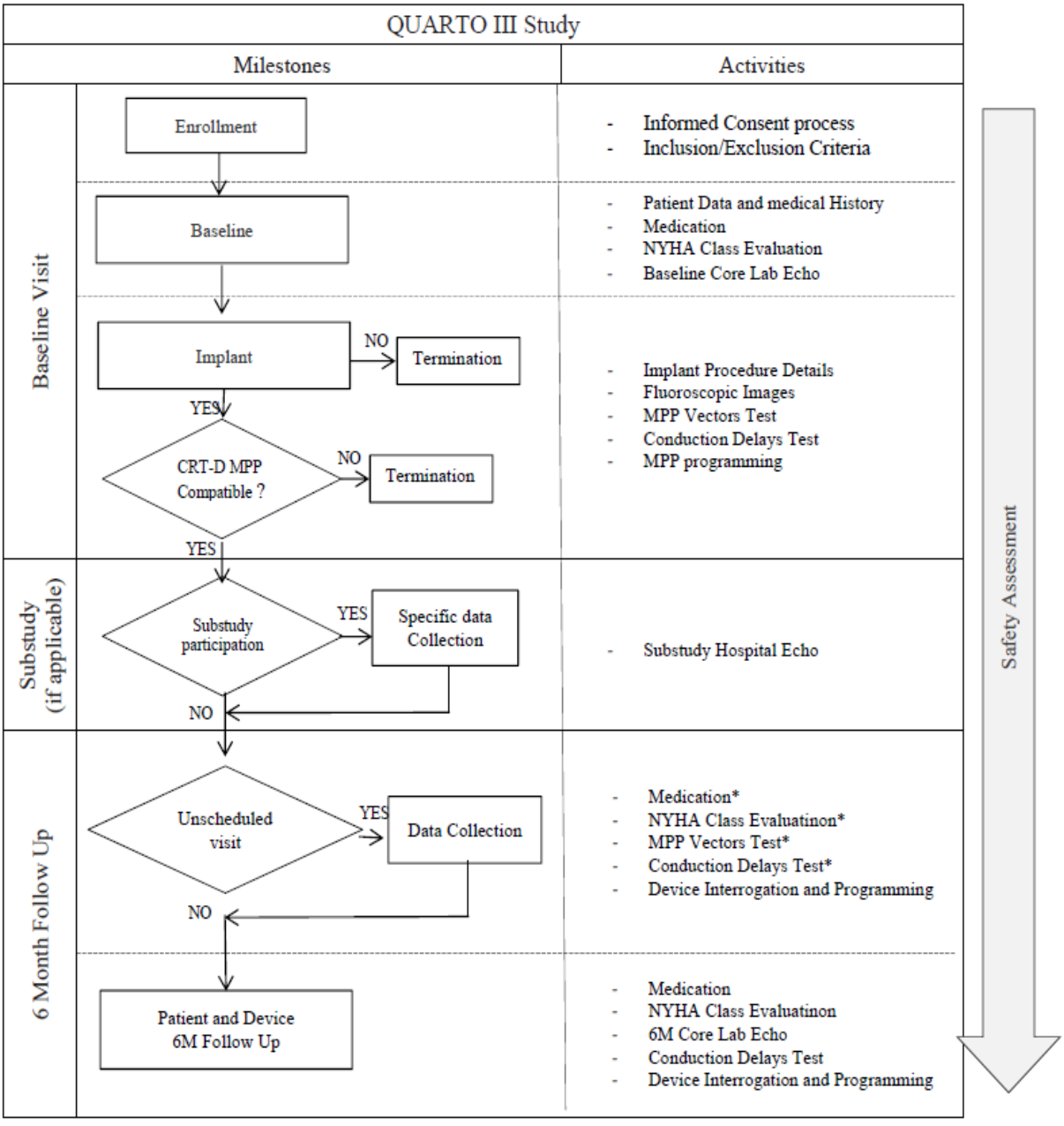


Figure 1: Flow Chart

6.2 Procedures

The clinical study will be conducted in accordance with the CIP. All parties participating in the conduct of the clinical study will be qualified by education, training, or experience to perform their tasks and this training will be documented appropriately. The clinical study will not commence until St. Jude Medical receives written approval from the IRB/EC and relevant regulatory authorities and all required documents have been collected from the site(s).
All the mandatory procedures are listed in the following tables and detailed in the next pages:

Visit / Study Activity	Enrollment Visit	Baseline visit	Implant Visit (within 7 days)	Substudy visit* (within 7 days of implant)	Unscheduled FU	6M Follow Up (+/- 30 days)
Patient Informed Consent Process	X					
Inc/Exc criteria	X					
Patient Data and Medical History		X				
Current Cardiac Medication		X			(X)	X
NYHA Class Evaluation		X			(X)	X
Core Lab Echocardiography		X			(X)	X
Implant Procedure Details			X			
MPP Vector Test			X		(X)	
Conduction Delays Test			X		(X)	X
Device Interrogation and Programming			X		(X)	X
MPP Programming			X		X	(X)
Fluoroscopy Images			X			
Substudy Inc/Exc criteria*				X		
Substudy Echocardiography*				X		
Adverse Event	(X)	(X)	(X)	(X)	(X)	(X)
Hospitalization	(X)	(X)	(X)	(X)	(X)	(X)
Protocol Deviation	(X)	(X)	(X)	(X)	(X)	(X)
Withdrawal	(X)	(X)	(X)	(X)	(X)	(X)
Death	(X)	(X)	(X)	(X)	(X)	(X)

*Only for selected Sites; (X) if applicable

Table 1: List of all study specific activities/procedures

The Case Report Forms used to complete all the information detailed above are summarized in the table below:

Visit / CRFs	Baseline Visit	Implant Visit	Substudy Visit* (within 7 days implant)	Unscheduled	6 Month (+/-30 days)
Enrollment Form	X	-	-	-	-
Baseline Form	X	-	-	-	-
Implant Form	-	X	-	-	-
Substudy Enrollment Form*	-	-	X	-	-
Substudy Echo Form*	-	-	X	-	-
Follow Up Form	-	-	-	(X)	X
Deviation Form	(X)	(X)	(X)	(X)	(X)
Adverse Event Form	(X)	(X)	(X)	(X)	(X)
Hospitalization Form	(X)	(X)	(X)	(X)	(X)
System Revision Form	(X)	(X)	(X)	(X)	(X)
Withdrawal Form	(X)	(X)	(X)	(X)	(X)
Death Form	(X)	(X)	(X)	(X)	(X)

*Only for selected sites; (X) if applicable

Table 2: Case Report Forms (CRF)

Informed Consent Procedure and Inclusion/Exclusion Criteria check:

Patient's eligibility criteria and Informed consent Procedure is performed before any study related activity.

Patient Data and Medical History:

Subject's demographic data will be collected at the Baseline Visit together with cardiomyopathy etiology, implant indication and co-morbidities.

Current Cardiac Medication

The current cardiac medications will be collected al Baseline, while during the Follow-up Visits only the changes will be documented.

NYHA Class Evaluation

The patient´s New York Heart Association class will be assessed at Baseline and during all Follow-up visits.

Implant Procedure Details

Implant Procedure details (standard CRT-D implant) will be collected at Implant visit.

Indicate model n°, serial n° and date of implant of entire implanted system (CRT-D device, Right Atrial (RA) lead, RV lead and LV lead).

Final positions of all the implanted leads must be specified: right atrium, right ventricle and left ventricle lead positions. Additionally the final position of the LV poles will be collected.

Fluoroscopy Images Collection (EDC upload)

As the lead placement is important to understanding the patient's response to CRT-D, two Fluoroscopy images are requested to be collected:

- LAO (Left Anterior Oblique, 45°±10°) (mandatory)
- RAO (Right Anterior Oblique, 45°±10°) (mandatory)
- AP (Anterior - Posterior) If available

The position of all leads must be clearly visible to allow matching with the venous anatomy. These anonymized images should be uploaded to the Electronic Data Capture (EDC) system .

MPP Vector Test

In order to allow future activation of MPP, specific LV pacing capture thresholds and Phrenic Nerve Stimulation (PNS) tests must be performed for the 4 cathodes during the implant.

The test is considered positive in case is possible to identify at least 2 vectors from different Groups (with different Cathodes) [redacted]

Conduction Delays Test

The conduction delays between right and left ventricle will be performed during Implant and at 6 Month follow up (with RV paced). [redacted] and will end in about one minute.

Device Interrogation and Programming

Device will be interrogated and all the diagnostics retrieved. Standard sensing, pacing and impedance measurements will be performed for all implanted leads at implant and each in-clinic follow-up.

The recommendation for the MPP programming in this study are (see Appendix E. Guidelines):

MPP feature: MPP feature will be TURNED ON in all patients with positive MPP Vector Test at implant. If the Investigator decides not to turn ON the MPP feature or there are not enough vectors available to activate this feature, the patient will be excluded from the study.

MPP Cathode Selection: The pacing configuration will be chosen by the investigator following one of the 2 different approaches:

- Electrical approach: choose the most electrically separated vectors based on the data provided [redacted]
- Anatomical approach: choose the most anatomically separated vectors based on the position of each pole, documented through fluoroscopic images.

In this study, the Electrical approach is recommended. According the results of the Conduction Delays Test (with RV Paced) LV1 should be the one with the shortest conduction time, and LV2 the one with the longest conduction time.

Pacing Vectors Selection: The anode of the pacing configuration will be chosen by the investigator based on the results of the capture threshold and PNS obtained in the MPP Vector Test.

MPP delays programming: In this study the following general MPP programming is recommended:

- MPP pacing sequence: LV first: LV1 $\xrightarrow{D1}$ LV2 $\xrightarrow{D2}$ RV
- Timing Delays: use the minimum delays of 5 ms between LV1-LV2 and LV2-RV.

[redacted]

Echocardiography (Core Lab)

Echocardiography images will be obtained according to the Echo Protocol at Baseline and 6 Month visit. They will be submitted to an independent Echo Core Lab for central evaluation and assessment.

The Baseline Echocardiography will be performed at any time after the patient signs the Patient Informed Consent, within 7 days before and 48 hours after the CRT-D implant procedure (with the CRT-D in No Pacing). The 6 Month Echocardiography will be performed during the 6 Month visit.

The Echocardiography must be recorded in DICOM format and sent/uploaded to the Echo Core Lab within 72 hours (3 working days). The Core Lab will analyze the Baseline and the 6 Month Echocardiography and provide the evaluation of the CRT response based on the LVESV reduction. In addition, the following data will be analyzed and measured by the Core Lab:

- LVEDD and LVESD
- LVEDV and LVESV
- LVEF

[redacted]

- Mitral Insufficiency
- Dyssynchrony measured by the strain rate (speckle tracking echocardiography) between the anteroseptal segment and the posterior wall (in patients which it is available)

Substudy Echocardiography

An additional Echocardiography will be obtained at the Substudy Visit according to the Echo Protocol. It will be recorded in DICOM and RAW file. This Echocardiography will not be sent/uploaded to the Echo Core Lab but evaluated locally at hospital. The following substudy data will be measured and collected at site:

- Left Ventricular Outflow Tract (LVOT) diameter (although only one measure is mandatory, 3 measurements are recommended)
- Cardiac Output (CO) by Velocity Time Integral (VTI) value under 5 different pacing methods:
  - No Pacing
  - MPP using Electrical approach: choose the most electrically separated vectors (LV1 and LV2) based on the data provided by t[redacted] and PNS obtained in the MPP Vector Test.
  - MPP using Anatomical approach: choose the most anatomically separated vectors (LV1 and LV2) based on the position of each pole (documented through fluoroscopic images) and the capture threshold and PNS obtained in the MPP Vector Test.
  - SPP: choose the vectors LV1 and LV2 of the approach (Electrical or Anatomical) with the best CO, and measure the data in:
    - SPP with LV1
    - SPP with LV2

6.3 Enrollment Visit

The Enrollment will be performed within 7 days before the Implant Procedure. The following enrollment activities are performed after the subject has been screened and must occur before any study procedure/visit.

- The principal or delegated study personnel are responsible for screening all potential subjects to determine subject eligibility for the study.
- If a patient meets all inclusion criteria and does not meet any of the exclusion criteria, he/she is eligible for the investigation.
- Inform the eligible patient verbally about the investigation and provide the information sheet and consent form to the patient.
- Provide ample time to the patient to read and understand the information sheet and consent form and to consider participation in the clinical investigation.
- Obtain the signature and date from the eligible patient on the Ethics Committee (EC) approved informed consent form.

- If an eligible patient does not sign and date the informed consent form, he cannot participate in the investigation. No further protocol required activities are performed.
- Obtain the signature and date from the principal or delegated investigator on the EC approved consent form.
- The subject is enrolled in the investigation when the patient signs the EC approved consent form.
- Provide one original signed version of the informed consent form to the subject (signed by both subject and investigator)
- File second original signed version of the informed consent form in the Investigator Site Binder (ISB).
- Record enrollment information (name of the study, date of consent and Inclusion/exclusion information) in the hospital records and complete and submit the Enrollment form in a timely manner (recommended within 5 days)
- Notification of enrollment to the sponsor will take place only when the sponsor receives the enrollment form

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

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

In case the subject was already consented to participate in the study, but does not meet inclusion/exclusion criteria, the following actions will be taken:

- Document enrollment information (name of the study, date of consent and inclusion/exclusion) in the hospital records; complete the Enrollment and Termination Forms. The forms must be authorized/approved by the principal or delegated investigator.
- Inform the subject about the Termination.
- Refer to Table 2: “Case Report Forms”.
- Complete study deviation for inclusion/exclusion not met.
- The Ethics Committee (EC) should be notify appropriately about any deviation with regards to obtaining the informed consent

6.4 Baseline Visit (within 7 days of Enrollment)

The clinical data collection of the Baseline Visit will be performed after patient signs the Patient Informed Consent and within 7 days after the Enrollment visit. The following information will be collected to describe patient’s clinical status:

- Patient Data and Medical History
- Current Cardiac Medication
- NYHA Class Evaluation

- Core Lab Echocardiography
- Adverse Events and/or Hospitalization and/or Death and/or Protocol Deviation notification (if applicable)

A Baseline Core Lab Echocardiography will be performed at any time after the patient signs the Patient Informed Consent, within 7 days before and 48 hours after the CRT-D implant procedure (with the CRT-D in No Pacing).

The center must record the Echocardiography in DICOM format and send/provide it to the Core Lab within 72 hours (3 working days). The Core Lab will analyze the Echocardiography received and provide the evaluation of the measurements to St Jude Medical.

6.5 Implant visit (within 7 days of Enrollment)

The implant procedure of a SJM MPP compatible CRT-D system will be implanted with standard procedure within 7 days after the Enrollment.

The Implant Procedures Details will be collected at the Implant section:

- System information, model number, serial number and date of implant of entire implanted system (device, RA lead, RV lead and LV lead)
- Leads position and LV lead poles position
- Adverse Events and/or Hospitalization and/or Death and/or Protocol Deviation notification (if applicable)
- Fluoroscopy Images collection (EDC upload)

The following device tests will be collected at the Implant section:

- MPP Vector Test
- Conduction Delays Test
- MPP programming (ON)
- Final MPP configurations and method followed to decide it (Electrical delay approach or Anatomical approach)

There are no specific procedures to be done for the substudy patients.

6.6 Substudy Visit (within 7 days of the Implant)

For the patients participating in the substudy a Hospital Echocardiography will be performed within 7 days of the Implant procedure. Only patients in sinus rhythm in the moment of the Echocardiography can participate in this substudy.

The substudy data detailed in Section 6.0 Hospital Echocardiography will be measured and collected at site. This Echocardiography will not be sent/uploaded to the Echo Core Lab

6.7 Six Month Follow-up visit (In Clinic, 180 days +/- 30 days from device implant)

The 6 Month Follow-up visit must be performed in-clinic within 180 +/- 30 days from the implant procedure. The purpose of the 6 Month Follow-Up visit is to check the patient's and CRT-D system's status as well as collect the necessary data to satisfy the study endpoints.

The following information will be collected:

- Current Cardiac Medication
- NYHA Class evaluation
- Echocardiography (Core Lab)
- Device interrogation and Programming
- Adverse Events and/or Hospitalization and/or Death and/or Protocol Deviation notification (if applicable)

The center must record the Echocardiography in DICOM format and send/provide it to the Echo Core Lab within 72 hours (3 working days). The Core Lab will analyze the Echocardiography received and provide the evaluation of the measurements to St Jude Medical

The Core Lab will be the responsible of classifying the patients as responders or non-responders according to the result of the analysis of the material provided.

At the 6 Month visit the MPP programming will be according investigator´s discretion.

There are no specific procedures to be done for the substudy patients.

6.8 Unscheduled Visits (In Clinic)

If there is any change in the MPP programming an Unscheduled Follow-up Form should be completed. No specific activity is forecasted for this visit, however the center should document all of the following whenever applicable:

- Any changes in Current Cardiac Medication
- Any changes in NYHA Class
- MPP Vector Test
- Conduction Delays Test (if available)
- Any changes made to the MPP programming
- Any Adverse Events and/or Hospitalization and/or Death and/or Protocol Deviation notification

6.9 Description of activities performed by Sponsor Representatives

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

Sponsor personnel may:

- Provide technical support to the Investigators during device tests and programming
- Review medical charts to ensure accurate reporting of data in the electronic CRF (eCRF)

Sponsor personnel will not:

- Perform the informed consent process
- Practice medicine
- Provide medical diagnosis or treatment to subjects
- Discuss a subject's condition or treatment with a subject without the approval and presence of a health care practitioner
- Independently collect clinical investigational data
- Complete or sign study's Case report Forms

6.10 Subject study completion

When the subject's participation in the clinical study has been completed which will be latest after the 6 Months FU visit the subject will return to the medical care as per physician's recommendation.

6.11 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.

It is planned to enroll approximately [redacted] patients in the study from around [redacted] centers. The inclusion will be competitive and there is not any enrollment target per center.
It will be assured at the time of enrollment that the patients are able to follow the study schedule. Sponsor personnel will support the investigators and will ensure the completion of the Follow Ups. It is expected anyway a percentage of patients who will not complete the study procedures. This figure has been taken into account for the sample size calculation.

[redacted]

6.12 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

[redacted]

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.

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. 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 Termination 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 CLINICAL INVESTIGATION PLAN (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, ISO14155:2011 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 St. Jude Medical.

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

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

7.2 Adherence to the Clinical Investigation Plan

A deviation is defined as an event where the clinical investigator, site personnel, sponsor or sponsor representative did not conduct the clinical study according to the Clinical Investigational Plan, 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 Protocol Deviation Case Report Form. 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. Under emergency circumstances, deviations from the CIP to protect the rights, safety and well-being of human subjects may proceed without prior approval of the sponsor and the EC. Such deviations shall be documented and reported to the sponsor and the EC as soon as possible, but no later than 5 working days

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.

Investigators or the designee must notify St. Jude Medical of any protocol deviation as soon as possible and complete the Protocol Deviation CRF. All deviations must be reported to appropriate regulatory authorities according to the local regulation (as appropriate).

7.3 Repeated and serious non-compliance

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

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

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

8.0 ADVERSE EVENT, ADVERSE DEVICE EFFECT

8.1 Definitions

8.1.1 Medical device

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

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

8.1.2 Adverse Event (AE)

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

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

8.1.3 Serious Adverse Event (SAE)

An adverse event that led to:

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

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

8.1.4 Adverse Device Effect (ADE)

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

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

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

8.1.5 Serious Adverse Device Effect (SADE)

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

8.1.5.1 Unanticipated Serious Adverse Device Effect (USADE)

A serious adverse device effect which by its nature, incidence, severity or outcome has not been identified in the current version of the risk analysis report.

8.1.5.2 Anticipated Serious Adverse Device Effect (ASADE)

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

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

Safety surveillance within this study and the safety reporting both performed by the investigator, starts as soon as the subject is enrolled in this study (date of signature of the informed consent). The 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.

All adverse event data including deaths will be collected throughout the clinical study and will be reported to the Sponsor through the EDC system. The Investigator will record all adverse events and device deficiencies on the appropriate case report forms.

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

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

Reportable events to sponsor are considered:

- All Serious Adverse Events including Serious Adverse Device Effect and all Adverse Device Effects are to be documented and reported to the sponsor maximum 24 hours after becoming aware of the event
- Non-Serious Adverse Events documentation and reporting are limited to cardiovascular events. Non-serious events are to be reported as soon as possible but not later than 2 weeks after becoming aware

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

In case of EDC failure, notify Sponsor via AdverseEvent@sjm.com or via Fax (please refer to the Investigator Site Binder, section "Sponsor Contact Details" for further details about Fax numbers).

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.

All adverse events will be reported as per applicable regulatory requirements.

8.3 Subject Death

8.3.1 Procedure for recording and reporting subject death

All subject deaths are to be documented and reported to the sponsor within 24 hours after becoming aware of the event.

The timing of the Death will be classified as:

- Pre-procedure Death (before the Implant/procedure)
- Peri-Procedure Death (within <=30 days of the implant/procedure)
- Post-Procedure Death (within >30 days after implant/procedure)

Should death occur, the investigator is requested to record death information in the hospital records and immediately document the information on the Death form. By completing the form the sponsor will be notified.
In case of EDC failure, notify Sponsor via AdverseEvent@sjm.com or via Fax (please refer to the Investigator Site Binder, section "Sponsor Contact Details" for further details about Fax numbers).

Patient Death can be an outcome of a serious adverse event (SAE) or serious adverse device effect (SADE).

- Death is therefore related to an SAE/SADE: all efforts to obtain the SAE/SADE details should be made and the Adverse Event form must be completed
- The patient's death is an Early Conclusion of the subject's participation in the investigation. Therefore, the investigator is requested to complete the Termination form
- The investigator must notify the EC / IRB, if appropriate, in accordance with national and local laws and regulations

9.0 DATA MANAGEMENT

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

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

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

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.

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 (DMP) 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.

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 CRFs shall be validated by the principal investigator or delegated site personnel as specified on the Signature and Delegation Log. In case of modifications after the validation, the eCRFs should be re-approved.

10.0 MONITORING

It is the responsibility of St. Jude Medical as the sponsor of the study to ensure the study is conducted, recorded, and reported according to the approved protocol, subsequent amendment(s), applicable regulations, and guidance documents. Monitoring will be conducted according to the St. Jude Medical Clinical Monitoring standard operating procedure.

Prior to beginning the study, St. Jude Medical will contact the investigator or designee to discuss the study and data requirements. A St. Jude Medical monitor will periodically review the subject records and associated source documents.

The investigator shall make subject and study records available to the clinical monitor for 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.

11.0 REGULATORY INSPECTIONS

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

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

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

An investigator will permit authorized governmental agency employees to inspect and copy records that identify subjects, upon notice that governmental agency has reason to suspect that adequate informed consent was not obtained, or that reports required to be submitted by the investigator, to the Sponsor or 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

The primary endpoint analysis will be based on the intention-to-treat (ITT) principle including all protocol deviatons. Secondary per-protocol (PP) analysis excluding all major protocol deviators will also be conducted. If the results obtained from these analyses are different, an exploration of the data to search for the reason will be performed.
For the primary endpoint analysis, the following inequality hypothesis will be tested:

- H0: Proportion of responders at 6 months with the MPP feature activated at baseline [redacted]
- H1: Proportion of responders at 6 months with the MPP feature activated at baseline [redacted]

All results will be expressed in terms of [redacted]% corresponding confidence intervals and p-values. P-values less than [redacted]% will be considered significant.

12.2 Sample size

The sample size calculation is based on the primary endpoint, proportion of CRT responders at 6 months who have the MPP feature activated at baseline.

[redacted]

[redacted]

In order to detect t[redacted]difference between the two responder rates, a total of [redacted]patients need to have analyzable endpoint data at 6 months.
From clinical experience, it is assumed that some patients will drop out of the study ([redacted]during the [redacted]

12.3 Statistical hypotheses, method and analytical procedures for Sub-study endpoint

[redacted] The sub-study endpoint data will be reported using frequencies and percentages.

[redacted]

For this exploratory analysis, the following inequality hypothesis will be tested:

- H0: Proportion of patients who achieve a greater hemodynamic response, measured by Cardiac Output, with a MPP configuration within 7 days after implant ≤ [redacted]
- H1: Proportion of patients who achieve a greater hemodynamic response, measured by Cardiac Output, with a MPP configuration within 7 days after implant > [redacted]

P-values less than [redacted]will be considered significant. Corresponding [redacted] confidence interval will also be reported. [redacted]
have been co[redacted]

12.4 Pass/fail criteria to be applied to the results of the clinical study

Not applicable.

12.5 The provision for an interim analysis, when applicable

Not applicable.

12.6 Criteria for the termination of the clinical study on statistical grounds

Not applicable.

12.7 Procedures for reporting any deviation(s) from the original statistical plan

Any deviations from the Statistical analysis plan will be documented in a note to file

12.8 The specification of subgroups for analysis

Subgroup analysis will be performed for Ischemic and non-ischemic patients.

12.9 Procedures that take into account all the data

Primary endpoint analysis will take into account all available data.

12.10 The treatment of missing, unused or spurious data, including drop-outs and withdrawals

No imputation techniques will be used for missing data.

12.11 The exclusion of particular information for the testing of the hypothesis, if relevant, and

Not applicable.

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

There is no minimum or maximum for the number of patients to be enrolled for each center.

13.0 DOCUMENT RETENTION

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

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

All original subject files must be stored for the longest possible time permitted by the regulations at the hospital, research institute, or practice in question. If archiving can no longer be maintained at the site, the investigator will notify the sponsor.

All data and documents will be made available on request of the relevant authorities in case of an audit.

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

14.0 AMENDMENTS TO CLINICAL INVESTIGATIONAL PLAN

Study related documents such as, the 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 informed of the changes and a new consent be signed and dated by the investigator 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 OUTSOURCING OF DUTIES AND FUNCTIONS

The sponsor may transfer any or all of the duties and functions related to the clinical study, including monitoring, to an external organization (such as a Clinical Research Organization (CRO) or individual contractor), but the ultimate responsibility for the quality and integrity of the clinical study will reside with the sponsor. All requirements applying to the sponsor will also apply to the external organization inasmuch as this organization assumes the clinical study related duties and functions of the sponsor.

15.1 Echocardiography Core Lab

Service details are outlined in the Service Agreement, and can be provided upon request.

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
- Recommendation from Data Safety Monitoring Board (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 24 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 2013 (refer to Appendix C: Declaration of Helsinki)
- 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.

18.0 BIBLIOGRAPHY

[1] "Task Force for Diagnosis and Treatment of Acute and Chronic Heart Failure. ESC Guidlines for the Diagnosis and Treatment of Acute and Chronic Heart Failure 2012," *European Heart Journal. Doi: 10.1093/eurheartj/ehs104.*

[2] Dickstein K, Cohen-Soal A, Filippatos G, McMurray JJ, Ponikowski P, Poole-Wilson PA, Stromberg A, Van Veldhuisen DJ, Atar D, Hoes AW, Keren A, Mebazaa A, Nieminen M, Priori SG and Swedberg K, "ESC guidelines for the diagnosis and treatment of acute and chronic heart failure 2008: the Task Force for the diagnosis and treatment of acute and chronic heart failure 2008 of Europear Society of Cardilogy," *Developed in collaboration with the Heart Failure Association of the ESC (HFA) and endorsed by the European Society of Intensive Care Medicine (ESCIM). Eur J Heart Fail 2008; 10:933-989.*

[3] Davie AP, Francis CM, Caruana L, Sutherland GR and McMurray JJ, "Assessing diagnosis in heart failure: which features are any use?," *QJM 1997;90:335-339.*

[4] Mant J, Doust J, Roalfe A, Barton P, Cowie MR, Glasziou P, Mant D, McManus RJ, Holder R, Deeks J, Fletcher K, Qume M, Sohanpal S, Sanders S and Hobbs FD, "Systematic review and individual patient data meta-analysis of diagnosis of heart failure with modelling of implications of different diagnostic strategies in primary care," *Health Technol Assess 2009;13:1-207,iii.*

[5] Oudejans I, Mosterd A, Bloemen JA, Valk MJ, van Velzen E, Wielders JP, Zuithoff NP, Rutten FH and Hoes AW, "Clinical evaluation of geriatric outpatients with suspected heart failure: value of symptoms, signs and additional test," *Eur J Heart Fail 201 (1) 1;13:518-527.*

[6] Fonseca C, "Diagnosis of heart failure in primary care," *Heart Fail Rev 2006:11:95-107.*

[7] Kelder JC, Cramer MJ, van Wijngaarden J, van Tooren R, Mosterd A, Moons KG, Lammers JW, Cowie MR, Grobbee DE and Hoes AW, "The diagnostic value of physical examination and additional testing in primary care patients with suspected heart failure," *Circulation 2011;124:2865-2873.*

[8] Farwell D, Patel NR, Hall A, Ralph S and Sulke AN, "How many people with heart failure are appropriate for biventricular resynchronization?," *Eur Heart J 2000;21(15):1246-50.*

[9] Hare JM, "Cardiac-resynchronization therapy for heart failure," *N Engl J Med 2002;346(24):1902-5.*

[10] Liu P, Arnold M, Belenkie I and et al, "The 2001 Canadian Cardiovascular Society consensus guideline update for the management and prevention of heart failure," *Can J Cardiol 2001:17Suppl E:5E-25E.*

[11] Liu P, Arnold JM, Belenkie I and et al, "The 2002/3 Canadian Cardiovascular Society consensus guideline update for the diagnosis an management of heart failure," *Can J Cardiol 2003;19(4):347-56.*

[12] Tsuyuki RT, Shibata MC, Nilsson C and Hervas-Malo M, "Contemporary burden of illness of congestive heart failure in Canada," *Can J Cardiol 2003;19(4):436-8.*

[13] Lloyd-Jones D, Adams RJ, Brown TM, Carnethon M, Dai S, De Simone G and et al, "Executive summary:Heart disease and stroke statistics 2010 update: A report from the American Heart Association," *Circulation 2010; 121:948-54.*

[14] Roger VL, Go AS, Lloyd-Jones DM, Adams RJ, Berry JD, Brown TM, Carnethon MR, Dai S, de Simone G, Ford ES, Fox CS, Fullerton HJ, Gillespie C, Greenlund KJ, Hailpern SM, Heit JA, Ho PM, Howard VJ, Kissela BM, Kittner SJ, Lackland DT, Lichtman JH, Lisabeth LD, Makuc DM, Marcus GM, Marelli A, Matchar DB, McDermott MM, Meigs JB, Moy CS, Mozaffarian D, Mussolino ME, Nichol G, Paynter NP, Rosamond WD, Sorlie PD, Stafford RS, Turan TN, Turner MB, Wong ND and Wylie-Rosett J, "Heart disease and stroke statistics 2011 update: A report from the american heart association," *Circulation 2011; 123;e18-e209.*

[15] Abraham WT, Fisher WG, Smith AL and et al, "Cardiac resynchronization in chronic heart failure," *N Engl J Med 2002;346(24):1845-53.*

[16] Auricchio A, Ding J, Spinelli JC and et al, "Cardiac resynchronization therapy restores optimal atrioventricular

mechanical timing in heart failure patients with ventricular conduction delay," *J Am Coll Cardiol 2002; 39(7):1163-9.*

[17] Stellbrink C, Auricchio A, Butter C and et al, "Pacing therapies in congestive heart failure II study," *Am J Cardiol 2000;86(9Suppl 1):K138-K43.*

[18] Stellbrink C, Breithardt OA, Franke A and et al, "Impact of cardiac resynchronization therapy using hemodynamically optimized pacing on left ventricular remodeling in patients with congestive heart failure and ventricular conduction disturbances (1)," *J Am Coll Cardiol 2001;38(7):1957-65.*

[19] St John Sutton MG, Plappert T, Abraham WT and et al, "Effect of cardiac resynchronization therapy on left ventricular size and function in chronic heart failure," *Circulation 2003;107(15):1985-90.*

[20] Strickberger SA, Conti J, Daoud EG and et al, "Patient selection for cardiac resynchronization therapy:from the Council on Clinical Cardiology Subcommittee on Electrocardiography and Arrhythmias and the Quality of Care and Outcomes Research Interdisciplinary Working Group,in collaboration with the HRS," *Circulation 2005;111(16):2146-50.*

[21] Abraham WT, Fisher WG, Smith AL, Delurgio DB, Leon AR, Loh E, Kocovic DZ, Packer M, Clavell AL, Hayes DL, Ellestad M, Trupp RJ, Underwood J, Pickering F, Truex C, McAtee P and Messenger J, "Cardiac resynchronization in chronic heart failure," *N Engl J Med 2002; 346:1845-1853.*

[22] Cleland JG, Daubert JC, Erdmann E, Freemantle N, Gras D, Kappenberger L and Tavazzi L, "The effect of cardiac resynchronization on morbidity and mortality in heart failure," *N Engl J Med 2005;352:1539-1549.*

[23] Salukhe TV, Francis DP and Sutton R, "Comparison of medical therapy, pacing and defibrillation in heart failure (companion)trial terminated early;combined biventricular pacemaker-defibrillators reduce all-cause mortality and hospitalization," *International journal of cardiology 2003;87:119-120.*

[24] Pires LA, Abraham WT, Young JB and Johnson KM, "Clinical predictors and timing of new york heart association class improvement with cardiac resynchronization therapy in patients with advanced chronic heart failure. Results from the multicenter insync randomized clinical evaluation (miracle) and....," *Am Heart J 2006;151:837-843.*

[25] Birnie DH and Tang AS, "The problem of non-response to cardiac resynchronization therapy," *Curr Opin Cardiol 2006;21:20-26.*

[26] J. Toquero Ramos, L. Ruiz Bautista, P. Beltrán Correas, J. M. Fernández Villanueva, V. Castro Urda, A. Restrepo Cordoba, J. Goirigolzarri Artaza , I. Fernández Lozano, A. Ruiz Jurado and S. Alyoun Alonso, "Estimulación Multipunto mediante Captura Anódica VI a través de un Electrodo Cuadripolar: Evaluacion Hemodinámica no Invasiva," *Rev Esp Cardiol. ,* vol. 67 Supl1:405, no. 6004-65, 2014.

[27] F. J. Cabrera-Bueno, J. Olagüe Ros, I. Fernández-Lozano, J. J. García Guerrero , J. Fernández de la Concha, A. Hernández-Madrid, J. M. Tolosana Viu, A. Barrera Cordero , J. Osca Asensi, V. Moñivas Palomero, A. Ruiz Jurado, E. Llorente Hernangómez and J. Alzueta Rodríguez, "Improvement in Hemodynamic Response Using a New Quadripolar LV Lead," *Europace,* vol. 14 Suppl.1 June 2012, no. Abstract 176P-25, p. i60, 2012.

[28] Pappone C. et al., "Multipoint Left Ventricular Pacing in a Single Coronary Sinus Branch Improves Mid-Term Echocardiography and Clinical Response to Cardiac Resynchronization," *Journal of Cardiovascular Electrophysiology. 2014 Aug 11.Doi:10.1111/jce.12513.*

[29] Gutleben et al, "Multisite Left Ventricular Pacing is Safe and Improves Cardiac Hemodynamic in Heart Failure Patients-Results from a 1 month Follow-up Study," *abstract HRS 2012.*

[30] Papone C., et al, "Improvement in 3-month echocardiographic response with multisite left ventricular pacing in cardiac resynchronization therapy patients," *HRS 2013 Poster session PO02. May 9,2013.*

[31] Thibault et al, "Multisite Pacing with a Quadripolar Left Ventricular Lead Improves Acute Hemodynamics," *Abstract HRS 2011.*

[32] Papone C., et al, "Multisite left ventricular pacing in a single coronary sinus branch improves systolic and diastolic acute hemodynamic response assessed with pressure-volume loops," *Abstract HRS 2013.*

[33] Papone C., et al, "Left ventricular pacing from a site of late electrical activation improves acute hemodynamics in CRT patients implanted with a quadripolar left ventricular lead," *Abstract HRS 2013.*

[34] Thibault B, Dubuc M, Khairy P, Guerra PG, Macle L, Rivard L, Roy D, Talajic M, Karst E, Ryu K, Paiement P and

Farazi TG, "Acute haemodynamic comparison of multisite and biventricular pacing with a quadripolar left ventricular lead," *Europace. 2013 Jul;15(7):984-91.*

[35] Rinaldi et al, "Acute hemodynamic benefits of multisite left ventricular pacing in CRT recipients," *Abstract ACC 2012.*

[36] Rinaldi et al, "Multisite left ventricular pacing improves acute mechanical dyssynchrony in heart failure patients," *Abstract ACC 2012.*

APPENDIX A: ABBREVIATIONS

Select or add abbreviations used

Abbreviation	Term
ADE	Adverse Device Effect
AE	Adverse Event
AF	Atrial Fibrillation
ASADE	Anticipated Serious Adverse Device Effect
AV	Atrioventricular
BiV	Biventricular
CABG	Coronary Artery Bypass Graft
CO	Cardiac Output
CIP	Clinical Investigational Plan
CRF	Case Report Form
CRT-D	Cardiac Resynchronization Therapy- Defibrillator
DMP	Data Management Plan
EC	Ethics Committee
Echo	Echocardiography
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
EF	Ejection Fraction
HF	Heart Failure
ICD	Implantable Cardioverter Defibrillator
IRB	Institutional Review Board
ISO	International Organization for Standardization
LV	Left Ventricle
LVEDD	Left Ventricle End Diastolic Diameter
LVEDV	Left Ventricle End Diastolic Volume
LVEF	Left Ventricle Ejection Fraction
LVESD	Left Ventricle End Systolic Diameter
LVESV	Left Ventricle End Systolic Volume
LVOT	Left Ventricle Outflow Tract
MPP	MultiPoint™ Pacing
NYHA	New York Heart Association
PCS	Patient Care System
PI	Principal Investigator
PM	Pacemaker
PNS	Phrenic Nerve Stimulation
PTCA	Percutaneous Transluminal Coronary Angioplasty
RA	Right Auricle
RV	Right Ventricle
SADE	Serious Adverse Device Effect
SAE	Serious Adverse Event

SPP	SinglePoint Pacing
SC	Steering Committee
SJM	St. Jude Medical
USADE	Unanticipated Serious Adverse Device Effect
VTI	Velocity Time Integral
WMA	World Medical Association

APPENDIX B: CIP REVISION HISTORY

[redacted]

[redacted]

APPENDIX C: DECLARATION OF HELSINKI

Adopted by the 18th WMA General Assembly, Helsinki, Finland, June 1964 and amended by the:

29th WMA General Assembly, Tokyo, Japan, October 1975 35th WMA General Assembly, Venice, Italy, October 1983

41st WMA General Assembly, Hong Kong, September 1989

48th WMA General Assembly, Somerset West, Republic of South Africa, October 1996 52nd WMA General Assembly, Edinburgh, Scotland, October 2000

53rd WMA General Assembly, Washington DC, USA, October 2002 (Note of Clarification added)

55th WMA General Assembly, Tokyo, Japan, October 2004 (Note of Clarification added) 59th WMA General Assembly, Seoul, Republic of Korea, October 2008

64th WMA General Assembly, Fortaleza, Brazil, October 2013

Preamble

- The World Medical Association (WMA) has developed the Declaration of Helsinki as a statement of ethical principles for medical research involving human subjects, including research on identifiable human material and data.
  The Declaration is intended to be read as a whole and each of its constituent paragraphs should be applied with consideration of all other relevant paragraphs.
- Consistent with the mandate of the WMA, the Declaration is addressed primarily to physicians. The WMA encourages others who are involved in medical research involving human subjects to adopt these principles.

General Principles

- The Declaration of Geneva of the WMA binds the physician with the words, “The health of my patient will be my first consideration,” and the International Code of Medical Ethics declares that, “A physician shall act in the patient's best interest when providing medical care.”
- It is the duty of the physician to promote and safeguard the health, well-being and rights of patients, including those who are involved in medical research. The physician's knowledge and conscience are dedicated to the fulfilment of this duty.
- Medical progress is based on research that ultimately must include studies involving human subjects.
- The primary purpose of medical research involving human subjects is to understand the causes, development and effects of diseases and improve preventive, diagnostic and therapeutic interventions (methods, procedures and treatments). Even the best proven interventions must be evaluated continually through research for their safety, effectiveness, efficiency, accessibility and quality.
- Medical research is subject to ethical standards that promote and ensure respect for all human subjects and protect their health and rights.
- While the primary purpose of medical research is to generate new knowledge, this goal can

never take precedence over the rights and interests of individual research subjects.

- It is the duty of physicians who are involved in medical research to protect the life, health, dignity, integrity, right to self-determination, privacy, and confidentiality of personal information of research subjects. The responsibility for the protection of research subjects must always rest with the physician or other health care professionals and never with the research subjects, even though they have given consent.
- Physicians must consider the ethical, legal and regulatory norms and standards for research involving human subjects in their own countries as well as applicable international norms and standards. No national or international ethical, legal or regulatory requirement should reduce or eliminate any of the protections for research subjects set forth in this Declaration.
- Medical research should be conducted in a manner that minimizes possible harm to the environment.
- Medical research involving human subjects must be conducted only by individuals with the appropriate ethics and scientific education, training and qualifications. Research on patients or healthy volunteers requires the supervision of a competent and appropriately qualified physician or other health care professional.
- Groups that are underrepresented in medical research should be provided appropriate access to participation in research.
- Physicians who combine medical research with medical care should involve their patients in research only to the extent that this is justified by its potential preventive, diagnostic or therapeutic value and if the physician has good reason to believe that participation in the research study will not adversely affect the health of the patients who serve as research subjects.
- Appropriate compensation and treatment for subjects who are harmed as a result of participating in research must be ensured.

Risks, Burdens and Benefits

- In medical practice and in medical research, most interventions involve risks and burdens.
  Medical research involving human subjects may only be conducted if the importance of the objective outweighs the risks and burdens to the research subjects.
- All medical research involving human subjects must be preceded by careful assessment of predictable risks and burdens to the individuals and groups involved in the research in comparison with foreseeable benefits to them and to other individuals or groups affected by the condition under investigation.
  Measures to minimise the risks must be implemented. The risks must be continuously monitored, assessed and documented by the researcher.
- Physicians may not be involved in a research study involving human subjects unless they are confident that the risks have been adequately assessed and can be satisfactorily managed.
  When the risks are found to outweigh the potential benefits or when there is conclusive proof of definitive outcomes, physicians must assess whether to continue, modify or immediately stop the study.

Vulnerable Groups and Individuals

- Some groups and individuals are particularly vulnerable and may have an increased likelihood of being wronged or of incurring additional harm.
  All vulnerable groups and individuals should receive specifically considered protection.
- Medical research with a vulnerable group is only justified if the research is responsive to the health needs or priorities of this group and the research cannot be carried out in a non-vulnerable group. In addition, this group should stand to benefit from the knowledge, practices or interventions that result from the research.

Scientific Requirements and Research Protocols

- Medical research involving human subjects must conform to generally accepted scientific principles, be based on a thorough knowledge of the scientific literature, other relevant sources of information, and adequate laboratory and, as appropriate, animal experimentation. The welfare of animals used for research must be respected.
- The design and performance of each research study involving human subjects must be clearly described and justified in a research protocol.
  The protocol should contain a statement of the ethical considerations involved and should indicate how the principles in this Declaration have been addressed. The protocol should include information regarding funding, sponsors, institutional affiliations, potential conflicts of interest, incentives for subjects and information regarding provisions for treating and/or compensating subjects who are harmed as a consequence of participation in the research study.
  In clinical trials, the protocol must also describe appropriate arrangements for post- trial provisions.

Research Ethics Committees

- The research protocol must be submitted for consideration, comment, guidance and approval to the concerned research ethics committee before the study begins. This committee must be transparent in its functioning, must be independent of the researcher, the sponsor and any other undue influence and must be duly qualified. It must take into consideration the laws and regulations of the country or countries in which the research is to be performed as well as applicable international norms and standards but these must not be allowed to reduce or eliminate any of the protections for research subjects set forth in this Declaration.
  The committee must have the right to monitor ongoing studies. The researcher must provide monitoring information to the committee, especially information about any serious adverse events. No amendment to the protocol may be made without consideration and approval by the committee. After the end of the study, the researchers must submit a final report to the committee containing a summary of the study's findings and conclusions.

Privacy and Confidentiality

- Every precaution must be taken to protect the privacy of research subjects and the confidentiality of their personal information.

Informed Consent

- Participation by individuals capable of giving informed consent as subjects in medical research must be voluntary. Although it may be appropriate to consult family members or community leaders, no individual capable of giving informed consent may be enrolled in a research study unless he or she freely agrees.
- In medical research involving human subjects capable of giving informed consent, each potential subject must be adequately informed of the aims, methods, sources of funding, any possible conflicts of interest, institutional affiliations of the researcher, the anticipated benefits and potential risks of the study and the discomfort it may entail, post-study provisions and any other relevant aspects of the study. The potential subject must be informed of the right to refuse to participate in the study or to withdraw consent to participate at any time without reprisal. Special attention should be given to the specific information needs of individual potential subjects as well as to the methods used to deliver the information.
  After ensuring that the potential subject has understood the information, the physician or another appropriately qualified individual must then seek the potential subject's freely-given informed consent, preferably in writing. If the consent cannot be expressed in writing, the non-written consent must be formally documented and witnessed.
  All medical research subjects should be given the option of being informed about the general outcome and results of the study.
- When seeking informed consent for participation in a research study the physician must be particularly cautious if the potential subject is in a dependent relationship with the physician or may consent under duress. In such situations the informed consent must be sought by an appropriately qualified individual who is completely independent of this relationship.
- For a potential research subject who is incapable of giving informed consent, the physician must seek informed consent from the legally authorised representative. These individuals must not be included in a research study that has no likelihood of benefit for them unless it is intended to promote the health of the group represented by the potential subject, the research cannot instead be performed with persons capable of providing informed consent, and the research entails only minimal risk and minimal burden.
- When a potential research subject who is deemed incapable of giving informed consent is able to give assent to decisions about participation in research, the physician must seek that assent in addition to the consent of the legally authorized representative. The potential subject's dissent should be respected.
- Research involving subjects who are physically or mentally incapable of giving consent, for example, unconscious patients, may be done only if the physical or mental condition that prevents giving informed consent is a necessary characteristic of the research group. In such circumstances the physician must seek informed consent from the legally authorised representative. If no such representative is available and if the research cannot be delayed, the study may proceed without informed consent provided that the specific reasons for involving subjects with a condition that renders them unable to give informed consent have been stated in the research protocol and the study has been approved by a research ethics committee. Consent to remain in the research must be obtained as soon as possible from the subject or a legally authorised representative.
- The physician must fully inform the patient which aspects of their care are related to the

research. The refusal of a patient to participate in a study or the patient's decision to withdraw from the study must never adversely affect the patient-physician relationship.

- For medical research using identifiable human material or data, such as research on material or data contained in biobanks or similar repositories, physicians must seek informed consent for its collection, storage and/or reuse. There may be exceptional situations where consent would be impossible or impracticable to obtain for such research. In such situations the research may be done only after consideration and approval of a research ethics committee.

Use of Placebo

- The benefits, risks, burdens and effectiveness of a new intervention must be tested against those of the best proven intervention(s), except in the following circumstances:
  Where no proven intervention exists, the use of placebo, or no intervention, is acceptable; or
  Where for compelling and scientifically sound methodological reasons the use of any intervention less effective than the best proven one, the use of placebo, or no intervention is necessary to determine the efficacy or safety of an intervention
  and the patients who receive any intervention less effective than the best proven one, placebo, or no intervention will not be subject to additional risks of serious or irreversible harm as a result of not receiving the best proven intervention.

  Extreme care must be taken to avoid abuse of this option.

Post-Trial Provisions

- In advance of a clinical trial, sponsors, researchers and host country governments should make provisions for post-trial access for all participants who still need an intervention identified as beneficial in the trial. This information must also be disclosed to participants during the informed consent process.

Research Registration and Publication and Dissemination of Results

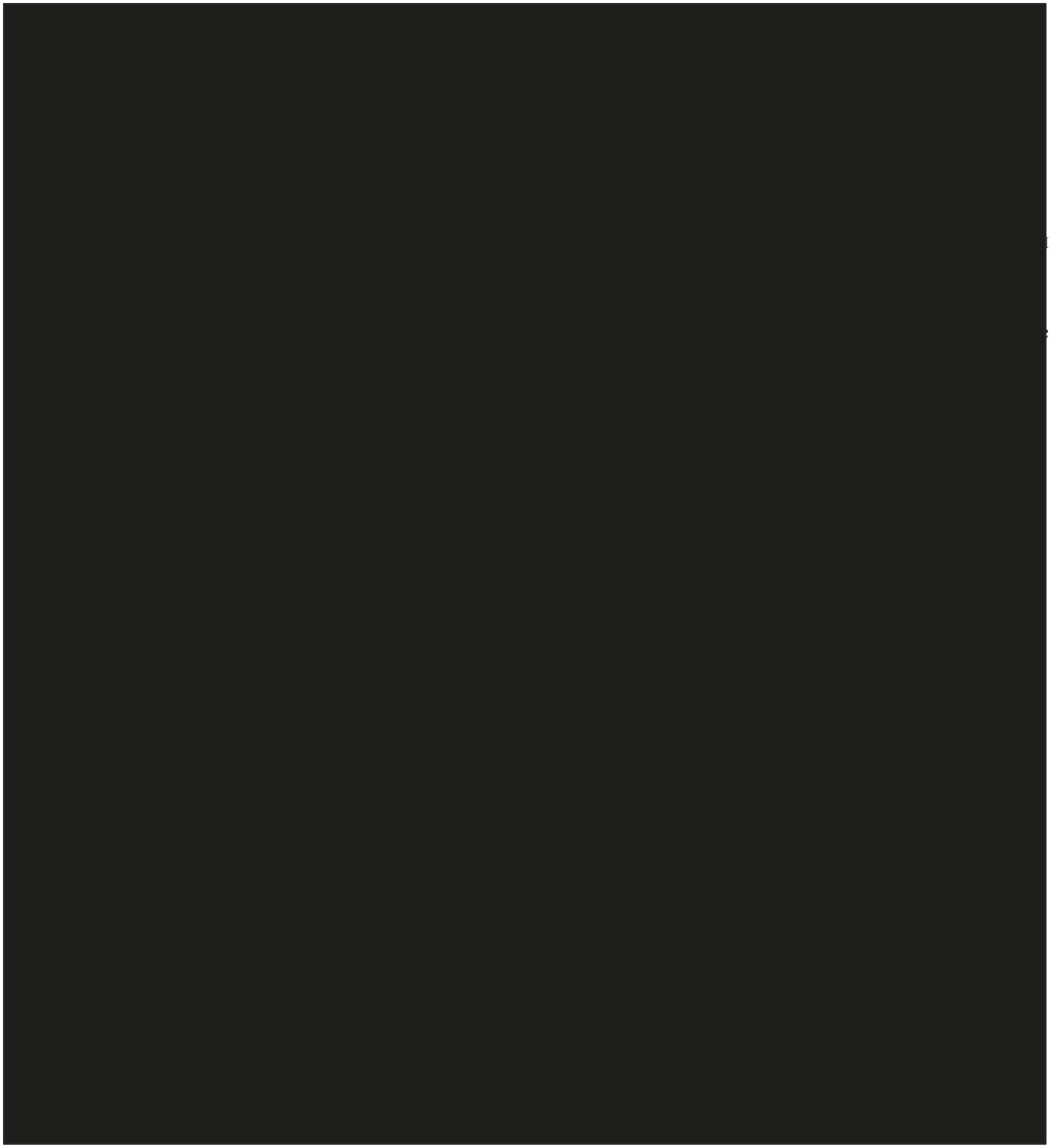
- Every research study involving human subjects must be registered in a publicly accessible database before recruitment of the first subject.
- Researchers, authors, sponsors, editors and publishers all have ethical obligations with regard to the publication and dissemination of the results of research. Researchers have a duty to make publicly available the results of their research on human subjects and are accountable for the completeness and accuracy of their reports. All parties should adhere to accepted guidelines for ethical reporting. Negative and inconclusive as well as positive results must be published or otherwise made publicly available. Sources of funding, institutional affiliations and conflicts of interest must be declared in the publication. Reports of research not in accordance with the principles of this Declaration should not be accepted for publication.

Unproven Interventions in Clinical Practice

- In the treatment of an individual patient, where proven interventions do not exist or other known interventions have been ineffective, the physician, after seeking expert advice, with informed consent from the patient or a legally authorised representative, may use an unproven

intervention if in the physician's judgement it offers hope of saving life, re-establishing health or alleviating suffering. This intervention should subsequently be made the object of research, designed to evaluate its safety and efficacy. In all cases, new information must be recorded and, where appropriate, made publicly available.

APPENDIX D: PROGRAMMING GUIDELINES



[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

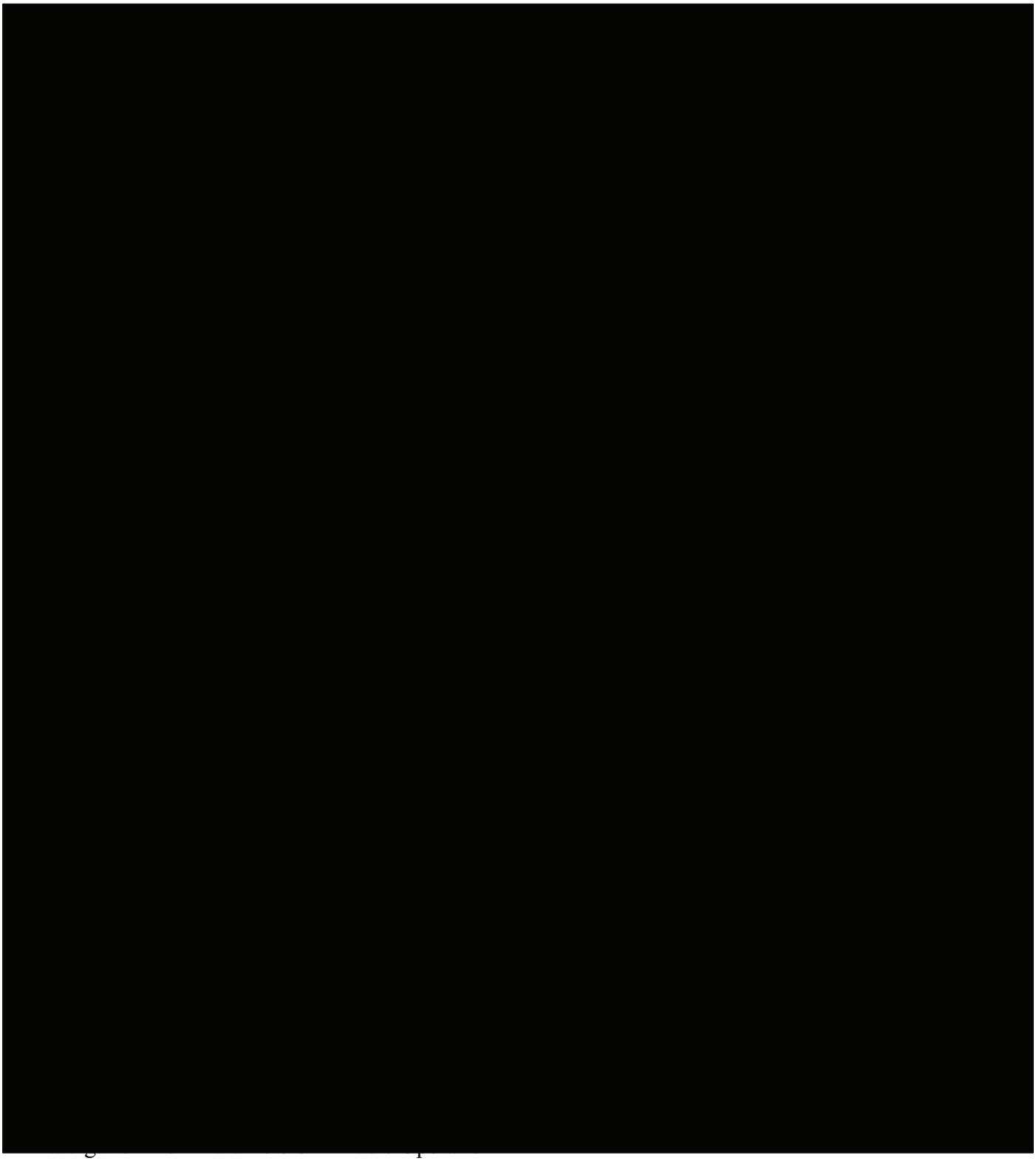
[redacted]

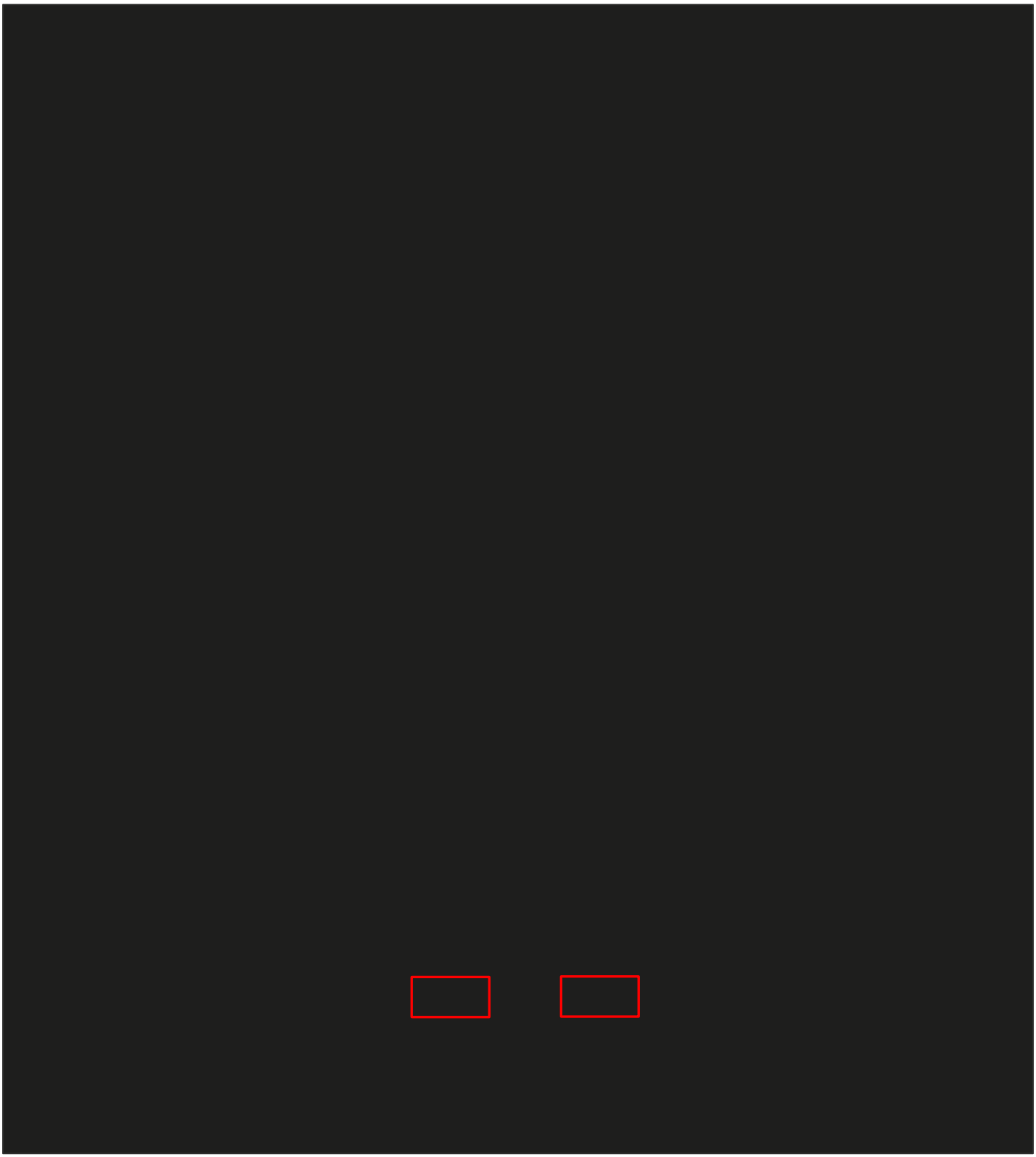
[redacted]

[redacted]

[redacted]

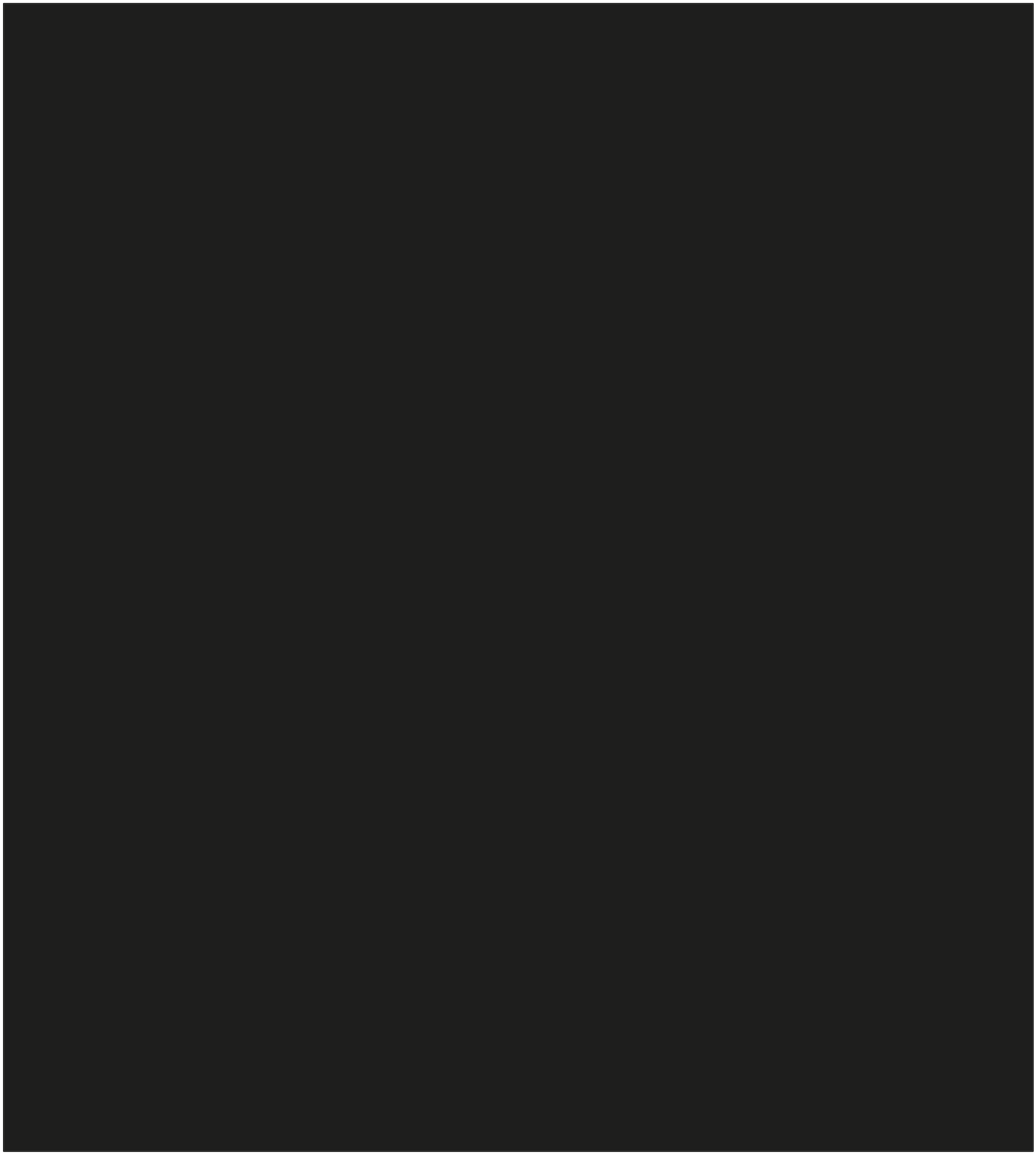
[redacted]





[redacted]

[redacted]



APPENDIX E: DATA COLLECTION METHOD

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

study.

[redacted]

[redacted]

[redacted]

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: SAMPLE INFORMED CONSENT

APPENDIX H: CASE REPORT FORMS