MORE-CRT MPP

"MOre REsponse on Cardiac Resynchronization Therapy (CRT) with MultiPoint Pacing (MPP)"

Clinical Investigation Plan (CIP)

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Project Version : [redacted]
Version Date : [redacted]

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Clinical Investigation Plan (CIP)

Sponsor St. Jude Medical
[redacted]

VP Clinical Studies [redacted]
Signature

Date _____

Clinical Coordinating [redacted]
Investigator

Signature

Date [redacted]

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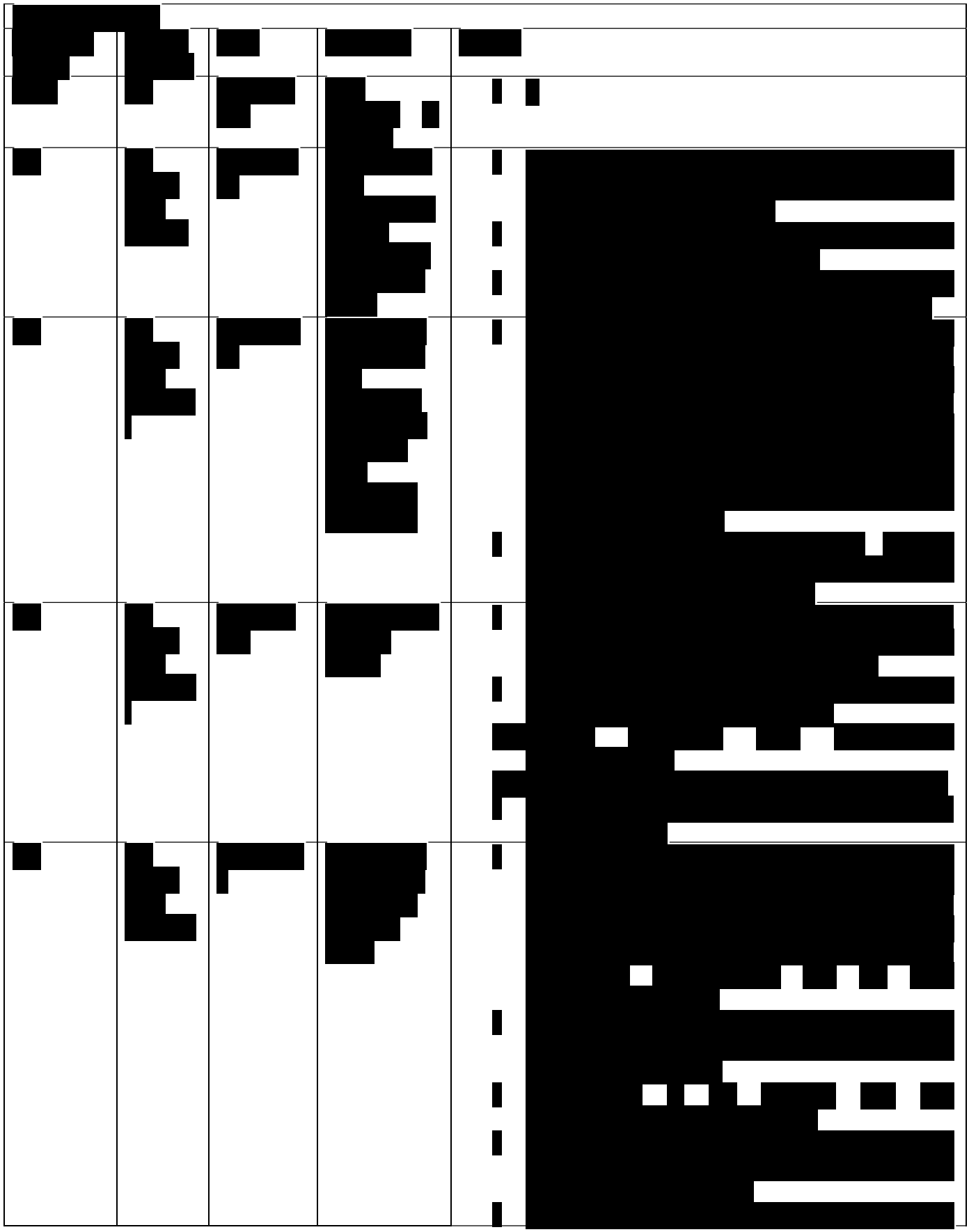
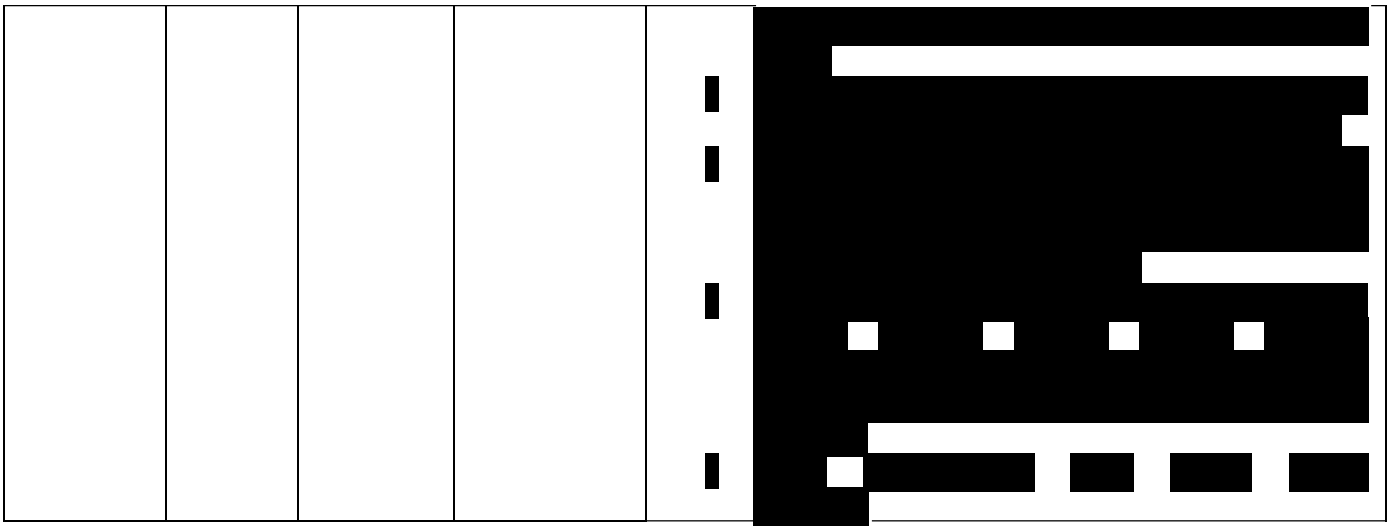
[redacted]





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1 Synopsis

Title:	"MOre REsponse on Cardiac Resynchronization Therapy (CRT) with MultiPoint Pacing (MPP)"
Acronym:	MORE-CRT MPP
Purpose:	The purpose of this Clinical investigation is to assess the impact of the Multi Point Pacing (MPP) feature at 12 months in the treatment of patients not responding to standard Cardiac Resynchronization Therapy (CRT) after 6 months. Due to a large number of combinations of parameters available for MPP programming, the MPP feature will be evaluated under two scenarios: (1) without mandating MPP programming parameters, and (2) with mandated MPP programming parameters.
Objectives:	**Primary Objective** To demonstrate that the activation of the MPP feature will increase the rate of CRT responders in patients that are classified as non-responders at 6 months of follow up.
	Secondary Objectives To assess the impact of the MPP feature on patients' functional and clinical status, as well as complication free survival time.
Endpoints:	**Primary Endpoint (assessed at 12 months)** Percentage of non-responder patients converted to responders after 6 months of MPP feature turned ON compared to baseline, as measured by Left Ventricular End Systolic Volume (LVESV) reduction of at least 15%.
	Secondary Endpoints (assessed at 12 months) • Reduction of LVESV between baseline and 6 month visit • Packer's Clinical Composite Score evaluation between the baseline and the 12 month visit; and between the 6 month and the 12 month visit • Reverse LV remodelling, measured as changes in LVESV, LVEDD and LVEF • NYHA Class changes • 6 minutes walking test changes • Quality of Life (MLWHF and EQ-5D) changes
Design:	This study is designed as a Prospective, Randomized, Multi-center Trial. Data will be collected at Enrollment, Baseline, Implant Procedure, Patient Classification, 6 Months and 12 Months Follow-Up. 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, clinical data and procedure details will be collected. After the Implant Procedure, the Patient Classification will be performed in

	order to identify the Qualified Subjects that will constitute the Study Population. During the 6 Months visit, the subject's response to CRT will be evaluated according to LVESV reduction: • Subjects with a LVESV reduction of at least 15% will be classified as Responders: those subjects will terminate their participation to the study and return to the center's standard practice. • Subjects with a LVESV reduction less than 15% will be classified as Non Responders: for those subjects the MPP feature will be activated according to randomization result and they will be followed up until 12 Months visit. During the 12 Months visit, the percentage of non-responder subjects converted to responders after 6 months of MPP feature turned ON will be assessed: • Subjects with a LVESV reduction of at least 15% between Baseline and 12 Months will be classified as Responders. • Subjects with a LVESV reduction less than 15% between Baseline and 12 Months will be classified as Non Responders. The investigation will be conducted in up to 250 centers worldwide. [redacted]
Devices used:	All subjects will be implanted with a CE-approved St. Jude Medical CRT device (CRT-D or CRT-P) compatible with MultiPoint Pacing feature and St. Jude Medical quadripolar left ventricular lead. Any commercially available and CE marked right atrial and right ventricular leads can be used in this investigation for both treatment arms. During the follow ups, implanted devices will be checked with Merlin® Patient Care System (model 3650 or newer, software version 17.2.1 or newer) programmer. All of the devices used in this investigation, have received appropriate regulatory certification (and are market released).
Subject Population:	Patients with Heart Failure that meet current ESC or ACCF/AHA/HRS Class I or IIa indications for CRT implant.

Patients presenting at the investigational site can be screened by a member of the investigational team previously trained on the CIP and delegated to do so. Patients who do not meet the inclusion/exclusion criteria are not eligible to participate in this investigation.

Patients meeting the inclusion/exclusion criteria will be fully informed about the investigation and will be asked to participate in the investigation. If the patient agrees, a duly signed and dated, EC and Sponsor approved, Patient Informed Consent form will be obtained.

Inclusion Criteria:
Eligible patients will meet ALL the following:

- Meets the current ESC or ACCF/AHA/HRS Class I or Class IIa indications for CRT implant (including upgrades from single or dual chamber ICDs)
- 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

Exclusion Criteria:
Patients will be excluded if they meet ANY of the following criteria:

- Already had a CRT device implanted
- Myocardial Infarction, unstable angina within 40 days prior the enrollment
- Recent cardiac revascularization (PTCA, Stent or CABG) in the 4 weeks prior the enrollment or planned for the 3 months following
- Cerebrovascular Accident (CVA) or Transient Ischemic Attack (TIA) in the 3 months prior the enrollment
- Primary valvular disease requiring surgical correction
- Atrial Fibrillation:
  - Persistent AF at the time of enrollment
  - Permanent AF not treated with AV node ablation within 2 weeks from the CRT implant
  - History or incidence of Paroxysmal or Persistent AF within 30 days prior the enrollment
- Unable to comply with the follow up schedule
- Less than 18 years of age
- Pregnant or are planning to become pregnant during the duration of the investigation
- Classification of Status 1 for cardiac transplantation or consideration for transplantation over the next 12 months
- Undergone a cardiac transplantation
- Life expectancy < 12 months
- Currently participating in any other clinical investigation

1.1 Investigation Flow Chart

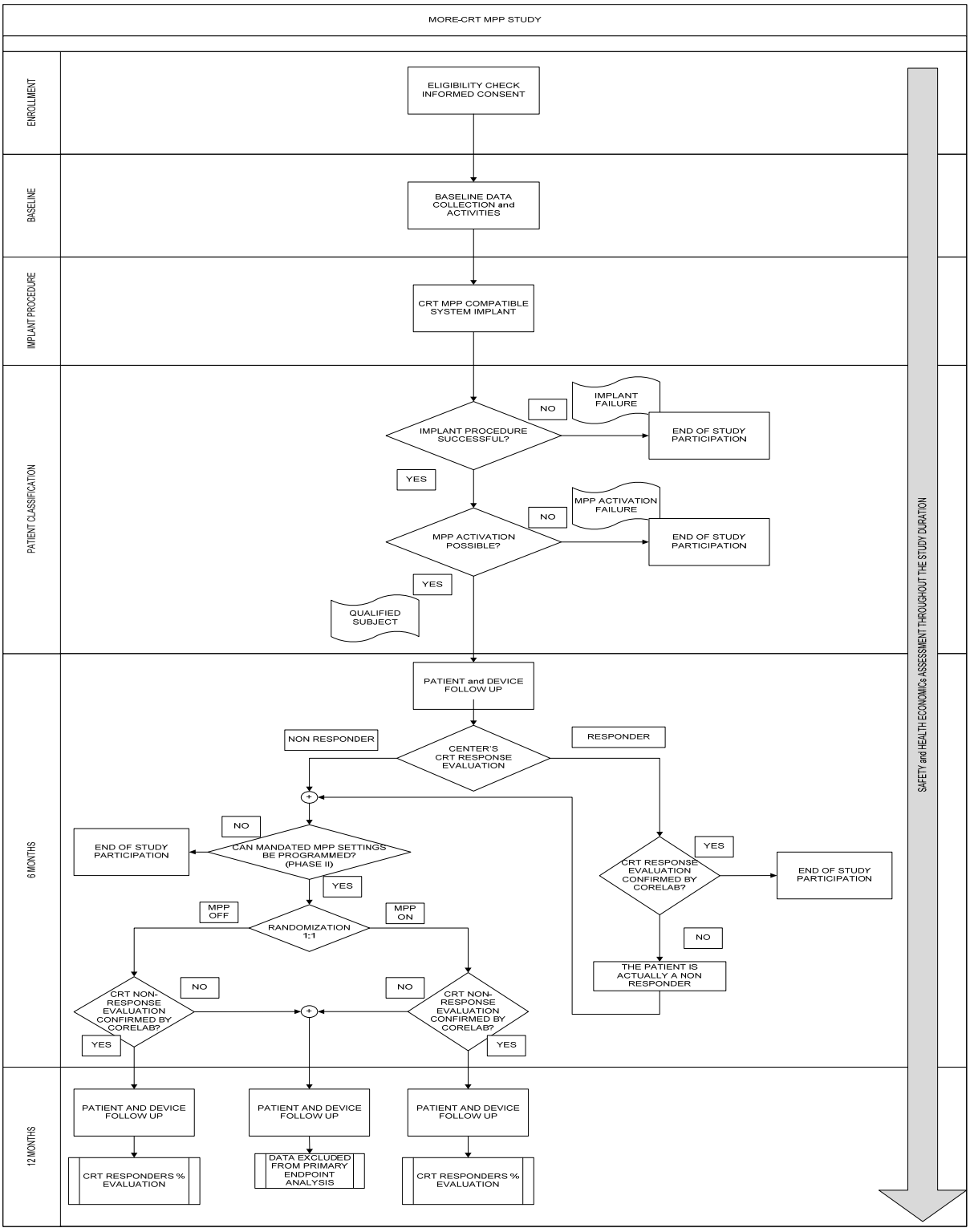


Figure 1: Flow Chart

1.2 Contacts

1.2.1 Sponsor

[redacted]

1.2.2 Coordinating Clinical Investigator

[redacted]

2 Background

Heart failure (HF) is an abnormality of cardiac structure or function leading to failure of the heart to deliver oxygen at the rate commensurate with the requirement of patient. European Society of Cardiology (ESC) 2012 guidelines defined HF as a syndrome in which patients have typical symptoms (e.g. breathlessness, swelling and fatigue) and signs (elevated jugular pressure, pulmonary crackles and displaced apex beat) resulting from an abnormality of cardiac structure or function[1].

HF is a varied clinical syndrome with complex pathophysiology, which continues to be defined, and often begins with a primary injury to the myocardium. Patients with HF experience decreased exercise capacity, inability to perform activities of daily living, diminished quality of life and an increased early mortality.

It is estimated that in the Western world more than 20 million patients suffer from end-stage HF. This indicates that the prevalence of this syndrome is 2-2.5% overall, increasing up to 10% among persons 70 years of age or older[2].
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[1-3].

Cardiac resynchronization therapy (CRT) using biventricular (BiV) pacing has been developed to restore synchrony in HF patients with delayed ventricular activation, predominantly of the left ventricle (LV). Studies have demonstrated that simultaneous or sequential BiV pacing restores the synchrony of contraction, reduces mitral regurgitation, and improves cardiac output[4, 5]. 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.[6-8]

Although a majority of treated patients show 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[9]. A summary of non-responder rate from various clinical studies has been performed by Birnie and Tang[10]. 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.

The cause for failed response to CRT is not completely understood; there is a general consensus, supported by growing evidence, that suboptimal LV lead placement accounts for a large percentage of patients who do not respond to CRT.

Some studies have shown that lateral and postero-lateral lead placements have more favorable results than other locations, but the link between lead location and clinical benefit is not yet well understood[11-16]. Several methods have been used in attempts to optimize lead placement including using intracardiac electrograms to locate the site of most delayed activation, measuring acute hemodynamic response based on lead location; using scar burden and location to predict response; and using electrical mapping to optimize epicardial Left Ventricle (LV) lead placement[17-22]. However, unfavorable coronary venous anatomy with narrow and tortuous tributaries, phrenic nerve stimulation, high capture thresholds, or pacing lead instability

may limit the use of any of these approaches. Moreover, each of the methods used to optimize LV lead placement to date are time consuming and some are more invasive than the implant itself, imposing potentially higher implant risks. Standard LV lead placement criteria for a stimulation electrode typically focuses on the location of mechanical stability, freedom from phrenic nerve stimulation, reasonable pacing thresholds, or the site of latest electrical activation. However, ischemic cardiomyopathy can cause non-uniform propagation of electrical activity over the myocardium due to scarred myocardial segments and density near the LV stimulation electrode[12]. Thus, a site of latest electrical activation may not always yield the optimal response. In such cases, the ability to pace from more than one left ventricular site may provide benefit.

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 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 pacing.
St. Jude Medical has developed a new family of quadripolar LV leads which increase the programmability by including one tip electrode and three ring electrodes. This quadripolar lead is called Quartet® LV lead (Model 1458Q, 1458QL, 1457Q, 1456Q and newer). If used with the Unify™ Quadra CRT-D device the system provides 10 different pacing vector options (VectSelect®) from the four pacing electrodes on the LV lead.
Furthermore, this lead allows pacing from any two of the 10 available vectors at the same time in a multi-point fashion (MultiPoint™ pacing or MPP).

MultiPoint™ pacing (MPP) is a new pacing feature in the Quadripolar CRT-D system that allows sequential pacing of the LV with two pacing vectors compared to one vector in a traditional CRT-D system. A combination of any two of the 10 available vectors with inter-stimulus delays can be used. MPP via one LV lead may have the potential to act as an alternative to non-invasively optimize LV lead placement, and it may improve hemodynamics and the response to CRT. Studies showed that simultaneously exciting a larger mass or volume of cardiac tissue results in faster depolarization velocity and shorter left ventricular trans-ventricular conduction times[23-24]. In addition, by capturing a larger volume of cardiac muscle, the site of latest intrinsic activation within the left ventricle may be more likely to be depolarized early, resulting in better synchronization and maximizing cardiac output.

Since MPP delivers two pulses at programmable delays (LV1 and LV2) to two LV sites, the initial volume of excited cardiac tissue is increased. 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[25-26] 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 Investigational Design

3.1 Purpose

The purpose of this clinical investigation is to assess the impact of the MultiPoint Pacing (MPP) feature at 12 months in the treatment of patients that are not responding to standard Cardiac Resynchronization Therapy (CRT). Due to a large number of combinations of parameters available for MPP programming, the MPP feature will be evaluated in two scenarios:

(1) without mandating MPP programming parameters, and
(2) with mandated MPP programming parameters.

3.2 Objectives

3.2.1 Primary Objective

To demonstrate that the activation of the MPP feature will increase the rate of CRT responders in patients that were already classified as non-responders at 6 months follow up.

3.2.2 Secondary Objectives

To assess the impact of MPP feature on patients functional and clinical status

3.3 Endpoints

3.3.1 Primary Endpoint

The primary endpoint of this study is evaluated at 12 months after enrollment and it is defined as the percentage of non-responder patients converted to responders after 6 months of MPP feature turned ON compared to baseline, as measured by Left Ventricular End Systolic Volume (LVESV) reduction of at least 15%.

3.3.2 Secondary Endpoint

The secondary endpoints of this study are evaluated at 12 months after enrollment and are defined as:

- Reduction of LVESV between baseline and 6 Months visit
- Packer's Clinical Composite Score evaluation between baseline and 12 Months visit and between 6 Months and 12 Months visits
- Reverse LV remodeling, measured as changes in LVESV, LVEDD and LVEF
- NYHA Class changes
- 6 minutes walking test changes
- Quality of Life (MLWHF and EQ-5D) changes

3.4 Investigational Type

This study is designed as a Prospective, Randomized, Multi-center Trial.

Data will be collected at Enrollment, Baseline, Implant Procedure, Patient Classification, 6 Months and 12 Months Follow-Up.

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, clinical data and procedure details will be collected.

After the Implant Procedure, the Patient Classification will be performed in order to identify the Qualified Subjects that will constitute the Study Population.

During the 6 Months visit, the subject's response to CRT will be evaluated at the center level according to LVESV reduction. Before randomization in the second phase of the study, all subjects will undergo testing to determine if the mandated MPP settings can be programmed (see below for MPP programming requirements in Phase II). For those subjects in whom the mandated MPP settings cannot be programmed before randomization at 6 months, their participation in the study will end (an early termination form must be completed).

- Subjects with a LVESV reduction of at least 15% will be classified as **RESPONDERS.** For those subjects, their participation in the study will end (if confirmed by the Core Lab), and they will then return to the center's routine follow up schedule/practice.
    - If the subject is evaluated as a Responder by the center and later as a Non Responder by the Core Lab, the center must randomize the subject and should call the subject back for an unscheduled visit (see 4.2.7) in case the randomization assignment is different from programmed.
- Subjects with an LVESV reduction of less than 15% will be classified as **NON RESPONDERS.** These subjects should be randomized and the device programmed to either MPP OFF or MPP ON per the randomization assignment (Please refer to section 3.8 "Randomization Procedure" for further details).
    - If the subject is evaluated as a Non Responder by the center and later as a Responder by the Core Lab, the subject continues to 12 Months visit but the data are excluded from the primary endpoint analysis.
- For those subjects randomized to MPP ON in the second phase of the study, the MPP feature should be programmed as follows:
    - MPP Vector combination: Two programmable vectors with widest spacing (≥30 mm between two cathodes). The 'Widest Spacing' feature within the VectSelect Quartet™ MultiVector Tools in the Merlin Patient Care System should be used to program to widest spacing.
    - LV1-LV2 delay: 5 ms
    - LV2-RV delay: 5 ms

During the 12 Months visit, the percentage of non-responder subjects converted to responders after 6 months of MPP feature turned ON and MPP feature turned OFF will be assessed:

- Subjects with a LVESV reduction of at least 15% between Baseline and 12 Months will be classified as Responders.
- Subjects with a LVESV reduction less than 15% between Baseline and 12 Months will be classified as Non Responders. Subjects who died due to cardiac cause post randomization will also be classified as Non Responders.

The investigation will be conducted in up to 250 centers worldwide.

3.5 Subject Population

The subject population enrolled in this investigation will be comprised of male and female patients. These subjects are patients who meet the specific eligibility criteria.

The enrollment phase will continue until approximately 5638 Qualified Subjects will be identified. Please refer to section "3.7 Subject Enrollment Classification" for the definition of Qualified Subject. In order to achieve this number, approximately 6898 subjects should be enrolled in the Study.

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.

3.6 Inclusion and Exclusion Criteria

A patient who meets all of the inclusion criteria and none of the exclusion criteria is eligible to participate in this investigation.

A patient is enrolled in this investigation only when he has provided a written signed / dated Patient Informed Consent form (refer to section 5.2 for the Informed Consent Process).

Once enrolled, a subject is expected to comply with the scheduled visits and required activities according to the protocol.
All subjects enrolled in the clinical investigation (including those withdrawn from the clinical investigation or lost to follow-up) shall be accounted for and documented in the Patient Identification Log, assigning an identification code linked to their names, alternative identification or contact information.
This log shall be kept up to date throughout the clinical investigation by the principal investigator or his/her authorized designee.
Since subject privacy and confidentiality of data must be maintained throughout the clinical investigation, this log will remain on site and the sponsor has no access to it.

3.6.1 Inclusion Criteria

Eligible patients will meet ALL the following criteria:

- Meets the current ESC Guidelines or ACCF/AHA/HRS Class I or Class IIa indications for CRT implant (including upgrades from single or dual chamber ICDs)
- 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

3.6.2 Exclusion Criteria

Patients will be excluded if they meet ANY of the following criteria

- Already had a CRT device implanted
- Myocardial Infarction, unstable angina within 40 days prior the enrollment
- Recent cardiac revascularization (PTCA, Stent or CABG) in the 4 weeks prior to enrollment or planned for the 3 months following
- Cerebrovascular Accident (CVA) or Transient Ischemic Attack (TIA) in the 3 months prior the enrollment
- Primary valvular disease requiring surgical correction
- Atrial Fibrillation:
    - Persistent AF at the time of enrollment

  - Permanent AF not treated with AV node ablation within 2 weeks from the CRT implant
  - History or incidence of Paroxysmal or Persistent AF within 30 days prior the enrollment
- Unable to comply with the follow up schedule
- Less than 18 years of age
- Pregnant or are planning to become pregnant during the duration of the investigation
- Classification of Status 1 for cardiac transplantation or consideration for transplantation over the next 12 months
- Undergone a cardiac transplantation
- Life expectancy < 12 months
- Currently participating in any other clinical investigation

3.7 Subject Enrollment Classification

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

- Eligibility Failure:
  Patients who provided the Informed Consent but failed to meet the Inclusion/Exclusion Criteria. These subjects' participation to the study will be terminated immediately.

- Implant Failure:
  Patients who provided the Informed Consent, meet the Inclusion/Exclusion criteria, but do not receive the CRT MPP compatible device because of implant failure or physician's decision. These subjects' participation to 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. These subjects' participation to the study will be terminated immediately.

- Qualified Subject:
  Patients who provided the Informed Consent, meet the Inclusion but not the Exclusion criteria, have been implanted with a CRT MPP compatible device, have MPP vector combinations to allow the MPP activation. These subjects will proceed in the study and constitute the Study Population.

3.8 Randomization Procedure

The Randomization procedure assigns subjects to the Treatment Group (MPP ON) or Control Group (MPP OFF) in a 1:1 ratio. Randomization should be based on the preliminary LVESV value measured at the center level at the 6 Months visit. However, this evaluation must be confirmed by the Echo Core Lab. In case of disagreement, the Core Lab evaluation will be considered the definitive one. The randomization will be stratified by center in order to obtain a homogeneous distribution. For further information on randomization, refer to section 4.2.5.

3.9 Point of Enrollment

Patients are considered enrolled in the clinical investigation from the moment the patient has provided written Patient Informed Consent form (refer to section 5.2 for the Informed Consent Process).

3.10 Expected duration of the Investigation

[redacted]

3.10.1 Expected duration of each subject's participation

The expected duration of each subject enrolled in the clinical investigation will be approximately:

- 12 months for subjects classified as Non Responders at the 6 Months visit
- 6 months for subjects classified as Responders at the 6 Months visit
- 1 month for subjects that are not Qualified during the Patient Classification visit

3.10.2 Number of Subjects required to be included in the Investigation

Approximately 5914 Qualified Subjects in both first and second phases of the study should be included in the Study Population.
Please refer to section "3.7 Subject Enrollment Classification" for Qualified Subject definition and section "7.1 Sample Size").

3.10.3 Estimated time needed to select this subject population (Enrollment Time)

The estimated time needed to enroll the number of subjects is 72 months.

3.11 Devices Used

All subjects will be implanted with a regulatory approved St. Jude Medical CRT device compatible with MultiPoint Pacing feature and St. Jude Medical quadripolar LV lead.
During the follow ups, implanted devices will be checked with Merlin® Patient Care System (model 3650 or newer, software version 17.2.1 or newer) 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.

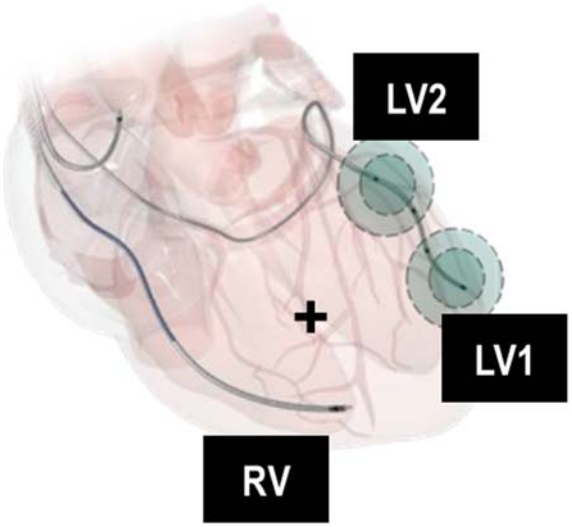
The CRT devices are equipped with an IS4-LLLL low voltage connector to facilitate implantation of an IS4 LV four electrode lead. Also, devices with a Q suffix have a high voltage DF4-LLHH bore that allows the use of Durata DF4 lead.

The Quartet™ LV lead is a quadripolar, over–the-wire design that enables implantation using either a stylet or guidewire. The lead has an open lumen and an opening at the lead tip to allow the use of a guidewire. The body has Optim™ lead insulation and a maximum lead body diameter of 5.1 Fr. Like the QuickSite® and Quickflex® left heart lead families, the distal portion of the Quartet™ is pre-shaped in an "s-curve" shape to provide stabilization of the distal tip in the coronary veins of the left ventricle. The outer lead body is covered with Fast-Pass™ coating that increases lubricity during initial implant.

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

Three titanium nitride (TiN) coated platinum/iridium (PtIr) ring electrodes are located on the lead at a distance of 20 mm (Mid 2), 30 mm (Mid 3) and 47 mm (Proximal 4) from the tip of the lead.

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



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

Please note that Vector numbering is for protocol use only and is not reflected on the Merlin® Patient Care System (model 3650 or newer) programmer

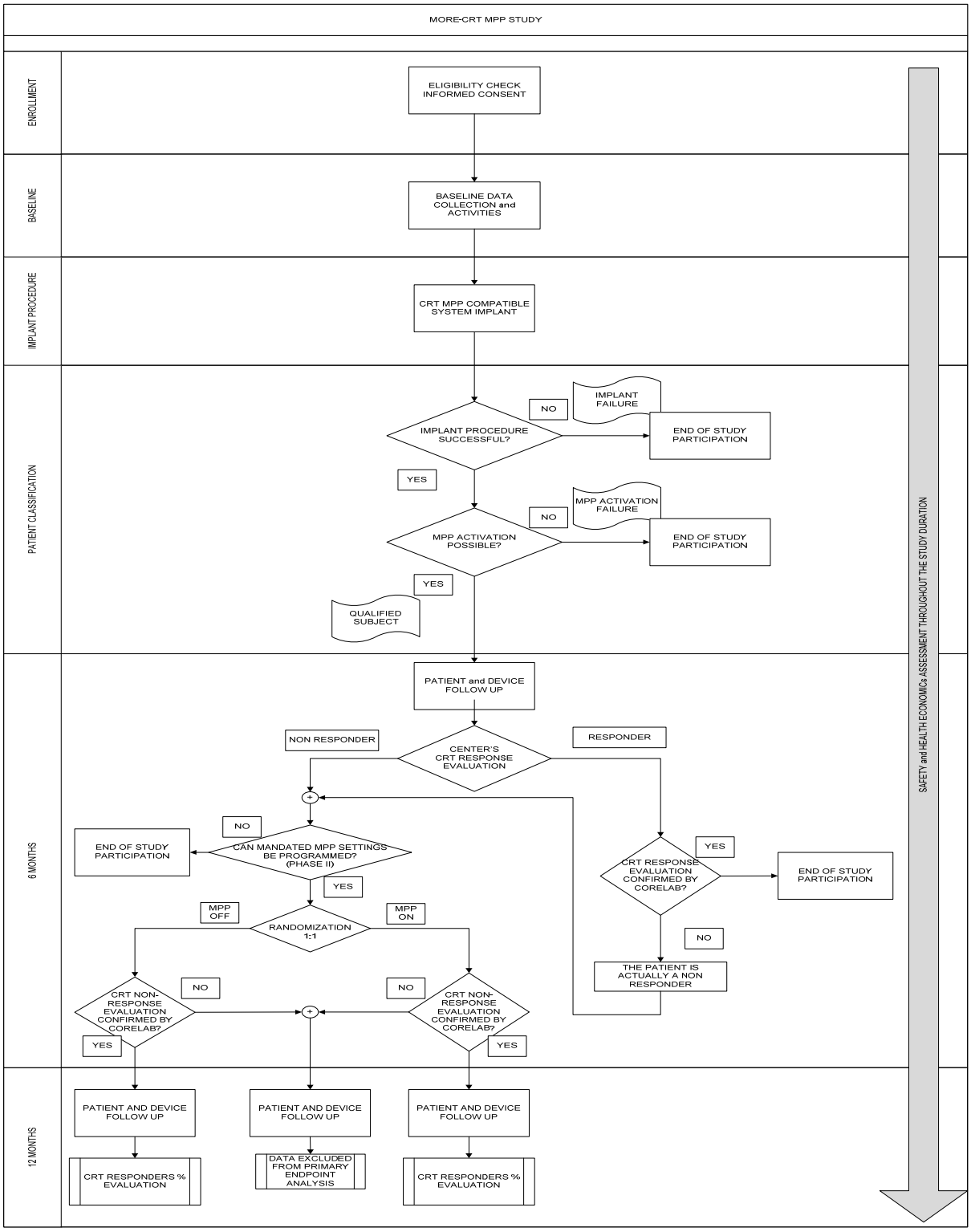
Please refer to Appendix C “Device Manuals” for further information.

3.11.1 **Control of Devices and Equipment**

Only regulatory approved and commercially available shelf-stock will be used within indications for the investigation. No specific device traceability is required.

4 Procedures

4.1 Investigation Flow Chart



4.2 Protocol Activities

The following table lists all electronic Case Report Forms (eCRFs) that are to be completed during the respective visits. Mandatory eCRFs are identified with an "X". eCRFs that are optional or have to be completed only in case of a certain event (i.e. Adverse Event) are marked with an "(X)"

Visit / CRFs	Enroll	Baseline	Implant Proc.	Patient Classification	6 Months FU	12 Months FU	Unsch FU
Enrollment Form	X						
Implant Form			X				
Patient Classification Form				X			
Baseline Form		X					
Echocardiography Form	X§				X	X	(X)
EQ-5D Form		X			X	X	(X)
MLWHF Form		X			X	X	(X)
Follow Up Form					X	X	(X)
System Revision Form			(X)	(X)	(X)	(X)	(X)
Deviation Form	(X)	(X)	(X)	(X)	(X)	(X)	(X)
Adverse Event Form	(X)	(X)	(X)	(X)	(X)	(X)	(X)
Termination Form	(X)	(X)	(X)	(X)	(X)	(X)	(X)
Death Form	(X)	(X)	(X)	(X)	(X)	(X)	(X)

(X): If applicable
X§: Baseline Echocardiography can be performed at any time from 3 months prior CRT implant (by an echo qualified study center).

Table 1: Data Collection: eCRF requested per visit

All the mandatory activities/procedures are listed in the following table and detailed in the next pages:

	Enroll	Baseline	Implant Proc.	Patient Classification	6 Month FU	12 Month FU
Informed Consent procedure	X					
Inclusion/Exclusion Criteria check	X					
Implant Procedure Details			X			
Fluoroscopy Images Collection (LAO and RAO – EDC upload)			X			
Implant Procedure Success Confirmation				X		
MPP Vector Test				X	X[$]	
Patient Data and Medical History		X				
Current Cardiac Medications		X				
Changes in Cardiac Medications					X	X
Patient Global Assessment					X	X
NYHA Class Evaluation		X			X	X
Randomization procedure (only for Non Responders to CRT)					X	
12-Lead ECG (EDC upload)		X			X	X
BNP/pro-BNP/ NT-pro-BNP Test *		(X*)			(X*)	(X*)
6 Minutes Hall Walking Test		X			X	X
EQ-5D Questionnaire		X			X	X
MLWHF Questionnaire		X			X	X
Echocardiography	X[§]				X	X
Preliminary LVESV Evaluation		X			X	
Conduction Delays Test			X	X	X	X
Device Test and Programming (EDC upload)			X	X	X	X
MPP Programming			X	X	X	

(X*): If performed as Standard of care at the site
X[$]: Testing of mandated MPP settings in Phase II before randomization (see section 4.2.5 for further details)
X[§]: can be performed at any time from 3 months prior CRT implant (by an echo qualified study center)

Table 2: List of all required activities/procedures

Informed Consent Procedure and Inclusion/Exclusion Criteria check:
Patient's eligibility criteria and Informed consent Procedure is performed before any study related activity. Please refer to section 4.2.1 "Enrollment visit" for further details.

Implant Procedure Details:
Implant Procedure details (standard CRT implant) will be collected at Implant visit.
Indicate model n°, serial n° and date of implant of entire implanted system (CRT device, RA lead, RV lead and LV lead), even in case of implant failure.
Final positions of all the implanted leads must be specified: right atrium, right ventricle and left ventricle lead positions.

Fluoroscopy Images Collection (EDC upload):
As the lead placement is important to understanding the subject's response to CRT, two anonymized Fluoroscopy images are requested to be collected:

- LAO (Left Anterior Oblique, 45°±10°)
- RAO (Right Anterior Oblique, 45°±10°).

The position of all leads must be clearly visible to allow matching with the venous anatomy. These anonymized images should be uploaded to the EDC system using the feature "Attachments to CRFs", for further details on this topic please refer to Appendix E "Guidelines" part 1.1.

Implant Procedure Success Confirmation:
In the Patient Classification visit, the confirmation of a successful implant procedure will be asked in order to classify the subject as Qualified Subject or not.

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 Patient Classification visit.
The test is considered positive in case is possible to identify at least 2 vectors from different Groups (with different Cathodes) free from Phrenic Nerve Stimulation (PNS) and with a Pacing Threshold that do not exceed 4.5V at 0.5ms pulse duration in CRT-D devices and at 0.4ms pulse duration in CRT-P devices.
Please refer to Appendix E "Guidelines" part 6 for the detailed testing procedure.

Subject Data and Medical History:
Subject's Year of Birth and Gender will be collected at the Baseline visit together with cardiomyopathy etiology and co-morbidities.

Current Cardiac Medications/Changes in Cardiac Medications:
The current cardiac medications will be collected at Baseline, while during the Follow-up Visits only the changes will be documented.

Patient Global Assessment:
The Patient Global Assessment will be performed at 6 and 12 Months Follow Up visits and will be used to calculate the Packer's Clinical Composite Score (CCS) together with NYHA Class evaluation, HF events and/or Cardiovascular death.
For further information regarding CCS please refer to Appendix E "Guidelines" part 2.

NYHA Class evaluation:

The subject's New York Heart Association class will be assessed at Baseline and during all Follow-up Visits.

Randomization procedure (only for Non Responders to CRT):
The randomization procedure will be performed at 6 Months Follow Up only for subjects that are classified as NON RESPONDERS to CRT. The randomization will be stratified by center and will assign the subjects either to MPP ON or MPP OFF in a 1:1 fashion.

12-Lead ECG (EDC upload):
A 12-lead ECG must be performed at Baseline, 6 and 12 Months Follow-up Visit.
The anonymized 12-Lead ECG (performed at paper speed 25mm/s or 50mm/s depending to center's preference) should be uploaded to the Electronic data Capture (EDC) system using the feature "Attachments to CRFs", for further details on this topic please refer to Appendix E "Guidelines" part 1.1.
The following data will be retrieved:

- Date of ECG
- Heart rate
- Atrial and Ventricular rhythms
- QRS width
- PR Interval
- LBBB or RBBB occurrences

B-Type natriuretic peptide (BNP), pro-BNP or NT-pro-BNP test (if performed per Standard of Care):
The BNP/pro-BNP/NT-pro-BNP test is used to measure the amount of stress on the subject's heart. If this test will be performed as per Standard of Care in the participating centers, the result will be collected at Baseline, 6 and 12 months follow-up. The test kit established at the investigational site will be used and intra-individual changes from Baseline to FU will be calculated.

6 Minute Hall Walk test:
The 6 Minute Hall Walk test is used to measure the subject's health status and must be completed at Baseline, 6 Months and 12 Months Follow Ups. The 6 Minute Hall Walk test measures the distance an individual is able to walk over a total of six minutes on a hard, flat surface. The goal is for the individual to walk as far as possible in six minutes. The individual is allowed to self-pace, rest as needed or interrupt the test at any time.

EQ-5D Questionnaire:
In order to assess the subject's health status, an EQ-5D questionnaire must be completed at Baseline, 6 Months and 12 Months Follow Ups.
Please refer to Appendix E: "Guidelines" Part 4 for further details

Minnesota Living With Heart Failure (MLWHF) Questionnaire:
In order to assess the subject quality of life, a MLWHF questionnaire must be completed at Baseline, 6 Months and 12 Months Follow Ups.
Please refer to Appendix E: "Guidelines" Part 5 for further details

Echocardiography:
Echocardiography must be performed, according to the MORE-CRT MPP study Echo Protocol, only by Trained Site Personnel, at Baseline, 6 Months and 12 Months Follow-ups.

Baseline Echo can be performed at any time from 3 Months prior CRT implant; however, the center must be already Echo Qualified at the time echo is being performed and the echo should not be provided to the CoreLab until after the patient has signed the Informed Consent.
The echocardiography must be recorded in DICOM format and sent/uploaded to the Echo Core Lab within 24 hours (1 working day).
The Core Lab will analyze the Echocardiography received and provide the evaluation of the CRT response based on the LVESV reduction within 72 hours of reception of the echocardiography (3 working days).

Centers can limit the number of non-evaluable echoes by choosing a wide scan angle and using contrast to enhance image quality of the endocardial borders. However, must note that contrast enhanced images will also require contrast enhanced images at other study time points (baseline, 6M and 12M follow-up) for the same subject in order to allow for comparison by the Core Lab.

Preliminary LVESV Reduction Evaluation:
At the Baseline and 6 Month FU visits, the center will be asked to provide, together with the recorded Echocardiography, a calculation/assessment of the LVESV value and (at 6 Months FU) reduction.
This evaluation will preliminary help identify if the subject is a Responder or not and will be confirmed by the Echo Core Lab. In case of disagreement between the center and Core Lab evaluations, the Core Lab assessment will be considered as final.

At the 6 Month FU, if the subject is identified as a Non Responder, the Randomization procedure will take place. In case of disagreement between the center and Core Lab evaluations during this visit, the Core Lab assessment will be considered as final and the following actions will need to be performed:

- If the subject is evaluated as Non Responder by the center and as a Responder by the Core Lab: continues to 12 Months visit but the data are excluded from the primary endpoint analysis.
- If the subject is evaluated as a Responder by the center and as a Non Responder by the Core Lab: the center should call back the subject for the randomization procedure (within a reasonable time window (e.g. 2 weeks) after the 6M visit).

Conduction Delays Test:
The conduction delays between right and left ventricle will be performed during implant and each in–clinic follow up. This is an automatic test that can be performed via Merlin PCS programmer and will end in about one minute. Please refer to Appendix E: “Guidelines” part 3 for further details regarding the Conduction Delay test.

Device Test and Programming (EDC upload):
Device will be interrogated and all the diagnostics retrieved; standard sensing, pacing and impedance measurements will be performed for all implanted leads at each in-clinic follow-up.
Please refer to Appendix E “Guidelines” part 1.2 for further details on the “Upload Device Data” procedure.

The device programming will be left to Investigator's discretion with the exception of the MPP feature. It is suggested that AV delay optimization is performed per centers' preference.
Please see below the MPP Programming activity.
Follow-up session (including diagnostics) will be uploaded to the EDC system using the feature "Upload Device Data".

MPP Programming:
Overall device programming will be left to the Investigator's discretion with the exception of the MPP feature:

- **MPP should** NOT **be programmed** ON BEFORE the 6 Months FU
- At the 6 Months FU, the MPP feature will be programmed ON or OFF as per Randomization result (1:1) for subjects classified as NON RESPONDERS according to LVESV reduction less than 15%. Subjects randomized to MPP ON in the second phase of the study should be programmed as follows:
    - MPP Vector combination: Two programmable vectors with widest spacing (≥30 mm between two cathodes). The 'Widest Spacing' feature within the VectSelect Quartet™ MultiVector Tools in the Merlin Patient Care System should be used to program to widest spacing.
    - LV1-LV2 delay: 5 ms
    - LV2-RV delay: 5 ms

Please refer to Appendix E: "Guidelines" Part 2 for further details regarding subject's CRT response classification and Part 7 for further details about MPP Programming.

Attachment to CRF and Upload Device Session
Currently, two options are available to the centers to upload the requested documents: "Attachment to CRFs" and "Upload Device Data".
The "Attachment to CRFs" is designed to upload images, adobe acrobat files, and scanned documents.
The "Upload Device Data" is reserved for the upload of Device Session records saved in the Merlin PCS programmer. These files are in a compressed format, and they should not be modified before the upload procedure.
Please refer to Appendix E: "Guidelines" Part 1, 1.1 and 1.2 for further information regarding Attachment to CRFs and Upload Device session.

4.2.1 Enrollment Visit (In clinic)

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

- The principal or delegated investigator is responsible for screening all potential subjects to determine patient eligibility for the investigation.
- 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 investigation, date of consent and Inclusion/exclusion information) in the internal hospital records and complete the Enrollment form within 5 days of enrollment.
- Notification of enrollment to the sponsor will be completed only when the sponsor receives the enrollment form.

NOTE: As soon as the patient signs the Patient Informed Consent form, adverse events need to be reported according to the guidelines mentioned in sections 5.3.2 and 5.4.1.

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

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

- Document enrollment information (name of the investigation, date of consent and inclusion/exclusion) in the hospital records and complete the Enrollment and Withdrawal forms. The forms must be signed authorized / approved by the principal or delegated investigator.
- Refer to Tables 1 and 2 “Data Collection” and Appendix D “Data Collection Method”.
- Inform the subject about the Withdrawal.
- The EC/IRB and CA should be notified appropriately about any deviations with regards to obtaining the informed consent.

4.2.2 **Baseline Visit (In Clinic, between Enrollment and Implant)**

At Baseline the following information will be collected to describe subject’s clinical status:

- Demographics Data
- Cardiovascular History
- NYHA Class Evaluation
- Current Cardiac Medication
- Acknowledgement of any planned hospitalization for pre-existing condition, not study related (if applicable)
- Adverse Events and/or Protocol Deviation notification (if applicable)

The following activities will be performed at the baseline visit:

- 6 Minutes Hall Walk Test
- BNP/pro-BNP/NT-pro-BNP Test (if performed per Standard of Care)
- EQ-5D Questionnaire completion
- MLWHF Questionnaire completion
- Echocardiography
- Preliminary LVESV Evaluation
- 12-Lead ECG and upload to EDC portal

The center should send/provide the Echocardiography to the Echo Core Lab within 24 hours (1 working day).

The Core Lab will analyze the Echocardiography received and provide the evaluation of the LVESV Baseline value within 72 hours of reception of the echocardiography (3 working days).

4.2.3 Implant Procedure (In Clinic, within 30 days from Enrollment)

The implant procedure must be performed within 30 days from the enrollment. SJM MPP compatible CRT system will be implanted with standard procedure.

The following information will be collected at the Implant visit:

- Implant Procedure Details
- Adverse Events and/or Protocol Deviation notification (if applicable)

The following activities will be performed at the Implant visit:

- Device Test and Programming
- Conduction Delay Test
- Fluoroscopy image Collection and upload to EDC portal
- MPP programming (OFF)
- Upload of device session (as .zip-file) to EDC portal

4.2.4 Patient Classification (In Clinic, within 7 days post Implant)

The purpose of this visit is to double check the implanted CRT system and to perform the MPP Vector test in order to identify the Qualified Subjects that will constitute the Study Population.

The following information will be collected at the Patient Classification visit:

- CRT implant success confirmation
- Adverse Events and/or Protocol Deviation notification (if applicable)

The following activities will be performed at the Patient Classification visit:

- Device Test and Programming
- Conduction Delay Test
- MPP Vector test
- MPP programming (OFF)
- Upload of device session (as .zip-file) to EDC portal

Implant procedure and Classification visit are considered as two different visits. If both visits are performed on the same day, 2 different session records need to be uploaded to the EDC portal.

As only Qualified subjects will proceed in the study and constitute the Study Population, subjects will be classified as explained in section “3.7 Subject Enrollment Classification” using the above mentioned information.

4.2.5 6 Months Follow-Up Visit (In Clinic, 183 days +/- 14 days from Implant)

The purpose of the 6 Months Follow-Up visit is to check the subject’s and CRT system’s status as well as identifying subjects responding or not to CRT according to LVESV reduction between Baseline and 6 Months FU.

The following information will be collected at the 6 Months FU visit:

- Patient Global Assessment
- NYHA Class Evaluation

- Changes in Cardiac Medication
- Adverse Events and/or Protocol Deviation notification (if applicable)

The following activities will be performed at the 6 Months FU visit:

- Device Test and Programming
- Conduction Delay Test
- 6 Minutes Hall Walk Test
- BNP/pro-BNP/NT-pro-BNP Test (if performed per Standard of Care)
- EQ-5D Questionnaire completion
- MLWHF Questionnaire completion
- Echocardiography
- Preliminary LVESV Evaluation
- Randomization Procedure
- MPP programming (according to Randomization result)
- 12-Lead ECG and upload to EDC portal
- Upload of device session (as .zip-file) to EDC portal

Subject's response to CRT will be evaluated at the center level using the Preliminary LVESV Evaluation. Before randomization in the second phase of the study, all subjects will undergo testing to determine if the mandated MPP settings can be programmed (see below for MPP programming requirements in Phase II). For those subjects in whom the mandated MPP settings cannot be programmed before randomization at 6 months, the participation in the study will end (an early termination form must be completed).

- Subjects with a LVESV reduction of at least 15% will be classified as **RESPONDERS.** For those subjects, the participation in the study will end (if confirmed by the Core Lab), and they will then return to the center's routine follow up schedule/practice.

- If the subject is evaluated as a Responder by the center and as a Non Responder by the Core Lab, the center must randomize the subject and should call the subject back for an unscheduled visit (see 4.2.7) in case the randomization assignment is different from programmed.

- Subjects with an LVESV reduction less than 15% will be classified as **NON RESPONDERS.** These subjects should be randomized and the device programmed to either MPP OFF or MPP ON per the randomization assignment (Please refer to section 3.8 "Randomization Procedure" for further details).

- If the subject is evaluated as Non Responder by the center and as a Responder by the Core Lab, the subject continues to 12 Months visit but the data are excluded from the primary endpoint analysis.

Subjects randomized to the **MPP ON** group will undergo device programming before leaving the hospital:

- Device programming: MPP feature will be activated and programmed. Please refer to Appendix E: Part 6 and 7 for further details regarding MPP activation and required programming. No further device programming related to dyssynchrony is encouraged unless medically necessary.

- For those subjects randomized to MPP ON in the second phase of the study, the MPP feature should be programmed as follows:

    - MPP Vector combination: Two programmable vectors with widest spacing (≥30 mm between two cathodes). The 'Widest Spacing' feature within the VectSelect Quartet™ MultiVector Tools in the Merlin Patient Care System should be used to program to widest spacing.
    - LV1-LV2 delay: 5 ms
    - LV2-RV delay: 5 ms

The center should send/provide the Echocardiography to the Echo Core Lab within 24 hours (1 working day). The Core Lab will analyze the Echocardiography received and provide the evaluation of the CRT response based on the LVESV reduction within 72 hours of reception of the echocardiography (3 working days).

4.2.6 12 Months Follow-Up Visit (In Clinic, 365 days +/- 21 days from Implant, only for NON RESPONDERS)

The 12-Months Follow Up visit is the last protocol scheduled visit and will be performed only for those subjects classified as Non Responders by the center or Echo Core Lab during the 6 Month Follow Up visit.

Once completed, the subject ends his participation to the study and returns to the Center's routine follow up schedule.

The purpose of the 12 Months Follow-Up visit is to check the subject's and CRT system's status as well as identifying the overall percentage of non-responders converted to responders (according to LVESV reduction of at least 15%).

In this visit the primary and secondary endpoint of the study will be assessed.

The following information will be collected at the 12 Months Follow Up visit:

- Patient Global Assessment
- NYHA Class Evaluation
- Changes in Cardiac Medication
- Adverse Events and/or Protocol Deviation notification (if applicable)

The following activities will be performed at the 12 Months Follow Up visit:

- Device Test and Programming
- Conduction Delay Test
- 6 Minutes Hall Walk Test
- BNP/pro-BNP/NT-pro-BNP Test (if performed per Standard of Care)
- EQ-5D Questionnaire completion
- MLWHF Questionnaire completion
- Echocardiography
- 12-Lead ECG and upload to EDC portal
- Upload of device session (as .zip-file) to EDC portal

The center should send/provide the Echocardiography to the Echo Core Lab within 24 hours (1 working day).

The Core Lab will analyze the Echocardiography received and provide the evaluation of the CRT response based on the LVESV reduction to the sponsor.

4.2.7 Unscheduled Visits (In Clinic or Remote)

An Unscheduled Visit is defined as a follow up that is not explicitly requested by the protocol. An Unscheduled Visit should be documented by completing the appropriate forms as applicable, Adverse Event, System Revision, Death and/or Termination.

No specific activity is forecasted for this visit, however the center must document all of the following whenever applicable:

- Any performed procedure or test
- Any changes in subject's status (including NYHA Class and Medication)
- Any Adverse Event occurred
- Any changes made to the MPP programming
- Upload FU session (as .zip-file) to EDC system (if applicable)

4.2.8 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
- Provide the EQ-5D and the MLWHF Questionnaires to the Investigator

Review medical charts to ensure accurate reporting of data in the 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
- Assist the subject in the EQ-5D Questionnaire completion
- Assist the subject in the MLWHF Questionnaire completion

4.2.9 Description of post investigational provision of medical care

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

5 Clinical Investigation Conduct

5.1 Statements of Compliance

The investigation will be performed in accordance with the most current versions of the World Medical Association (WMA) Declaration of Helsinki and any regional and/or national regulations as appropriate.
ISO14155 shall be used as a guideline with following exceptions:

- Limited AE reporting → refer to section "5.3.2 Procedure for assessing, recording and reporting adverse events, adverse device effects, serious adverse events and serious adverse device effects"
- Device Deficiencies as this is a post-market study
- Device Accountability

The investigator shall not start enrolling patients or requesting informed consent prior to obtaining Ethics Committee approval and Competent Authority approval, if applicable, and authorization from the sponsor in writing for the investigation.

In case additional requirements will be imposed by the Ethics Committee or Competent Authority they shall be followed, if appropriate.

As sponsor, SJM has taken up general liability insurance in accordance with the requirements of the applicable local laws.
If required, additional subject coverage or an investigation specific insurance shall be provided by the Sponsor as well.

5.1.1 Adherence to the Clinical Investigation Plan

The principal investigator and delegates are required to adhere to the CIP in order to prevent subjects being exposed to unreasonable risks. On top of that, the principal investigator and delegates are required to be compliant with the signed Study Agreement, applicable national or local laws and regulations, and any conditions required by the appropriate EC or applicable regulatory authorities are expected as well.
Instances of failure, intentionally or unintentionally, to adhere to the requirements of the CIP are considered a deviation.

In some cases failure to comply with the protocol 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 investigational 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 protocol.

Simultaneously, in the event that adhering to the protocol might expose the subject to unreasonable risks, the investigator is also required to protect the rights, safety and well-being of the patient 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 an investigation.

The PI shall promptly report any deviations from the CIP to the Sponsor that affect the rights, safety or well-being of the subject or the scientific integrity of the clinical investigation, including those which occur under emergency circumstances. The reporting of these deviations should be done as soon as possible but no later than 72 hours after the investigator becomes aware. The investigator shall also notify promptly the EC, as per their requirements.

Any corrective and preventive actions required by the EC must be complied with by the site.

The sponsor will notify the Competent Authorities and EC as per their requirements.

5.1.2 **Repeated non-compliance**

In the event of repeated 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 (and local staff)

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

5.2 Informed Consent Process

5.2.1 **General Process**

Provision of the Informed Consent is mandatory. Informed Consent is required from all patients (or their legal representatives) prior to participation in the investigation. The process of obtaining Informed Consent shall comply with the most recent version of the declaration of Helsinki, ISO 14155 and all applicable regulations.
The principal investigator or his/her authorized designee will conduct the Informed Consent Process. This process will include a verbal discussion with the patient on all aspects of the clinical investigation that are relevant to the patient's decision to participate in the clinical investigation. It is crucial that this discussion is documented in the source documents (read hospital records of the patient).
The patient will be provided with the informed consent form that is written in a language that is understandable to the patient and has been approved by EC. The patient is given ample time to consider participation and ask questions if necessary. The patient's legal rights will not be waived nor the appearance that these will be waived. Native nontechnical language, understandable for the patient, will be used.
In order to avoid any possible coercion or undue improper influence on, or inducement of the patient to participate, the Sponsor requests the investigator to only sign the informed consent form once the patient has signed and dated the document and therefore decided to participate in the investigation.
Informed Consent of a patient shall always be indicated by personally dated signature of the patient and by the investigator responsible for conducting the Informed Consent process. It is crucial that the signature of the informed consent form is documented in the source documents (read hospital records of the patient).
One original signed consent document must be retained on file by the investigator and a second original signed consent document is provided to the subject (investigator's responsibility).

Important new information that becomes available throughout the clinical investigation will have to be provided in writing to new and existing patients. If relevant, all affected patients shall be asked to confirm their continuing informed consent in writing.

5.2.2 Special circumstances for informed consent

5.2.2.1 Subject needing legally authorized representatives

Informed consent may be given by the legal representative only if a subject is unable to make the decision to participate in a clinical investigation (e.g. infant, child and juvenile, seriously ill or unconscious subject, mentally ill person, mentally handicapped person). In such cases, the subject shall also be informed about the clinical investigation within his/her ability to understand.

5.2.2.2 Subject unable to read or write

Informed consent shall be obtained through a supervised oral process if a subject or legally authorized representative is unable to read or write. An independent witness shall be present throughout the process. The written informed consent form and any other information shall be read aloud and explained to the prospective subject or his/her legally authorized representative and, whenever possible, either shall sign and personally date the informed consent form. The witness also signs and personally dates the informed consent form attesting that the information was accurately explained and that informed consent was freely given.

5.3 Adverse Event, Adverse Device Effect

5.3.1 Definitions

5.3.1.1 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

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

5.3.1.3 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.

5.3.1.4 Adverse Device Effect (ADE)

An adverse event related to the use of a 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 medical device.
This definition includes any event resulting from the use error or from intentional misuse of the medical device.

5.3.1.5 Serious Adverse Device Effect (SADE)

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

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

Safety surveillance and reporting will be done for all subjects enrolled in this investigation.

Safety surveillance within this investigation and the safety reporting both performed by the investigator, starts as soon as the subject is enrolled in this investigation (date of signature of the informed consent form). The safety surveillance and the safety reporting will continue until the last investigational visit has been performed or the subject is deceased or the subject/investigator concludes his participation into the investigation.

Adverse Events Reporting

The investigator must report all SAEs and SADEs to the Sponsor as soon as possible but no later than outlined below.

Clinical Site	Reporting timelines
All Sites	SAEs or SADEs must be reported no later than 3 calendar days from the day the site personnel became aware of the event or as per the investigative site's local requirements, if the requirement is more stringent than those outlined.

The date the site staff became aware the event met the criteria of an SAE or SADE must be recorded in the source document.
The Investigator will further report the SAE or SADE to the local EC according to the institution's EC reporting requirements and in accordance with national and local laws and regulations.

Adverse events (including Adverse Device Effects) that are not serious will be reported to the Sponsor, as soon as possible after the occurrence of the event.

Non-Serious Adverse Events documentation and reporting are limited to cardiovascular events. Within cardiovascular, all arrhythmias that require medical assessment and/or intervention should be documented as serious adverse event.

All HF hospitalization ≥ 24 hours are to be documented and reported to the sponsor according to the reporting requirements for all SAEs and SADEs (Refer to Adverse Events Reporting section).

All HF hospitalization < 24 hours requiring administration of IV inotropes or diuretics are to be documented and reported to the sponsor according to the reporting requirements for all SAEs and SADEs (Refer to Adverse Events Reporting section).

Refer to table 1 'Data Collection' and Appendix D 'Data Collection Method'.

In case of EDC failure, notify Sponsor via Fax (please refer to the Investigator Site Binder, section 0.3 "Sponsor Contact Details" for further details about Fax numbers).

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

NOTE: If an adverse event is documented at the subject's last follow up visit, both the notification and follow-up information on the AE CRF are to be provided to the sponsor.

5.4 Subject Death

5.4.1 Procedure for recording and reporting Subject Death

All subject deaths are to be documented and reported to the sponsor according to the reporting requirements for all SAEs and SADEs (Refer to Adverse Events Reporting section).

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.
Refer to table 1 'Data Collection' and Appendix D 'Data Collection Method'
In case of EDC failure, notify Sponsor via Fax (please refer to the Investigator Site Binder, section 0.1 "Sponsor Contact Details" for further details about Fax numbers).

Subject 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 subject'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.

5.5 Criteria and procedures for subject withdrawal or discontinuation

Each subject should remain in the investigation until completion of the required follow up period; however, a subject's participation in the investigation may be discontinued. Should this occur, the reason for discontinuation must be documented in the source documents.
Subjects must be informed about their right to withdraw from the investigation 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 investigation 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 investigation at any time.
The subject's future care will not be influenced by a decision, voluntary or otherwise, to withdraw from the investigation. All reasonable efforts should be made to retain the subject in the clinical investigation until completion of the investigation.

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

- Subject refuses to continue participating in the investigation (refuse all subsequent testing/follow up)
- Subject does not meet the inclusion/exclusion criteria
- Subject's baseline Echo or 6 Month Echo is not analyzable or evaluable according to the Echo Core Lab.
- Subject had Permanent AF at the time of enrollment and no ablation has been performed within 2 weeks after the CRT implant
- Subject does not have a successful implant
- Subject does not meet criteria for turning MPP feature on
- 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 justified
- 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 investigation. (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 patient 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 patient's hospital records.
  2. If these attempts are unsuccessful, a certified letter should be sent to the subject's last known address or general practitioner (GP) and a copy of this letter should be maintained in the patient's hospital records.

If the subject misses two consecutive scheduled follow up visits and the above mentioned attempts to contact the subject/GP were unsuccessful, the subject will be considered 'Lost to Follow Up' and subject's Withdrawal form should be completed. The investigator ensures that all attempts are documented in the patient's hospital records.

5.6 Document and data control

5.6.1 Traceability of documents and data

The investigator shall ensure accuracy, completeness, legibility and timeliness of the data reported to the sponsor on the CRFs and in all required reports. Where copies of the original source document as well as print outs of original electronic source documents are retained, these shall be signed and dated by a member of the investigation site team with a statement that it is a true reproduction of the original source document.

5.6.2 Recording of data

Source documents shall be created and maintained by the investigation site team throughout the clinical investigation.
The data reported on the eCRFs shall be derived from, and be consistent with, these source documents, and any discrepancies shall 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.

5.6.3 Review of data

Data review can be done remotely as well as on-site by qualified sponsor personnel. At a minimum, eCRFs will be reviewed for completeness after data entry by the site and discrepancies will be created where needed. Additional needs for data review will be outlined in the Monitoring Plan (Refer to section 5.7.2).

5.7 Monitoring

The purpose of monitoring is to verify that the right and well-being of subjects are protected, that the reported data are accurate and complete and that the study is conducted in compliance with the approved CIP, subsequent amendments, GCPs and other applicable regulatory requirements.
St. Jude Medical shall assess the extent and nature of monitoring appropriate for the clinical study, including the strategy for source data verification, based on considerations such as the objective, design, complexity, size, critical data points, and endpoints of the clinical study. Results of this assessment shall be used to develop a monitoring plan.

Monitoring will be performed according to the applicable SJM SOPs and the study-specific Monitoring Plan and can be done by conducting on-site monitoring visits as well as by remote data review. The specific monitoring approach will be outlined in the Monitoring Plan (Refer to section 5.7.2).

5.7.1 Designated Monitors

Qualified clinical representative(s) will be identified to monitor this clinical study. A curriculum vitae and training records will be retained for any individual who has conducted monitoring activities during the course of the clinical study.

A list of monitors is available upon request.

5.7.2 Monitoring Plan

A project specific Monitoring Plan (MP) will be developed explaining at the minimum the monitoring strategy for the study (including frequency of visits and SDV requirements). This Monitoring Plan will be available upon request.

The Monitoring Plan may be updated and changed as needed. All revisions will be tracked and the most recent released version will take precedent over any other version.

5.7.3 Competent Authority (CA) Inspections

The investigator and/or delegate should contact SJM immediately upon notification of a CA inspection at the site. A clinical representative will assist the investigator and/or delegate in preparing for the audit.

An investigator who has authority to grant access shall permit authorized CA 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 investigation, shall permit authorized CA employees, at reasonable times and in reasonable manner, to inspect and copy all records relating to the investigation.

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

5.8 Investigation Termination

Suspension or premature termination of the investigation
The Sponsor reserves the right to stop the investigation at any stage, with appropriate written notice to the investigator.
Possible reasons for early termination of the investigation by the sponsor, either at local, national or international level, may include, but are not limited to:

- The therapy fails to perform as intended
- Occurrence of USADE which cannot be prevented in future cases
- Sponsor's decision, e.g. based upon significant delays in enrollment
- Recommendation from Steering committee and Sponsor
- Request from Regulatory bodies
- Request of Ethics Committee(s)

The investigation will be terminated according to applicable regulations.

The investigator may also discontinue participation in the clinical investigation with appropriate written notice to the Sponsor.
Should either of these events occur, the investigator shall return all documents to the sponsor; provide a written statement as to why the premature termination has taken place and notify the Ethics Committee and the Competent Authority (if applicable). Follow-up for all enrolled subjects will be as per center's practice.
The site shall be closed appropriately by the Sponsor.

5.8.1 Investigation Conclusion

The investigation will be concluded when:

- A Close Out has been performed AND
- The Final report has been provided

6 Risks and Benefits of the clinical investigation

6.1 Risks

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 (refer to Section 6).

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 VT is similar to that caused by standard BiV pacing.

6.2 Anticipated Adverse Events and Adverse Device Effects

6.2.1 **Associated with device or leads**

Possible adverse events (in alphabetical order) associated with the pacing system (CRT and leads) include but are not limited to the following:

- Acceleration of arrhythmias (caused by device)
- Death
- Exacerbation of heart failure
- Inappropriate shocks
- Inability to defibrillate
- Inhibited therapy for a ventricular tachycardia
- Interruption of function due to electrical or magnetic interference
- Lead abrasion
- Lead fracture
- Mechanical malfunction of the pacing lead
- Multiple counting of cardiac events including T-waves, P-waves, or supplemental pacemaker stimuli
- Shunting of energy from defibrillation paddles
- System failure due to ionizing radiation

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

6.2.2 **Associated with device or leads implant procedure**

Possible adverse events (in alphabetical order) associated with the implantation of pacing system (CRT device and leads) include but are not limited to:

- Acute hemorrhage/bleeding
- Air emboli
- Allergic reaction to contrast media
- Arrhythmia acceleration
- Body rejection phenomena
- Cardiac or venous perforation
- Cardiac tamponade

- Cardiogenic shock
- Chronic nerve damage
- Cardiac/coronary sinus dissection
- Cardiac/coronary sinus perforation
- Coronary sinus or cardiac vein thrombosis
- Death
- Excessive bleeding
- Extracardiac stimulation (phrenic nerve, diaphragm, chest wall)
- Fluid accumulation
- Hematoma/seroma formation
- Hemothorax
- Induced atrial or ventricular arrhythmias
- Infection
- Lead migration, dislodgment or poor lead placement
- Myocardial irritability
- Myocardial damage
- Myopotential sensing
- Pericardial effusion
- Pericardial rub
- Pneumothorax
- Prolonged exposure to fluoroscopic radiation
- Pulmonary edema
- Renal failure from contrast media used to visualize coronary veins
- Rise in threshold and exit block
- Thromboemboli
- Valve damage
- Venous occlusion

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

6.2.3 **Associated with subject's status/characteristics**

Possible adverse events (in alphabetical order) associated with the subject's unique response to a device or lead implantations includes but are not limited to:

- Allergic reaction to contrast media
- Body rejection phenomena
- Erosion
- Extrusion
- Endocarditis
- Excessive bleeding
- Histotoxic reactions
- Keloid formation
- Local tissue reaction; formation of fibrotic tissue; cyst formation
- Myocardial irritability
- Myocardial damage
- Myopotential sensing

6.3 Benefits

Subjects enrolled in this investigation may benefit as it is expected that the Multi Point 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[24-25] and it is believed that this additional improvement in LV function may benefit those subjects who are otherwise identified as non-responders to conventional BiV pacing.

6.4 Treatments in case of premature study termination

In case the study will be prematurely terminated, subjects will return to the Center's routine follow-up schedule. The device programming will be left at physician's discretion and no study-related activities will be performed.

7 Statistical considerations

The following section describes the statistical methods for the clinical investigation. Additional details on statistical analyses, including study cohorts, subgroup analyses and analysis of secondary endpoints are maintained in a separate Statistical Analysis Plan (SAP).

7.1 Primary Endpoint Hypothesis and Sample size

7.1.1 First phase of the study

The hypothesis and the sample size estimation in the first phase of the study are based on the purpose of this study, study design, and the primary endpoint.

The hypothesis for this study is set up as

H_0: $P_{OFF} \geq P_{ON}$ *vs* H_1: $P_{OFF} < P_{ON}$

With P_{OFF}: the proportion that the subjects are responders in the control group (MPP feature is OFF), with at least 15% reduction in LVESV at 12 months compared to baseline
With P_{ON}: the proportion that the subjects are responders in the treatment group (MPP feature is ON), with at least 15% reduction in LVESV at 12 months compared to baseline

[redacted]

7.1.2 Second phase of the study

The hypothesis and the sample size estimation in the second phase of the study are based on the purpose of this study, study design, and the primary endpoint.

The hypothesis for this study is set up as

H_0: $P_{OFF} \geq P_{ON}$ *vs* H_1: $P_{OFF} < P_{ON}$

With P_{OFF}: the proportion of subjects that are responders in the control group (MPP feature is OFF), with at least 15% reduction in LVESV at 12 months compared to baseline

With P_{ON}: the proportion of subjects that are responders in the treatment group (MPP feature is ON), with at least 15% reduction in LVESV at 12 months compared to baseline

[redacted]

[redacted]

[redacted]

7.2 Primary endpoint analysis

7.2.1 Timing of Analysis

7.2.1.1 Data Analysis of Phase I Subjects

The analysis will be performed when all randomized non-responder subjects (confirmed by the Echo Core Lab) from the Phase I study have either completed or crossed the 12 month visit window or discontinued before the 12 month visit.

7.2.1.2 Data Analysis of Phase II Subjects

The analysis will be will be performed when all randomized non-responder subjects (confirmed by the Echo Core Lab) from the Phase II study have either completed or crossed the 12 month visit window or discontinued before the 12 month visit.

7.2.2 Analysis methods

The number of responders and the percentage will be reported for each group. Chi-square test will be used for the comparison between the groups. In case the expected counts in each cell is less than 5, then Fisher's exact test will be used instead.

7.3 Secondary endpoints

All secondary endpoints will be compared between baseline and 12 months, 6 months against 12 months separately. As with the analysis of the primary endpoint, analysis of the secondary endpoints analysis will be conducted.

All continuous secondary endpoints will be summarized with the number of non-missing data, mean ± standard deviation, median and range (minimum – maximum). Paired t test will be used for the comparison within the group, and the equivalent non-parametric test, such as signed rank test or sign test, will be used in case the assumption for paired t test is violated. Comparison between groups will be performed using t-test, or equivalent non-parametric test, such as

Wilcoxon rank sum test, Kolmogorov-Smirnov test, when the assumption for t-test is violated. The normality assumption will be tested by the normality test with the aid of QQ plot.

All categorical secondary endpoints will be tabulated with number of occurrence and percentage. Chi-square test will be used for the comparison between the groups. In case the expected counts in each cell is less than 5, then Fisher's exact test will be used instead. Ordinal data will be analyzed using Cochran-Mantel-Haenszel method.

7.4 Analyses will also be carried out to explore the effect of MPP programming parameters on responder status. Analysis population

The following subjects will be excluded from the analysis for the primary endpoint.

- Subjects who give consent to participate in the clinical investigation but fail to complete the study follow up, due to a reason other than cardiac death.

- Subjects who have completed the clinical investigation but fail to have valid LVESV data at baseline visit, 6 months visit and 12 months visit.

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

Any deviations from the statistical analysis plan will be documented.

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

No imputation techniques will be used.

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

A minimum of 1 subject and maximum of 600 subjects can be recruited for each center.

8 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.
Investigational 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 collected or maintained for this clinical trial. 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 trial. All data will be secured against unauthorized access.

8.1 Data Management Plan

CRF data will be entered in a validated electronic database using Oracle Clinical.

The physician is required to enter the data through an electronic data capture system (EDC) system).

The Data Validation Procedure (DVP), which is part of the Data Management Plan (DMP), describes all the computerized data cleaning checks (validation rules) as programmed at the time of database set-up. However, these validation rules may change and be updated throughout the course of the investigation.
Manual review and Data Cleaning Convention (DCC) will be used in addition to computerized data cleaning checks, to check for discrepancies and to ensure consistency of the data.
More information will be provided in the DMP which may be updated as appropriate. All revisions will be tracked and include an effective date.
The DMP shall be available upon request.

9 Document Retention

The principal investigator (PI) shall maintain all essential clinical investigation documents from prior, during and (as specified) after the clinical investigation on file at the site for a minimum of 15 years (or longer if required by local legislation) after the termination of this investigation, 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 investigation to ensure that they no longer need to be retained on-site.

All original patient 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 shall be made available on request of the relevant authorities in case of an audit.

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

10 Amendments to Clinical Investigation Plan

The CIP, CRFs, Informed Consent form and other patient information, or other clinical investigation documents shall be amended as needed throughout the clinical investigation, and a justification statement shall be included with each amended section of a document. Proposed amendments to the CIP shall be agreed upon between the Sponsor and principal investigator, or the coordinating investigator.
The amendments to the CIP and the subject's Informed Consent shall be notified to, or approved by, the EC and regulatory authorities, if required. The version number and date of amendments shall 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 and subject prior to the subject's next follow up.
Administrative changes to, or formal clarifications of, the CIP may be required. They will be documented separately in writing and provided to the investigators. These clarifications will be incorporated when an amendment occurs.

11 Publication Policy

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

A 'Publication Agreement' will be signed between the Principal Investigator and the Sponsor

If such a Publication Agreement is not signed by both parties as a separate agreement but as part of an overall Clinical Trial Agreement, the publication policy should be part of such a Clinical Trial Agreement.

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

12 Investigation Organization

12.1 Investigation Management / Sponsor

The organization, which takes responsibility for the initiation and/or implementation and coordination for the investigation is St. Jude Medical, with offices located at:

St. Jude Medical

12.1.1 Sponsor Responsibilities

Sponsor's responsibilities are in accordance with applicable guidelines.
This includes but is not limited to the following activities:

- Sign off the clinical investigational plan before the start of the investigation or after modifications to the protocol;
- Develop the database;
- Select the clinical investigators;
- Train the clinical investigational sites;
- Activate the sites after receipt of the required documentation;
- Monitor participating centers by reviewing collected data and investigation documentation for completeness and accuracy in line with the Monitoring Plan;
- Perform the analysis;
- Ensure that all adverse events and adverse device effects are reported and reviewed with the clinical investigator(s) and where appropriate that all serious adverse events and serious adverse device effects are reported to the relevant authorities and Ethics Committee(s) and/or safety monitoring committee(s);
- Maintain an updated list of principal investigators, investigational sites and institutions. This list shall be available upon request.

SJM retains the right to terminate the participation of an investigator for any of, but not limited to, the following reasons:

- Concern for subject safety and welfare
- Failure to secure subject Informed Consent prior to any investigational activity
- Failure to report unanticipated adverse device effects within 72 hours to SJM and the EC
- Repeated non-compliance with this CIP or the Clinical Trial Agreement
- Inability to successfully implement this CIP
- Violation of the Declaration of Helsinki 2008 (refer to Appendix C)
- Violation of applicable national or local laws and regulations
- Falsification of data, or any other breach of ethics or scientific principles
- Loss of or unaccounted use of investigational device inventory

12.2 Clinical Investigators

This clinical investigation will be conducted by qualified investigators who have experience with:

- Implant and Follow up of Cardiac Resynchronization Therapy (CRT)
- Conduct of clinical investigations

12.2.1 **Investigator's responsibilities**

By agreeing to this Clinical Investigation Plan, the investigators accept to allow monitoring, audits, Ethics Committee and IRB review, and regulatory inspections that are related to the investigation. They also agree to provide authorized individuals with direct access to source data and documentation as well as the right to copy records, provided such activities do not violate subject consent and subject data confidentiality.
A principal investigator should have experience in and/or will be responsible for:

- Providing signed Clinical Trial Agreement and appropriate appendices;
- Providing the Sponsor with copies of any clinical-investigation-related communications between the Principal Investigator and the EC;
- Screening and selecting appropriate patients;
- Providing appropriate Ethics Committees Approved Informed Consent;
- Collecting and archiving of source data obtained prior to implant, during implant, at follow-up examinations and after the investigation has been completed;
- Strict adherence to the CIP testing requirements to provide for optimal safety and efficacious use of the device under clinical investigation;
- Adequate safety reporting;
- Supporting the monitor, and auditor, if applicable, in their activities to verify compliance with the CIP, to perform source data verification and to correct the case report forms where inconsistencies or missing values are identified.

It is acceptable for the Principal Investigator to delegate one or more functions to an associate or co-investigator, however, the Principal Investigator remains responsible for the proper conduct of the clinical investigation, complying with the investigational plan and collecting all required data. This delegation of specific functions shall be documented on the Signature and Delegation List (provided by Sponsor). The investigation is not transferable to other implant centers attended by the investigator unless prior approval is obtained from SJM.

12.2.2 **Clinical Coordinating Investigator**

In addition to the responsibilities of the investigators, the Clinical Coordinating Investigator will:

- Sign off the final version of the investigational protocol and after modifications to the protocol;
- Act as main contact for all investigators in case of medical questions related to the conduct of the investigation.

The following investigator has been appointed by the Sponsor as the Clinical Coordinating Investigator:

12.2.3 **Source Data and Patient Files**

The investigator has to keep a written or electronic patient files for every subject participating in the clinical investigation. In this hospital file, the available demographic and medical information of a subject has to be documented, in particular the following:

Name	Year of Birth	Concomitant Medication
Gender	Concomitant diseases	Scheduled follow ups
Subject History	Date of PIC	Observed AEs
PIC process	Clinical findings	
CIP required examination		

It should be possible to verify the inclusion and exclusion criteria for the investigation from the available data in this file. It must be possible to identify each subject by using this patient file.
Additionally, any other documents with source data have to bear at least the subject identification and the printing date printed by the recording device to indicate to which subject and to which investigational procedure the document belongs. The medical evaluation of such records should be documented as necessary and signed/dated by the investigator. All data recorded on the CRF must also be part of the subject's source data.

12.3 Boards

12.3.1 **Steering Committee (SC)**

The SC is championed by the Clinical Coordination Investigator (CCI) Prof. Christophe Leclercq. This committee will be actively involved in the investigation, and review its progress at regular intervals. At any time, this committee may request that the investigation be put on hold or even terminated for safety, ethical or other reasons. Steering Committee's components and specific activities are detailed in SC Charter document.

12.4 Outsourcing of duties and functions

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

12.4.1 **Echo CoreLab (EchoCL)**

The Echo CoreLab is entitled to bring specific echo expertise and scientific validation to the study by receiving and analyzing echo tests performed by all the centers participating in the study.
The Echo tests will be recorded by all participating sites in DICOM format and sent/uploaded to the CoreLab.

Centers will send/provide the Echocardiography tests to the Echo CoreLab within 24 hours (1 working day).

The CoreLab will analyze the Echocardiography received and provide the evaluation of the CRT response based on the LVESV value (at Baseline) or reduction (at 6-12 Months FU) within 72 hours of reception of the echocardiography (3 working days).

In case of disagreement between the center and CoreLab evaluations, CoreLab assessment will considered as final and the appropriate action will be performed.

12.4.2 **ECG Core Lab (ECG CL)**

The ECG Core Lab is entitled to bring specific ECG expertise and scientific validation to the study by receiving and analyzing ECG tests performed by all the centers participating in the study.

12.4.3 **Fluoroscopy Images Core Lab (FCL)**

The Fluoroscopy Images Core Lab is entitled to bring specific fluoroscopy images expertise and scientific validation to the study by receiving and analyzing fluoroscopy images recorded by all the centers participating in the study.

12.4.4 **EuroQoL (EQ-5D Questionnaire)**

EuroQoL Group comprises a network of international, multilingual, multidisciplinary researchers, originally from seven centers in England, Finland, the Netherlands, Norway and Sweden.

The process of shared development, local experimentation and lively discussion resulted in EQ-5D, a measure generating a single index value for health status with considerable potential for use in health care evaluation.

EQ-5D was initially developed simultaneously in Dutch, English, Finnish, Norwegian and Swedish. It is now widely used in many countries around the world and has been translated into most major languages with the Group closely monitoring the process.

EuroQoL provides certified translations of the EQ-5D patient questionnaires.

12.4.5 **MAPI Trust (MLWHF Questionnaire)**

MAPI Research Trust is a non-profit organization facilitating access to information in the fields of Patient-Reported Outcomes (PRO) and Epidemiology, promoting the use of scientific approaches in these fields and encouraging exchanges between academics, pharmaceutical companies and international organizations around the world.

MAPI Trust is the distributor of several different Quality of Life Questionnaires, including the Minnesota Living with Heart Failure QoL requested in this study.

MAPI is also responsible for the certified translations in different languages required when performing a multi-centric study.

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Appendix A: Abbreviations

Abbreviations used in this protocol:

Abbreviation	Term
ADE	Adverse Device Effect
AE	Adverse Event
ASADE	Anticipated Serious Adverse Device Effect
BNP	B-Type Natriuretic Peptide
CA	Competent Authority
CABG	Coronary Artery Bypass Graft
CCS	Clinical Composite Score
CCI	Clinical Coordination Investigator
CIP	Clinical Investigational Plan
CRF	Case Report Form
CPRB	Clinical Project Review Board
CRT	Cardiac Resynchronization Therapy
CVA	Cerebrovascular Accident
DCC	Data Cleaning Convention
DMP	Data Management Plan
DVP	Data Validation Procedure
EC	Ethics Committee
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
EQ-5D	EuroQol questionnaire
GP	General Practitioner
HF	Heart Failure
ICMJE	International Committee of Medical Journal Editors
IRB	Institutional Review Board
ISB	Investigator Site Binder
ISO	International Organization for Standardization
LAO	Left Side Antero-Posterior
LBBB	Left Bundle Branch Block
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
MLWHF	Minnesota Living With Heart Failure questionnaire
MP	Monitoring Plan
MPP	Multi Point Pacing Feature
NAP	Not Applicable
NYHA	New York Heart Association
PCS	Patient Care System
PGA	Patient's Global Assessment
PI	Principal Investigator
PNS	Phrenic Nerve Stimulation
POA	Power of Attorney
PTCA	Percutaneous Transluminal Coronary Angioplasty
RA	Right Atrium

RAO	Right Side Antero-Posterior
RBBB	Right Bundle Branch Block
RDC	Remote Data Capture
RV	Right Ventricle
SADE	Serious Adverse Device Effect
SAE	Serious Adverse Event
SC	Steering Committee
SJM	St. Jude Medical
TIA	Transient Ischemic Attack
USADE	Unanticipated Serious Adverse Device Effect
WMA	World Medical Association

Appendix B: 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 authorised 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 C: Device Manual

The manuals for the programmer and devices used in this investigation can be found on-line at www.sjmprofessional.com and should be consulted.

Appendix D: Data Collection Method

Sponsor/Investigators are required to prepare and maintain adequate an accurate case histories designed to record all observations and other data pertinent to the investigation on each subject 1:1. Source documents include all original records from which CRFs derive their data.
Worksheet can be provided. The purpose of these worksheets is to aid investigators in the capture of clinical investigational data and ensure all protocol required data, which is not captured in medical records, is recorded to support data for the investigation. These worksheets will not be a copy of the eCRFs, but will contain entry blanks for study required data not routinely collected by the investigators.

All documentation pertaining to clinical assessments and medical evaluations should be signed and dated by the appropriate clinical personnel.

Electronic Data Capture (EDC) will be used for this investigation, therefore, please find below instructions on how to access and use the eCRF application.

Access to eCRF application
The eCRF application is accessed through the internet and requires the use of a personal user account and password.
The following documents and information are required prior to receipt of personnel user account and password:

- Current signed and dated CV
- Completed Signature and Delegation List
- Documented training
- Email address and telephone

Personal user account and password are provided via email. User account and password are confidential and personal. They are not to be shared with other people.
The first time the application is accessed, the password will need to be changed.
If the password is forgotten and/or lost, a new password can be provided via email by following the instructions on the webpage.

Each center must be authorized to start enrolling patients in the investigation before access privileges to the application is made available.

Access privileges are based on the tasks assigned on the Signature and Delegation List and will be either:

- Data entry and review
- Data entry, review and sign off

All eCRFs must be completed, saved (‘save complete’) and approved by an investigator in a timely manner.

In order to ensure a timely event reporting to the authorities (as per local regulations), particular attention must be used with Adverse Events forms. **The Site is required to always “save as complete” the Adverse Event eCRFs.**

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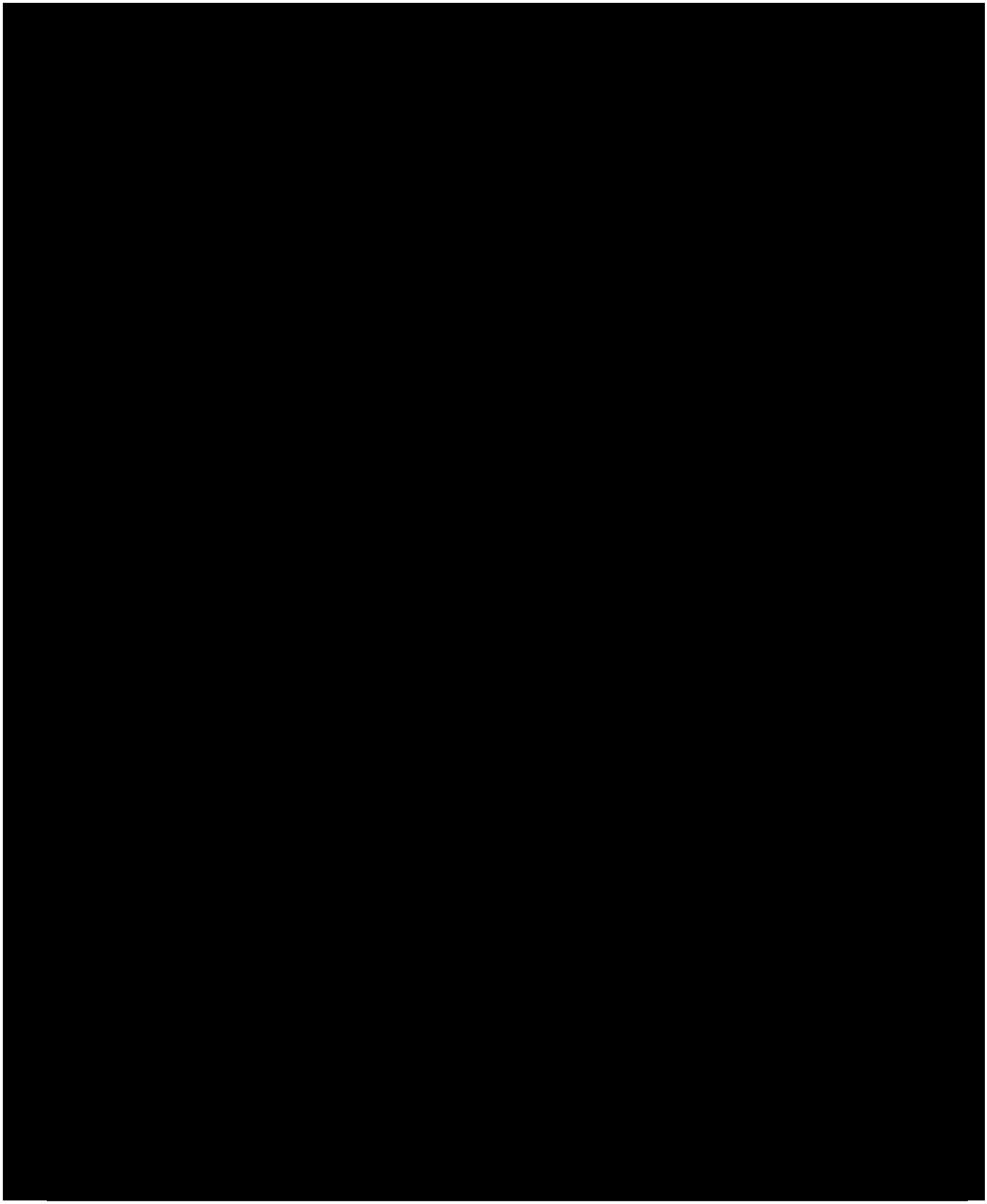

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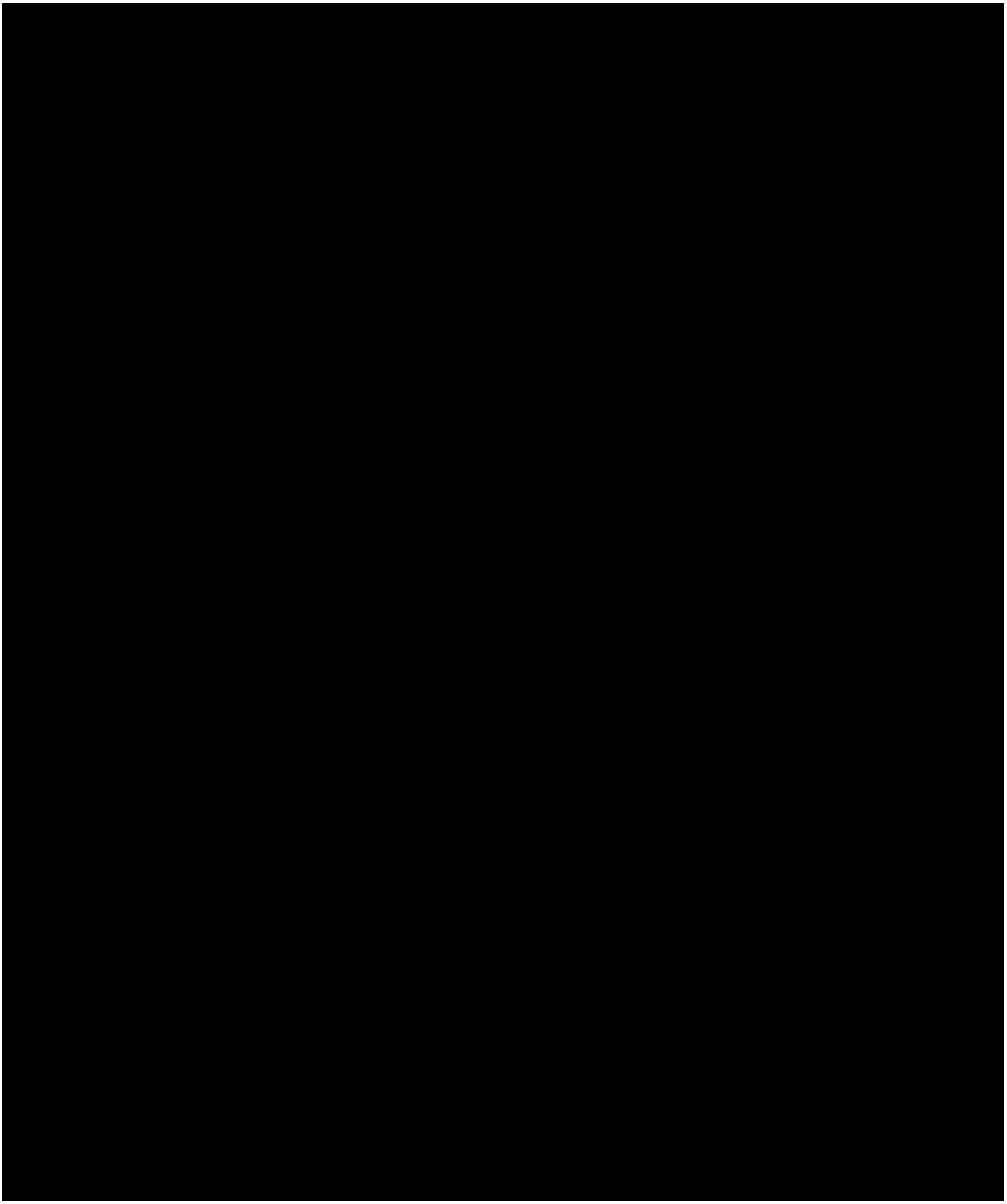

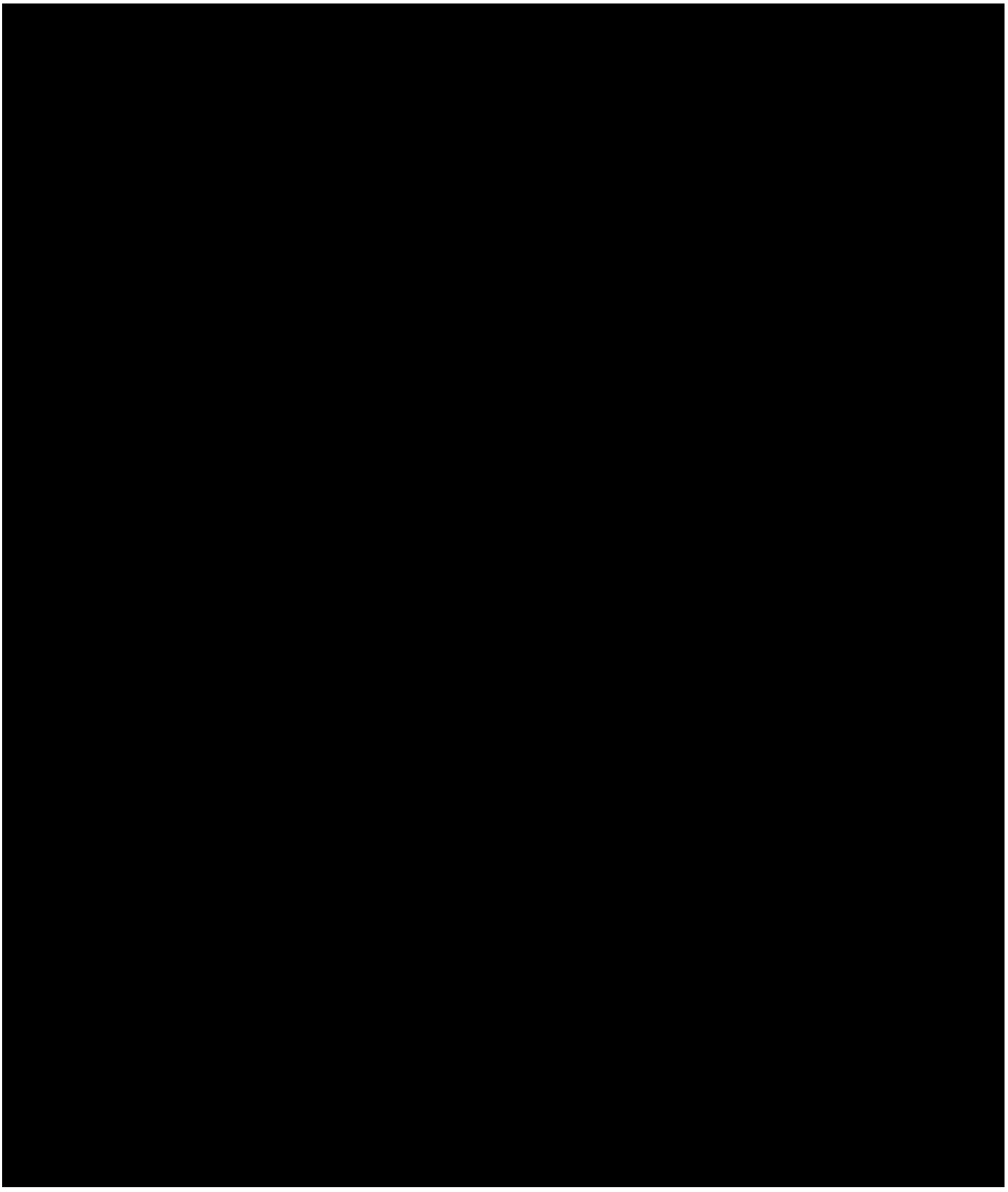

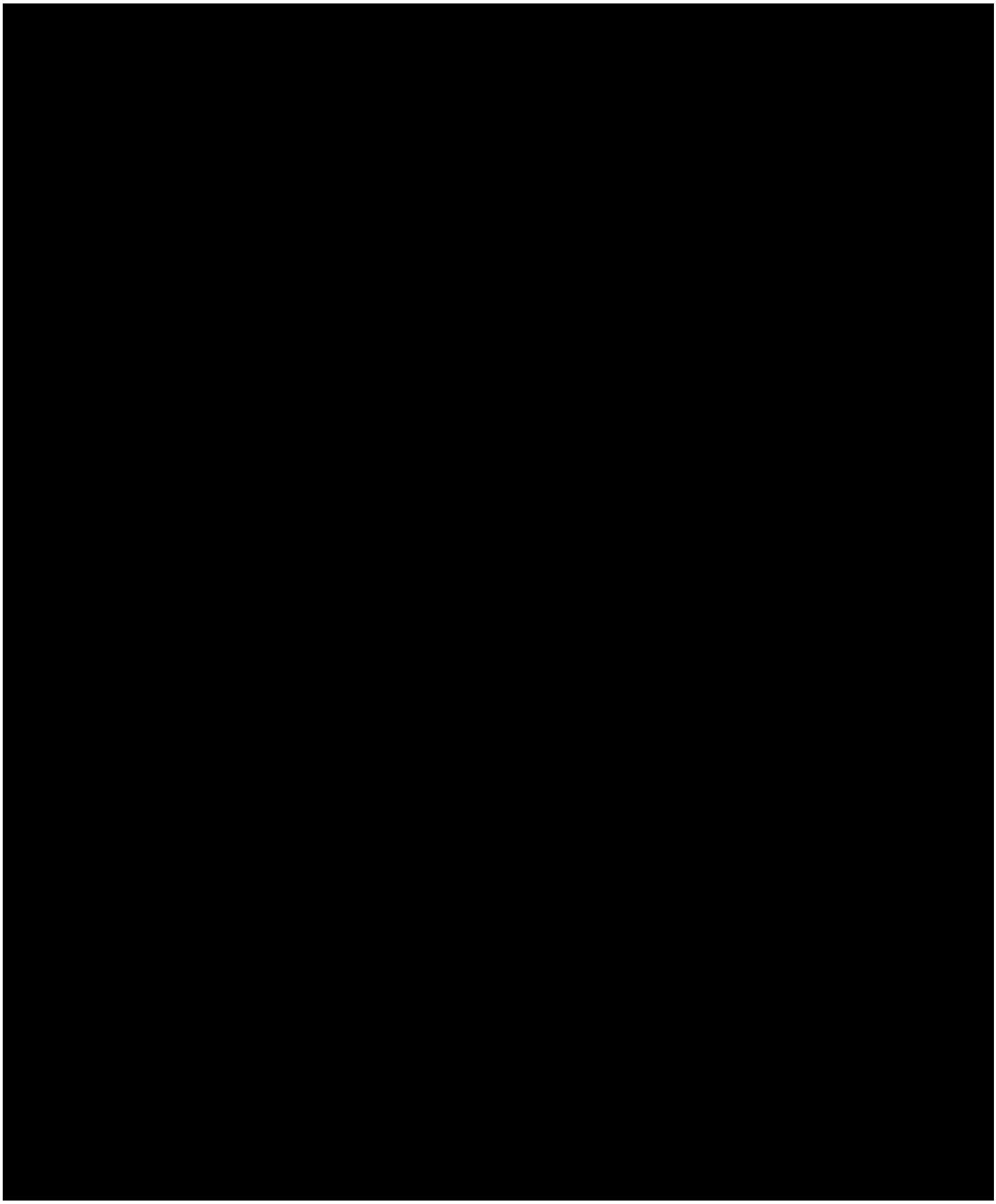

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Part 2 - Packer's Clinical Composite Score (CCS)

The Packer's Clinical Composite Score (CCS) will be assessed at 6 months and 12 months post implant.
The CCS includes 4 components: NYHA class, Patient Global Assessment (PGA), HF events, and cardiovascular death[27].

The NYHA Class evaluation and PGA will be determined by an Investigator interviewing subjects about their symptoms. Specifically, the PGA will be a single interview question that asks the subject to categorize how they feel compared to their previous visits as either:

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

At the 6 Months Follow Up visit, a PGA will be conducted to evaluate how the subject feels compared to the baseline visit before having the CRT system implanted.

At the 12 Months Follow Up visit, two different PGAs will be conducted:

- The first one will evaluate how the subject feels compared to the baseline visit before having the CRT system implanted and
- The second one will evaluate how the subject feels compared to the 6-month visit.

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

- Hospitalization or Emergency Department visit for HF ≥ 24 hours
- Hospitalization or Emergency Department visit for HF <24 hours requiring administration of IV inotropes or diuretics

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

Using the CCS decision algorithm described below, subjects are categorized as Improved, Worsened or Unchanged based on the following rules:

IMPROVED – subjects that demonstrate:

- At least a one-class improvement in NYHA Class OR improvement by PGA ("Better" or "Markedly better"
  AND
- No HF events as described above
  AND
- No Cardiovascular death

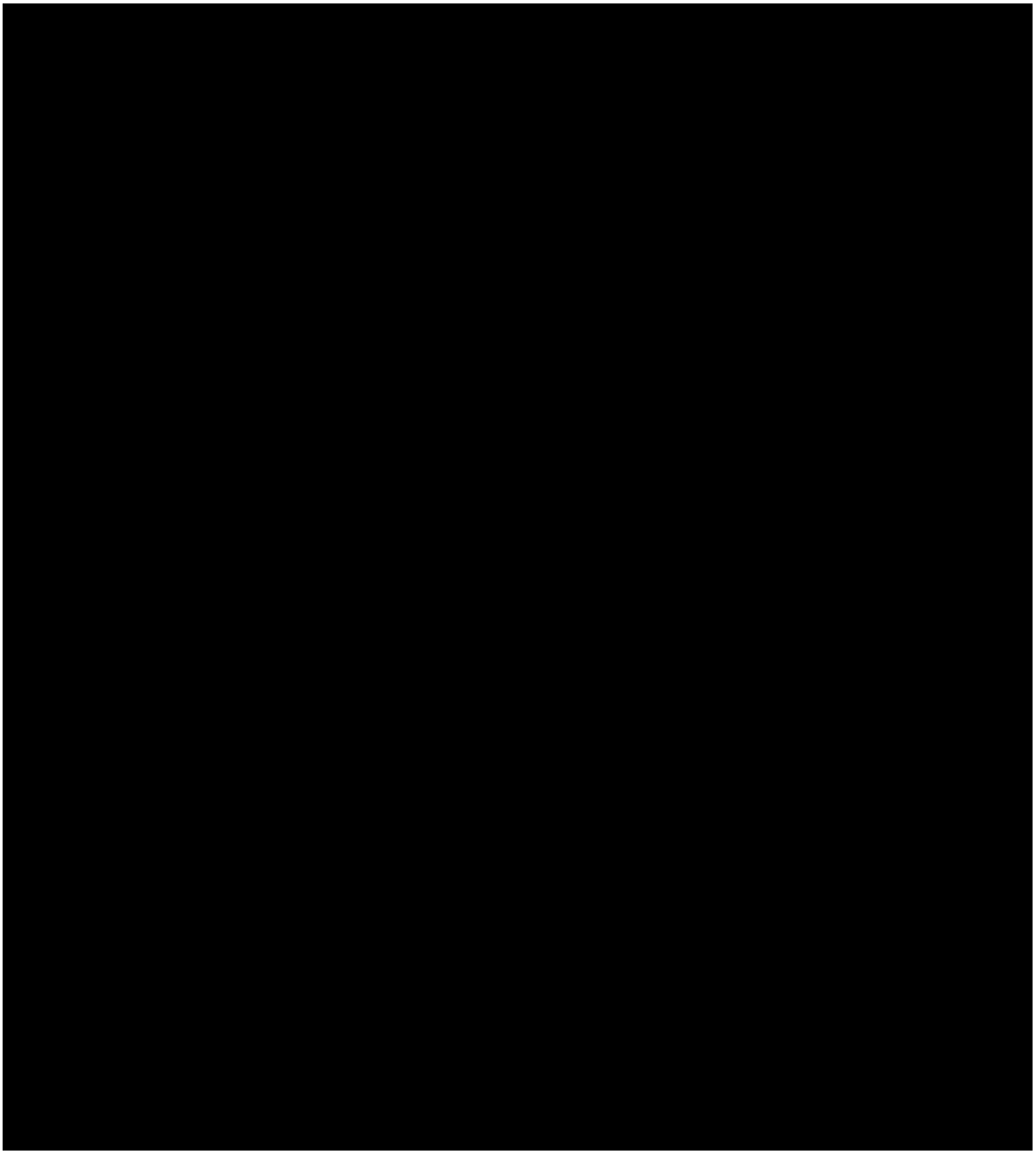
WORSENED – subjects that demonstrate:

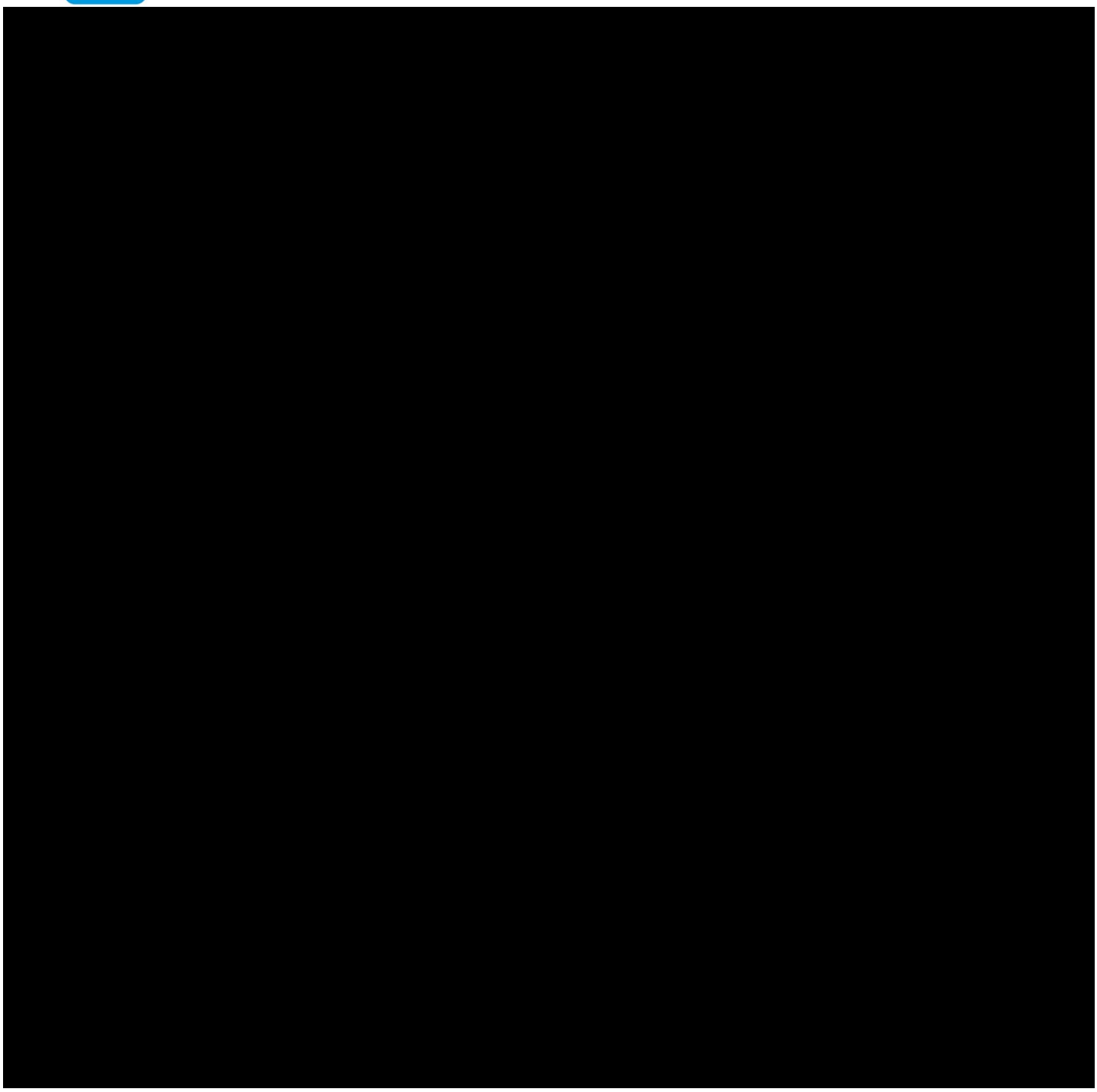
- Worsening in NYHA Class OR worsening by PGA ("Worse" or "Markedly worse"

OR
- Presence of HF events as described above
  OR
- Cardiovascular death

UNCHANGED – subjects that are neither “Improved” nor “Worsened”.

Clinical Composite Score Decision Algorhythm





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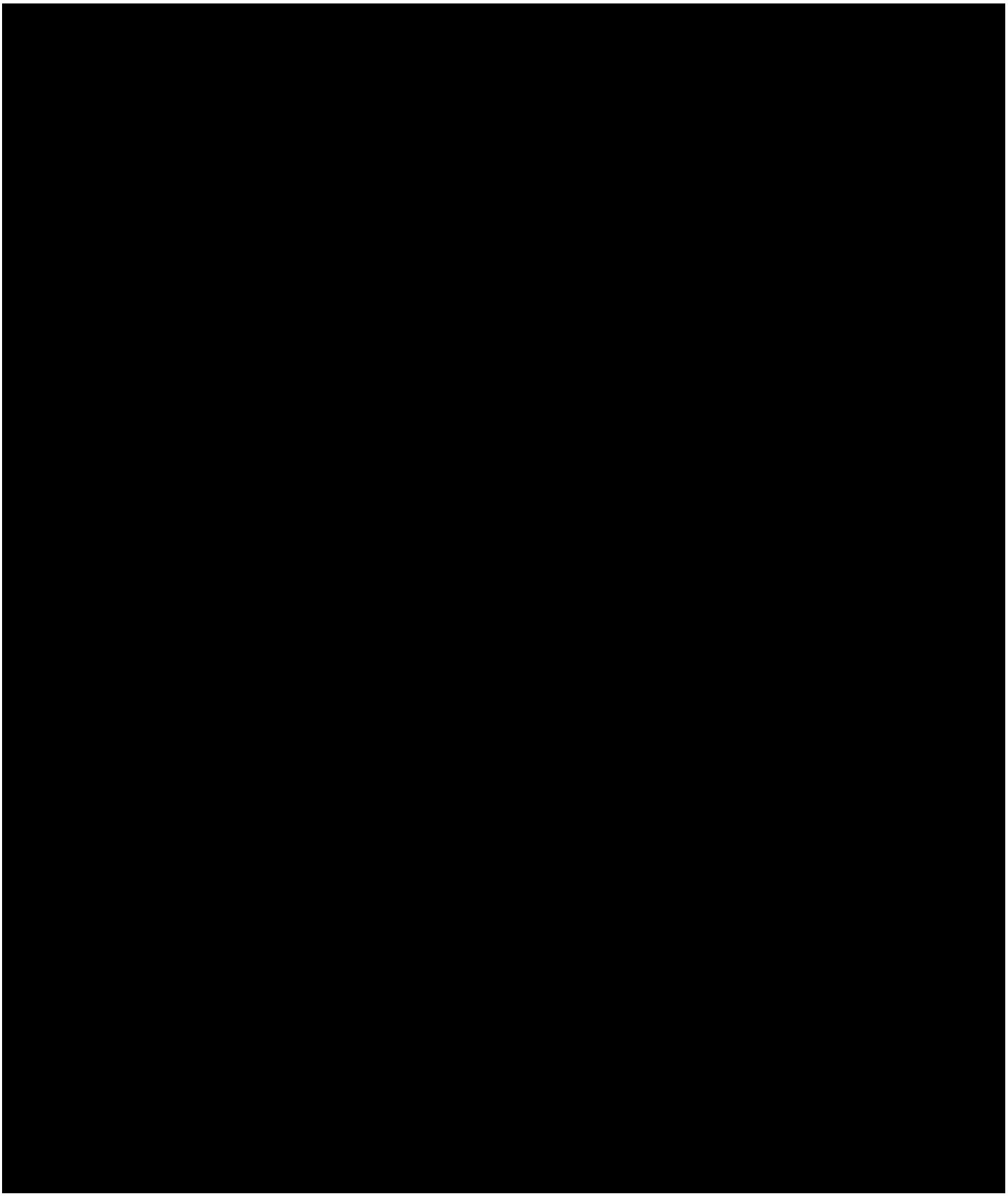
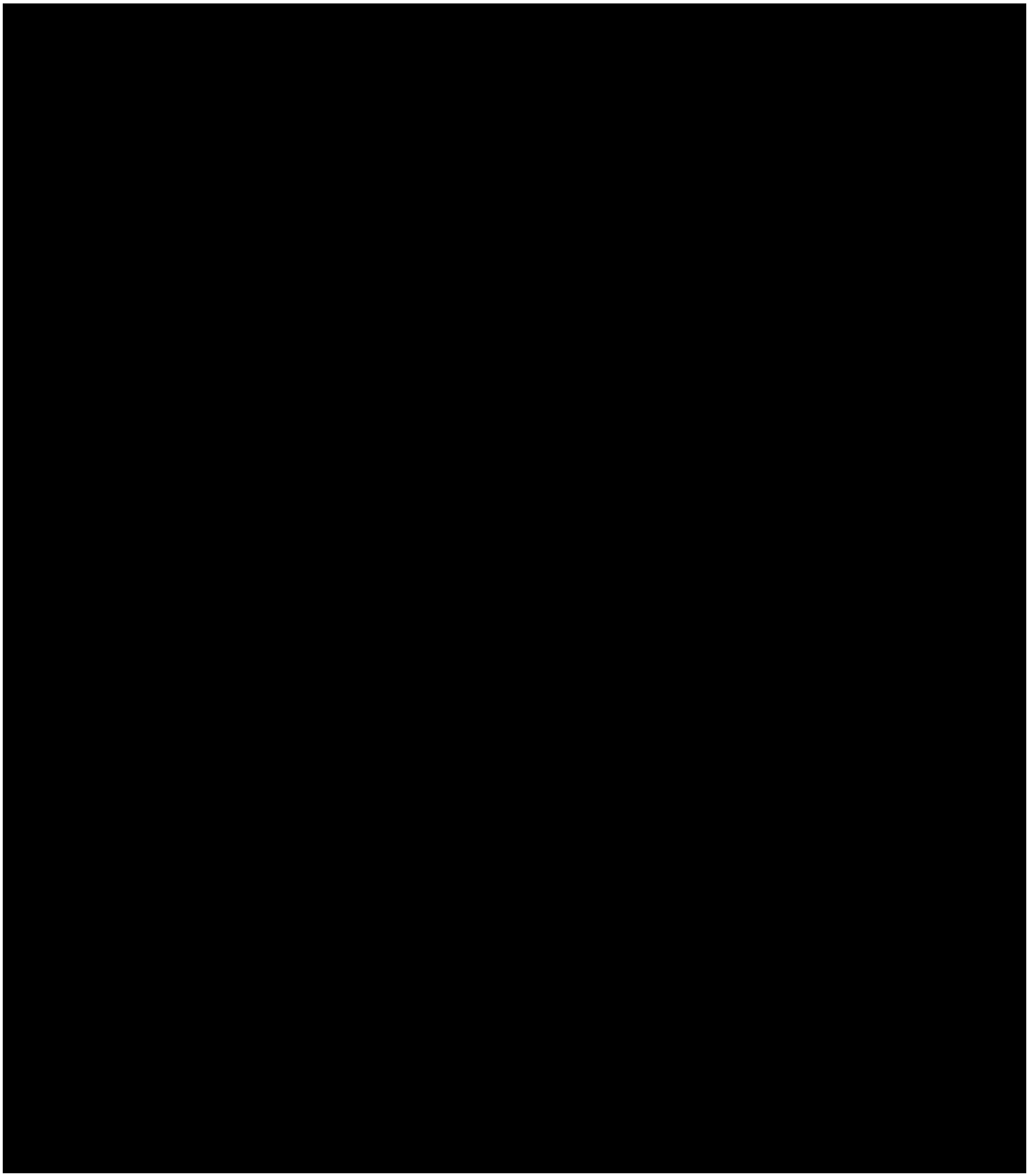
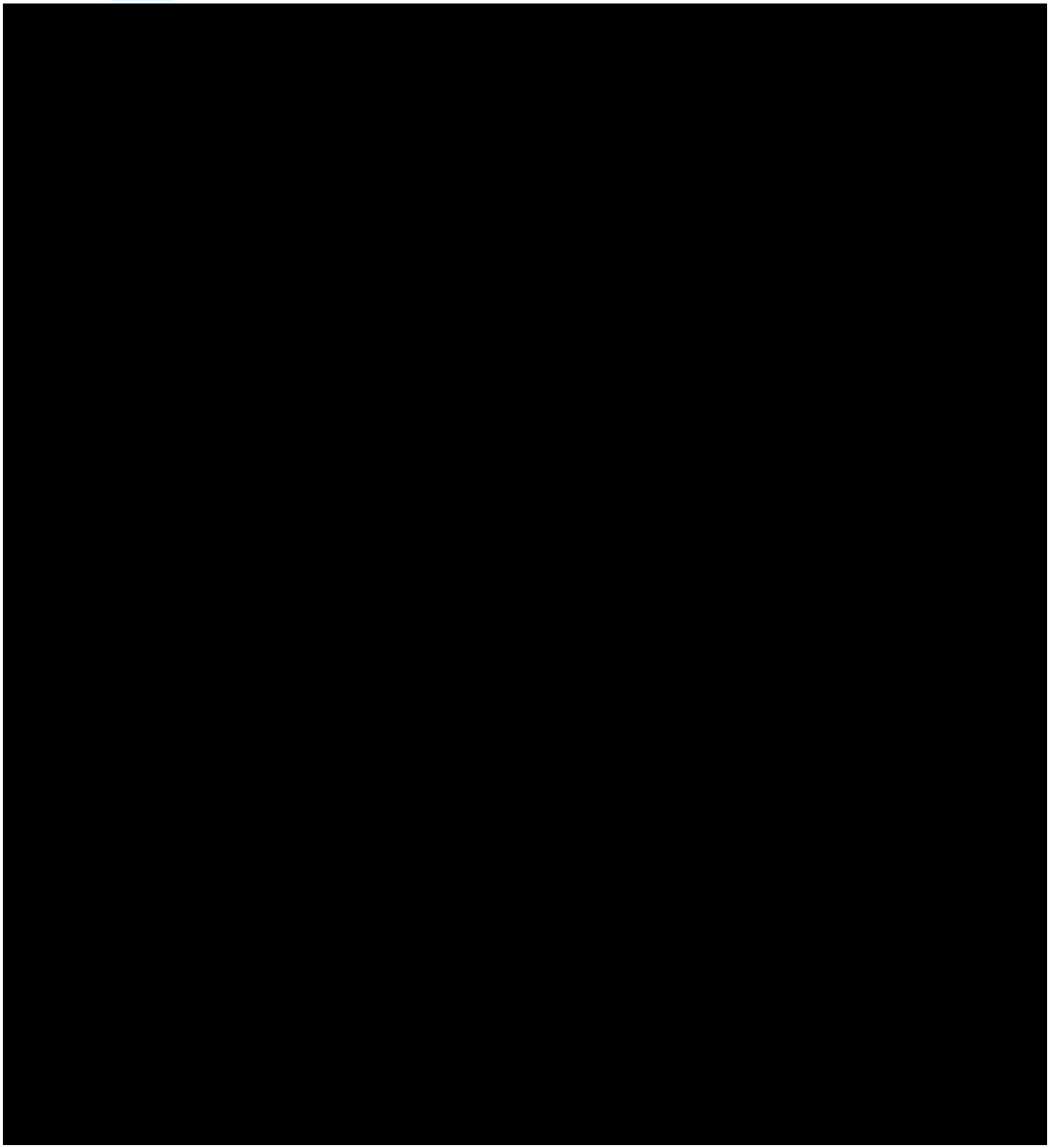
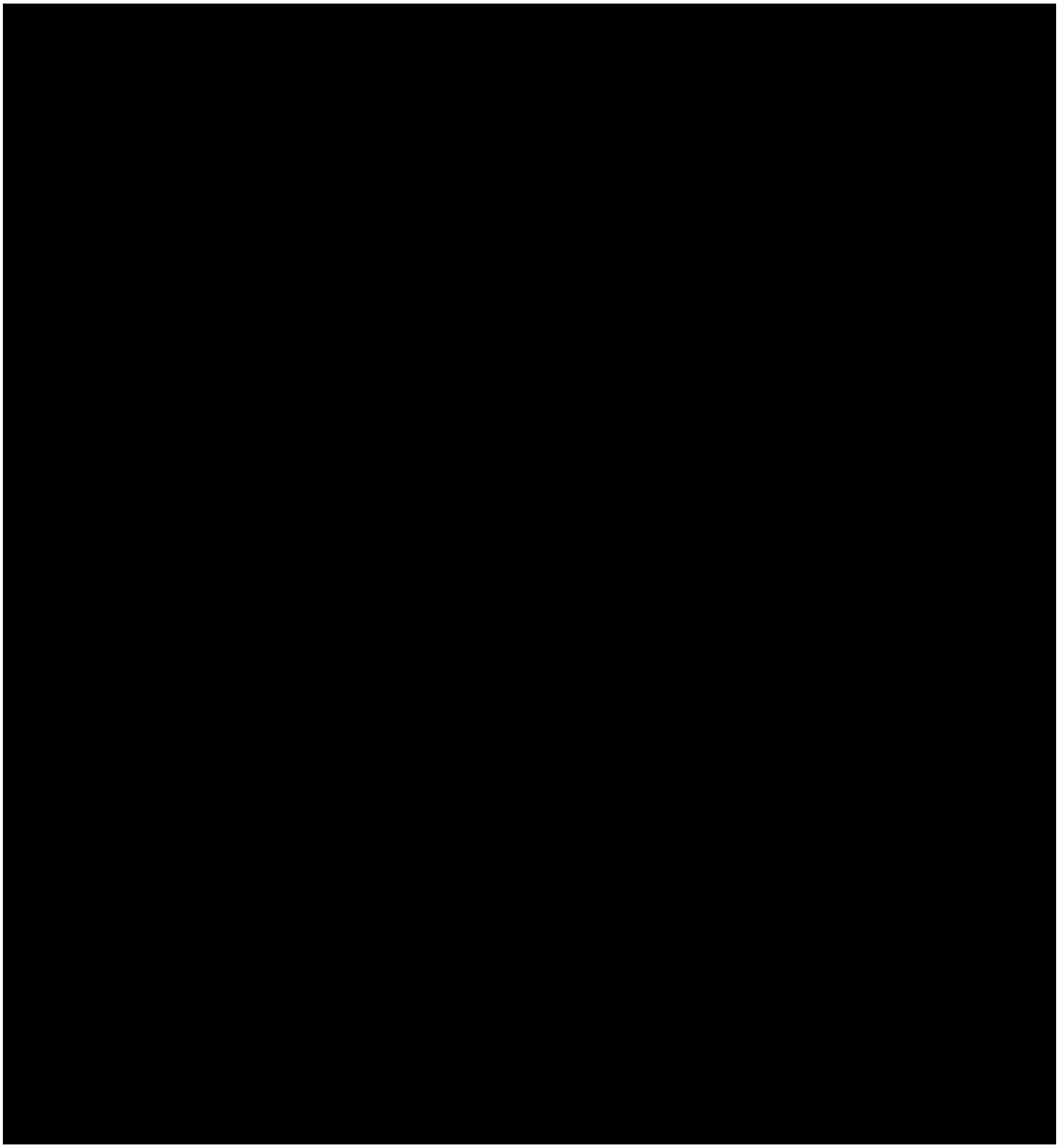








Part 4 – EQ-5D Questionnaire
Extract from "EQ-5D-3L User Guide – Basic on how to use the EQ-5D-3L instrument"
Version 4.0 April 2011, © EuroQol group 2011

[redacted]

1. Introduction

This guide has been developed in order to give users basic information on how to use EQ-5D. Topics include administering the instrument, setting up a database for data collected using EQ-5D as well as information about how to present the results. Also included are several frequently asked questions dealing with common issues regarding the use of EQ-5D and a list of currently available EuroQol Group products.

1.1. The EuroQol Group

- The EuroQol Group is a network of international multidisciplinary researchers devoted to the measurement of health status. Established in 1987, the EuroQol Group originally consisted of researchers from Europe, but nowadays includes members from North America, Asia, Africa, Australia, and New Zealand. The Group is responsible for the development of EQ-5D, a preference based measure of health status that is now widely used in clinical trials, observational studies and other health surveys.
- The EuroQol Group has been holding annual scientific meetings since its inception in 1987.
- The EuroQol Group can be justifiably proud of its collective scientific achievements over the last 20 years. Research areas include: valuation, EQ-5D use in clinical studies and in population surveys, experimentation with the EQ-5D descriptive system, computerized applications, interpretation of EQ-5D ratings and the role of EQ-5D in measuring social inequalities in self-reported health.
- The EuroQol Group's website (www.euroqol.org) contains detailed information about EQ-5D, guidance for users, a list of available language versions, EQ-5D references and contact details.

1.2. EQ-5D

EQ-5D is a standardised measure of health status developed by the EuroQol Group in order to provide a simple, generic measure of health for clinical and economic appraisal[1]. Applicable to a wide range of health conditions and treatments, it provides a simple descriptive profile and a single index value for health status that can be used in the clinical and economic evaluation of health care as well as in population health surveys (Figure 1).

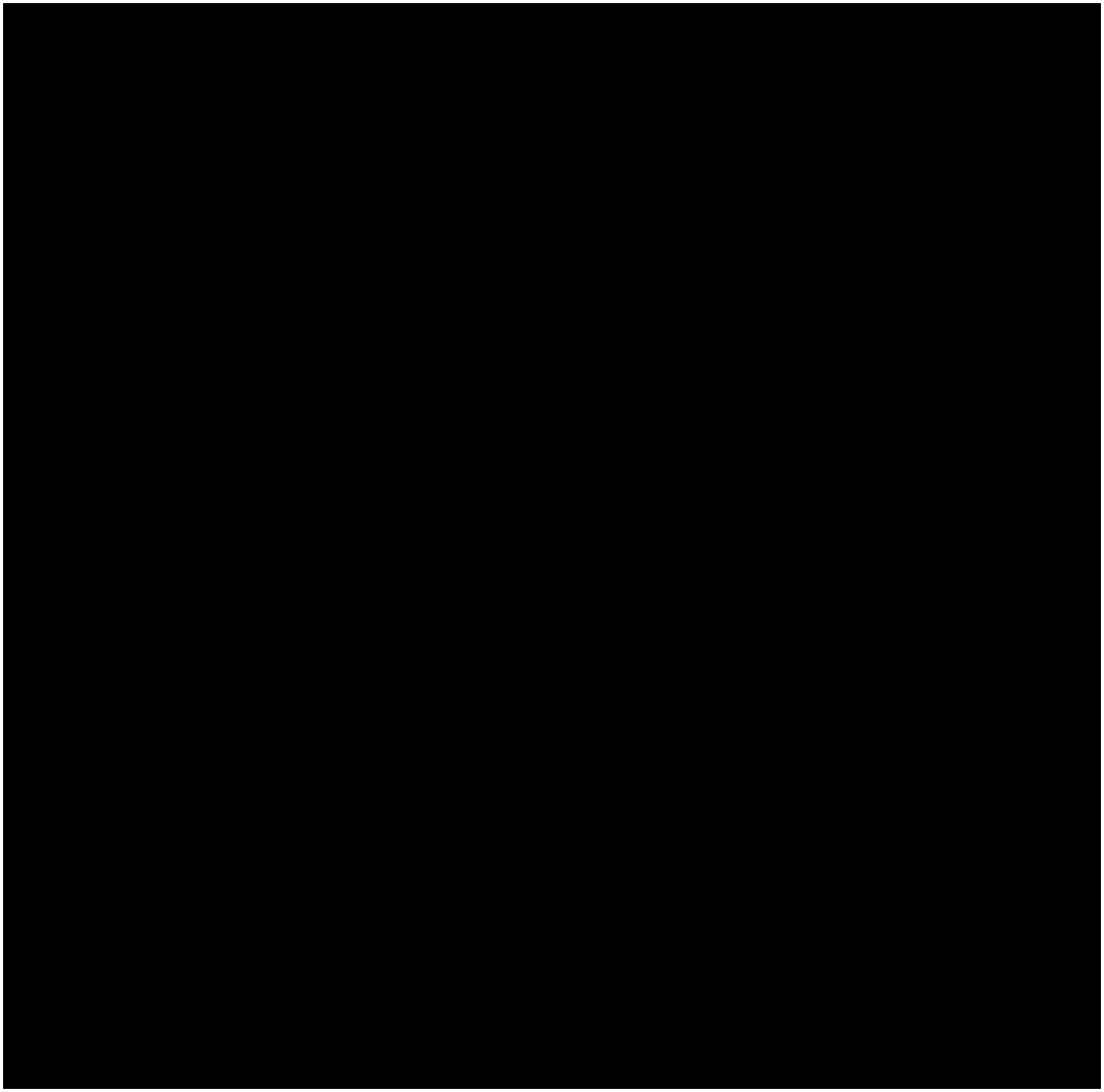
EQ-5D is designed for self-completion by respondents and is ideally suited for use in postal surveys, in clinics, and in face-to-face interviews. It is cognitively undemanding, taking only a few minutes to complete. Instructions to respondents are included in the questionnaire.

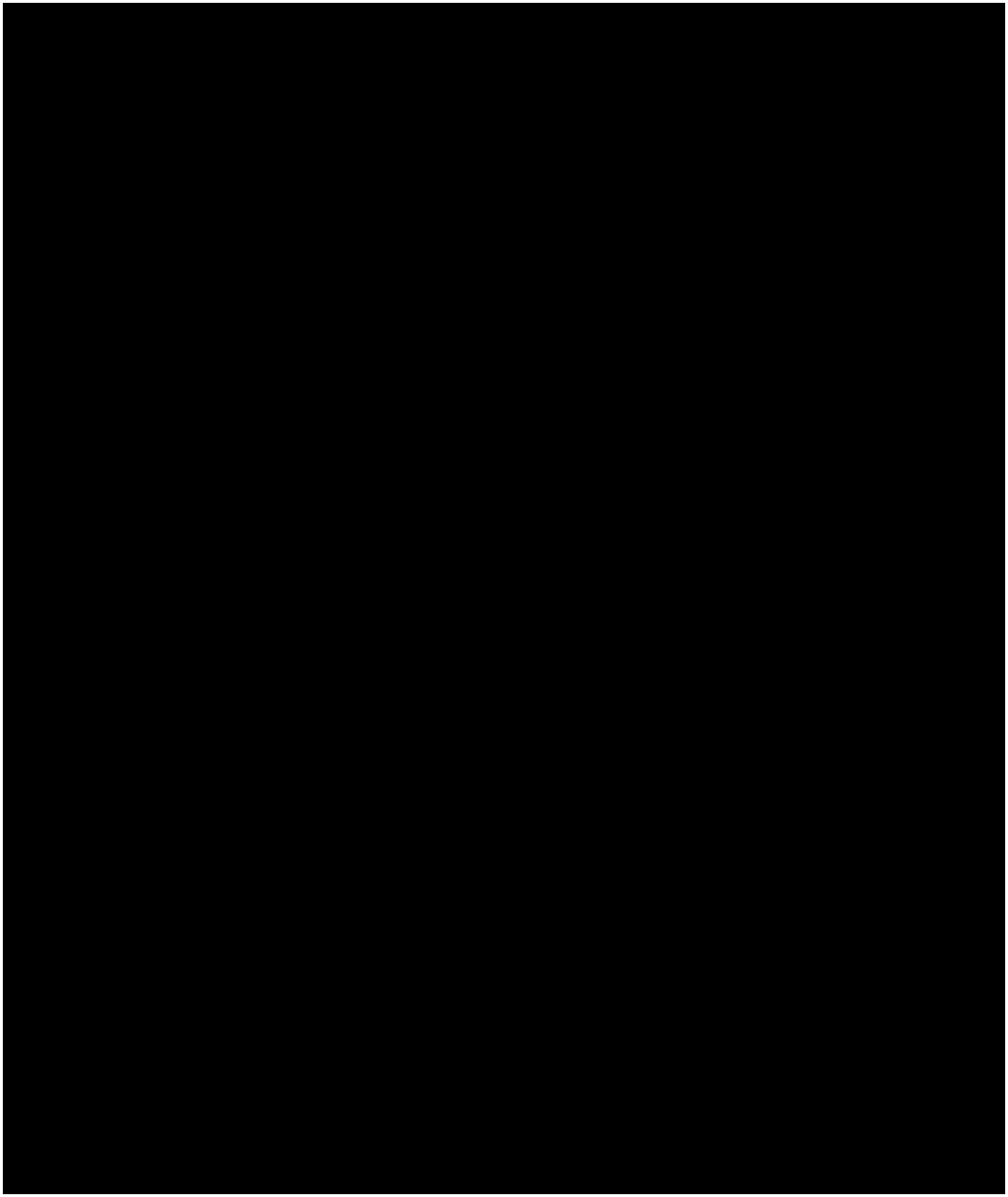
1.2.1. EQ-5D-3L

The EQ-5D 3 level version (EQ-5D-3L) was introduced in 1990. The EQ-5D-3L essentially consists of 2 pages - the EQ-5D descriptive system (page 2) and the EQ visual analogue scale (EQ VAS) (page 3). The EQ-5D-3L descriptive system comprises the following 5 dimensions: mobility, self-care, usual activities, pain/discomfort and anxiety/depression. Each dimension has 3 levels: no problems, some problems, extreme problems. The respondent is asked to indicate his/her health state by ticking (or placing a cross) in the box against the most appropriate statement in each of the 5 dimensions. The EQ VAS records the

[1] EuroQol Group. EuroQol-a new facility for the measurement of health-related quality of life. Health Policy 1990;16:199-208

respondent's self-rated health on a vertical, visual analogue scale where the endpoints are labelled 'Best imaginable health state' and 'Worst imaginable health state'. This information can be used as a quantitative measure of health outcome as judged by the individual respondents. **It should be noted that the numerals 1-3 have no arithmetic properties and should not be used as a cardinal score.**





Part 5: Minnesota Living with Heart Failure Questionnaire
Instructions for use:

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

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

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

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

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

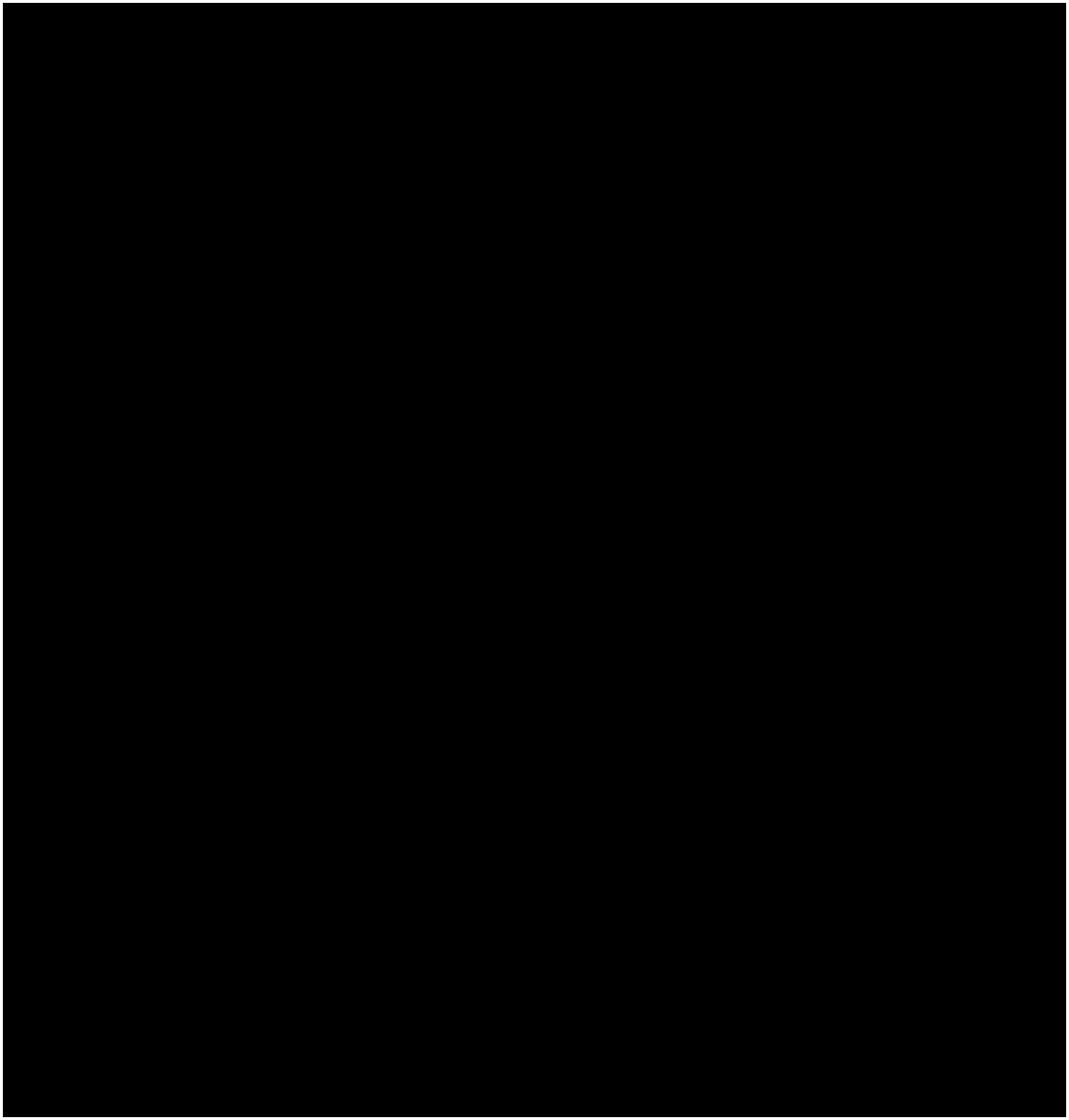
4. Let the patient read and respond to the other questions. The entire questionnaire may be read directly to the patient, being careful not to influence responses by verbal or physical cues.

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

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

LIVING WITH HEART FAILURE QUESTIONNAIRE

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



Part 6: MultiPoint Pacing Vectors Test

This appendix describes the test procedure (Vector Test) that needs to be performed in order to establish if the MPP feature can be turned ON. The feature will be tested at the Classification visit.

Vectors are divided in 4 groups depending on the Cathode.

Group A: includes all the possible vectors using D1 as cathode
Group B: includes all the possible vectors using M2 as cathode
Group C: includes all the possible vectors using M3 as cathode
Group D: includes all the possible vectors using P4 as cathode

[redacted]

In order to allow the MPP feature to be turned ON, a patient will need to have at least 2 vectors from different groups (with different Cathodes) that fulfills the following conditions:

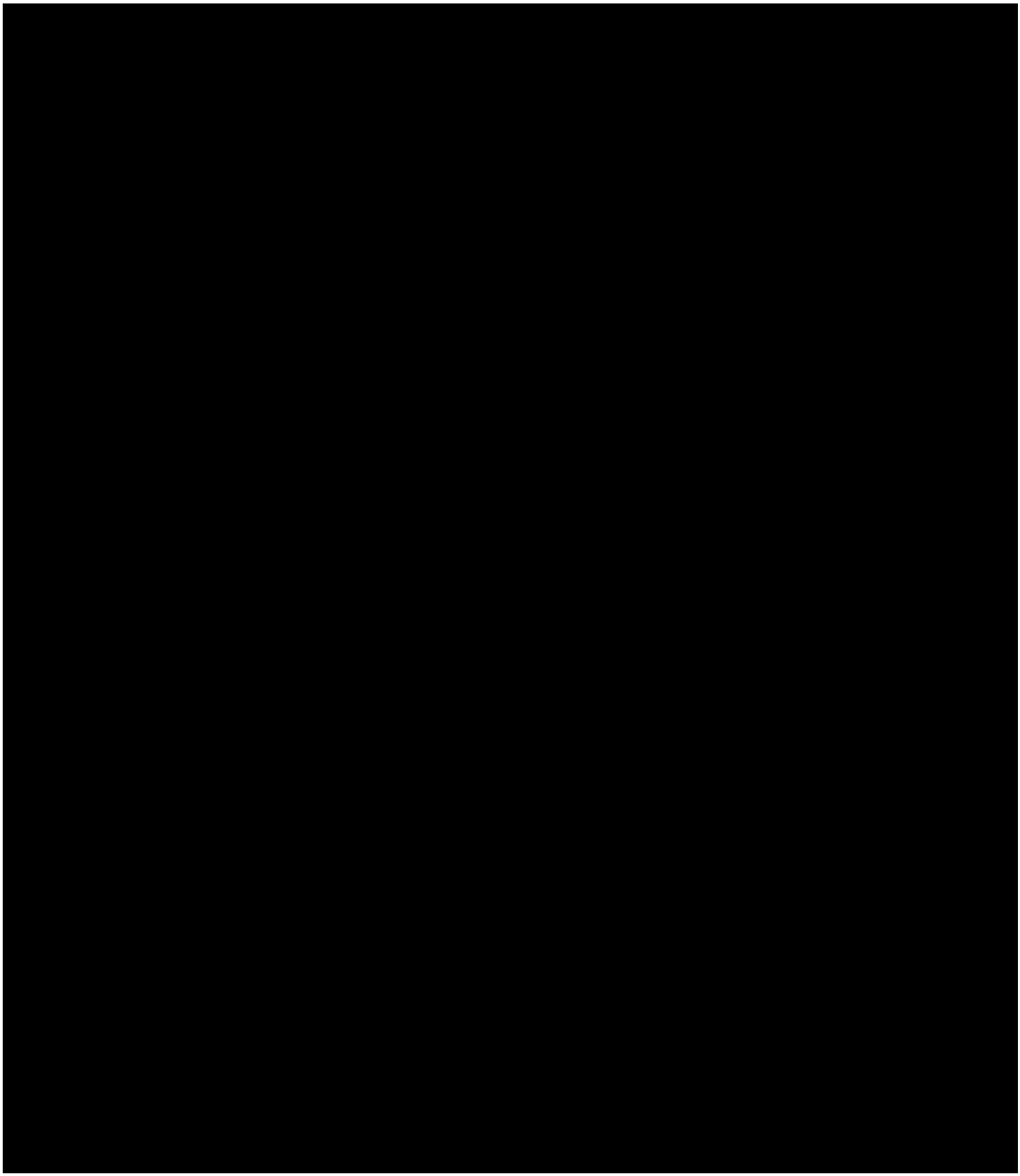
- [redacted]

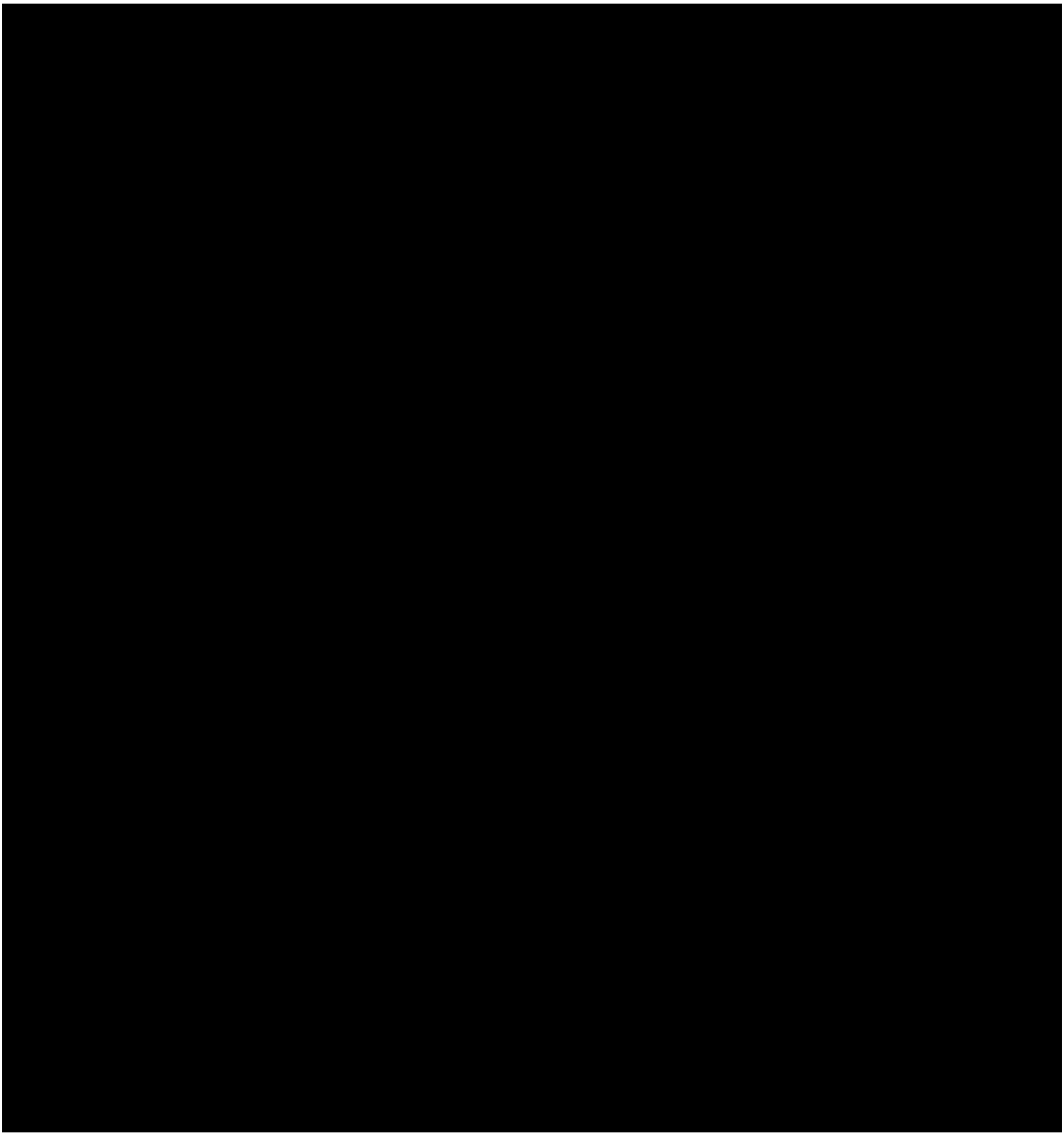
Example:

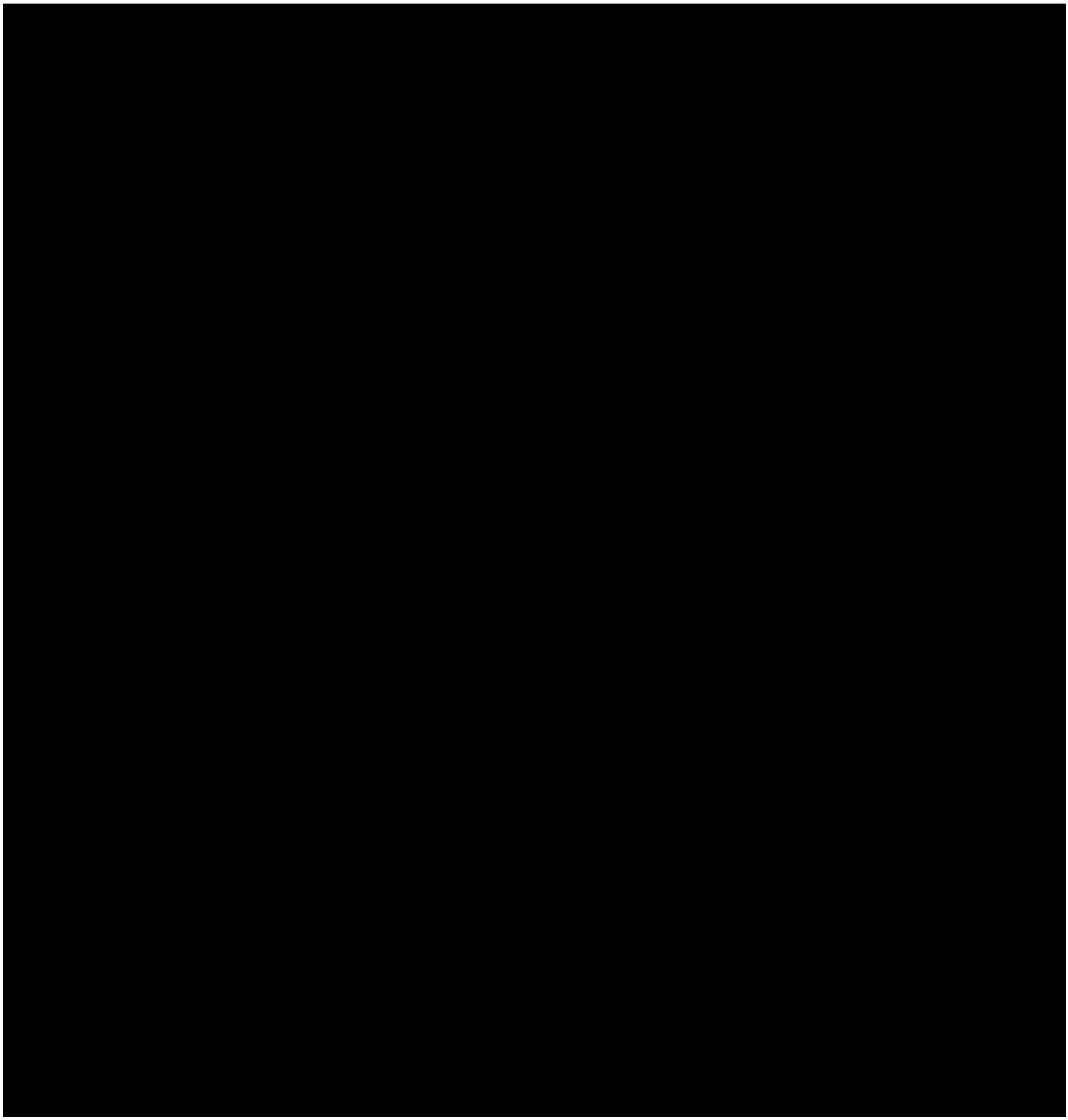
GROUP A: Test Vector D1-P4.
Is the Capture Threshold is lower than 4.5V at 0.5ms pulse width AND there is no PNS at 1 Volt above the Capture Threshold?

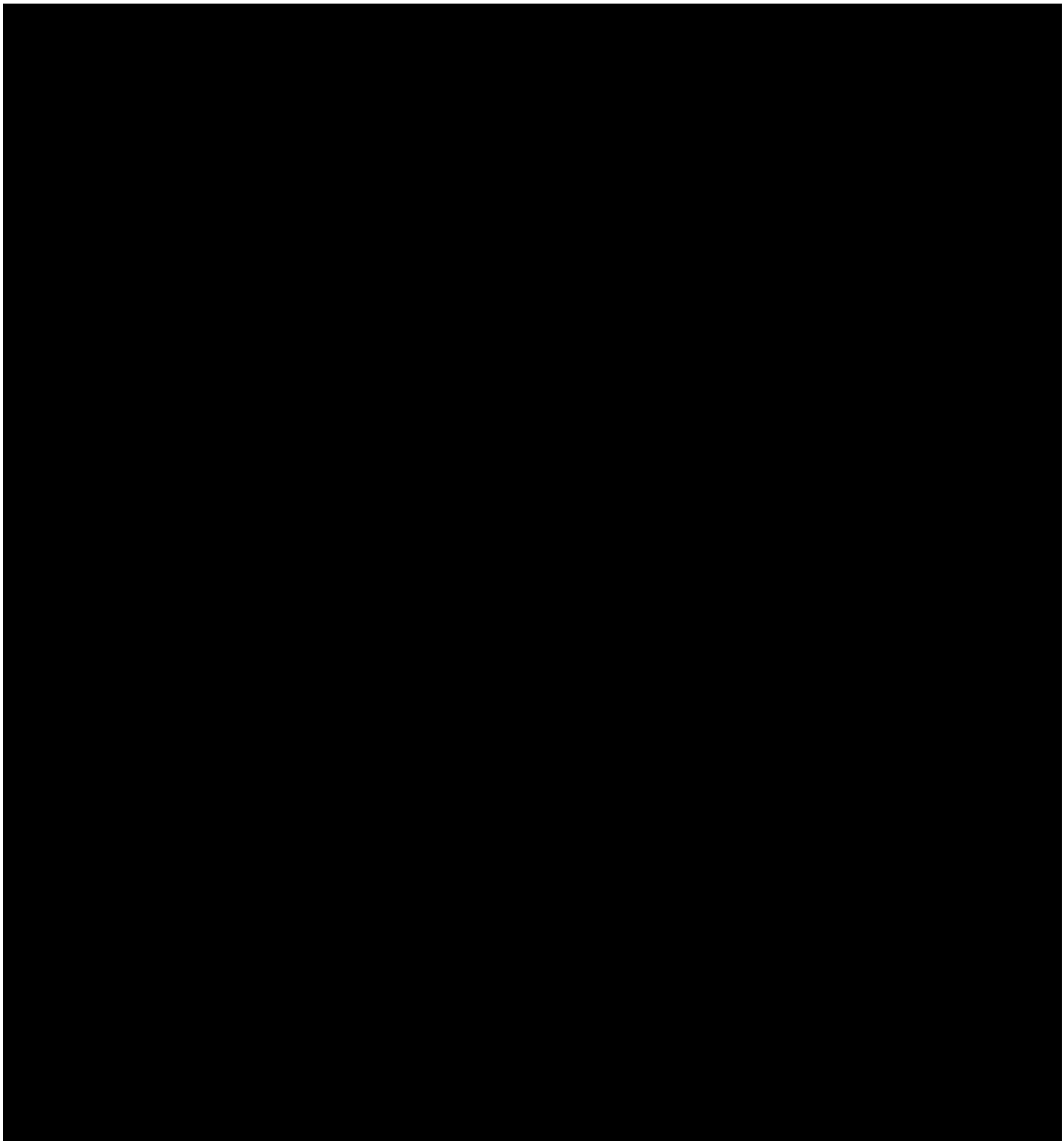
YES: First Vector found, please move to Group B.
NO: Please Test Vector D1-M2

[redacted]









Abbott	Study Document No: [redacted] Study Name: MORE CRT MPP

Statistical Analysis Plan

MORE-CRT MPP

"MOre REsponse on Cardiac Resynchronization Therapy (CRT) with MultiPoint Pacing (MPP)"

([redacted])

Statistical Analysis Plan (SAP)

Abbott	Study Document No: [redacted] Study Name: MORE CRT MPP
Statistical Analysis Plan	

Table of Contents

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1.0 INTRODUCTION

This document is a statistical analysis plan for the MORE-CRT MPP trial ([redacted]).

2.0 TRIAL OBJECTIVES

The objective of this clinical trial is to assess the impact of the MultiPoint Pacing (MPP) feature at 12 months in the treatment of patients that are not responding to standard Cardiac Resynchronization Therapy (CRT) after 6 months. Due to the many combinations of parameters available for MPP programming, the MPP feature will be evaluated in two scenarios:

(1) without mandated MPP programming parameters, and
(2) with mandated MPP programming parameters.

The primary objective is

- To demonstrate that the activation of the MPP feature will increase the rate of CRT responders in patients who are classified as non-responders at 6 months of follow-up.

The secondary objective is

- To assess the impact of the MPP feature on patients' functional and clinical status

3.0 TRIAL DESIGN

This study is designed as a prospective, randomized, multi-center trial. Data will be collected at Enrollment, Baseline, Implant Procedure, Patient Classification, and at 6-month and 12-month follow-up visits.

At the 6-month visit, the subject's response to CRT will be evaluated according to left ventricular end systolic volume (LVESV) reduction as follows:

- Subjects with a LVESV reduction of at least 15% relative to baseline will be classified as responders: these subjects will terminate their participation in the study and return to the center's standard practice.

- Subjects with a LVESV reduction of less than 15% relative to baseline will be classified as non-responders: for these subjects, the MPP feature will be activated according to randomization result (MPP ON versus MPP OFF) and they will be followed until the 12-month visit.

In the **first phase** of the study (Phase I), for those subjects who are randomized to **MPP ON**, the MPP feature is programmed at the physician's discretion.

[redacted]

In the **second phase** of the study (Phase II), for those subjects who are randomized to **MPP ON**, the MPP feature will be programmed with mandated parameters as follows:

- MPP vector combination: Two programmable vectors with the widest spacing ([redacted]) between the two cathodes. The 'Widest Spacing' feature within the VectSelect Quartet™ MultiVector Tools in the Merlin Patient Care System should be used to program to widest spacing.
- LV1-LV2 delay: [redacted]
- LV2-RV delay: [redacted]

At 12 months, responder status will be assessed as follows:

- Subjects with LVESV reduction of at least 15% between Baseline and 12 months will be classified as responders.
- Subjects with LVESV reduction of less than 15% between Baseline and 12 months, or who died due to cardiac cause prior to the 12-month visit, will be classified as non-responders.

The percentage of non-responder subjects converted to responders after 6 months of MPP ON versus OFF will be assessed.

4.0 TRIAL ENDPOINTS

4.1 Primary Endpoint

The primary endpoint of this study is evaluated at 12 months after implant (6 months after randomization) and is defined as the percentage of non-responder subjects converted to responders compared to baseline, as measured by LVESV reduction of at least 15%.

4.2 Secondary Endpoints

- Reduction of LVESV between baseline and 6 Months visit
- Packer's Clinical Composite Score evaluation between baseline and 12 Months visit and between 6 Months and 12 Months visits
- Reverse LV remodeling, measured as changes in LVESV, [redacted] and LVEF
- NYHA Class changes
- 6 minutes walking test changes
- Quality of Life (MLWHF and EQ-5D) changes

5.0 STATISTICAL METHODS

This trial has one primary endpoint and 6 secondary endpoints.

5.1 Primary Endpoint Hypothesis

[redacted]

5.1.1 Analysis Methods

The hypothesis will be tested at the one-sided 2.5% significance level. The null hypothesis will be rejected if the 97.5% lower confidence bound (LCB) for the difference between the proportion of subjects who are responders in the treatment group (MPP ON) and the proportion of subjects who are responders in the control group (MPP OFF), (P_{ON}-P_{OFF}), is greater than 0. The 97.5% LCB will be calculated using the Wald asymptotic confidence limits for difference of binomial proportions. [redacted]

5.1.2 Analysis Population

The primary endpoint analysis will be carried out on three subject cohorts:

- The **first subject cohort** (Cohort #1) [redacted]
- The **second subject cohort** (Cohort #2) [redacted]
- The **third subject cohort** (Cohort #3) [redacted]

5.1.3 Sample Size

Phase I Sample Size

[redacted]

Phase II Sample Size

[redacted]

5.1.4 Sensitivity Analyses

[redacted]

5.1.5 Timing of Analysis

Data Analysis of Phase I Subjects

The analysis will be performed when all randomized non-responder subjects (confirmed by the Echo Core Lab) from Phase I study have either completed or crossed the 12-month visit window or discontinued before the 12-month visit. This analysis will be carried out on Cohort #1.

Data Analysis of Phase II Subjects

One interim analysis and a final analysis will be conducted.

- Interim Analysis

  [redacted]

  [redacted]

- The final analysis will be performed when all randomized non-responder Phase II subjects have either completed or crossed the 12-month visit window or discontinued before the 12-month visit.

- [redacted]
- [redacted]

5.1.6 Poolability Analysis

The poolability analysis between Cohort #2 and Cohort #3 subjects is planned at the interim and final analysis as follows:

[redacted]

5.1.7 Supplemental Analysis

[redacted]

5.1.8 Subgroup Analyses

The following analyses of the primary endpoint may be performed for the following subgroups using the same datasets as those included in the primary endpoint analysis for publication purpose:

- [redacted]

[redacted]

[redacted]

5.2 Secondary Endpoints

5.2.1 Percent reduction (%) in LVESV from baseline to 6 months

Percent reduction (%) in LVESV from baseline to 6 months will be summarized as sample size, mean, standard deviations, median and range. Subjects with missing LVESV at either Baseline or 6 months visit will be excluded from this analysis.

5.2.2 Packer's Clinical Composite Score evaluation between baseline and 12 Months visit and between 6 months and 12 months visits.

Using the Packer's clinical composite score (CCS), subjects are categorized as Improved, Worsened or Unchanged based on the following rules:

- "Worsened" – subjects that demonstrate:
  - Worsening in NYHA Class at last observation carried forward (LOCF) OR worsening by PGA ("worse" or "markedly worse") at LOCF

    OR
  - Presence of HF events as described in CIP

    OR
  - Cardiac death
- "Improved" – subjects that demonstrate:

- At least a one-class improvement in NYHA Class at LOCF OR improvement by PGA ("better" or "markedly better") at LOCF

  AND

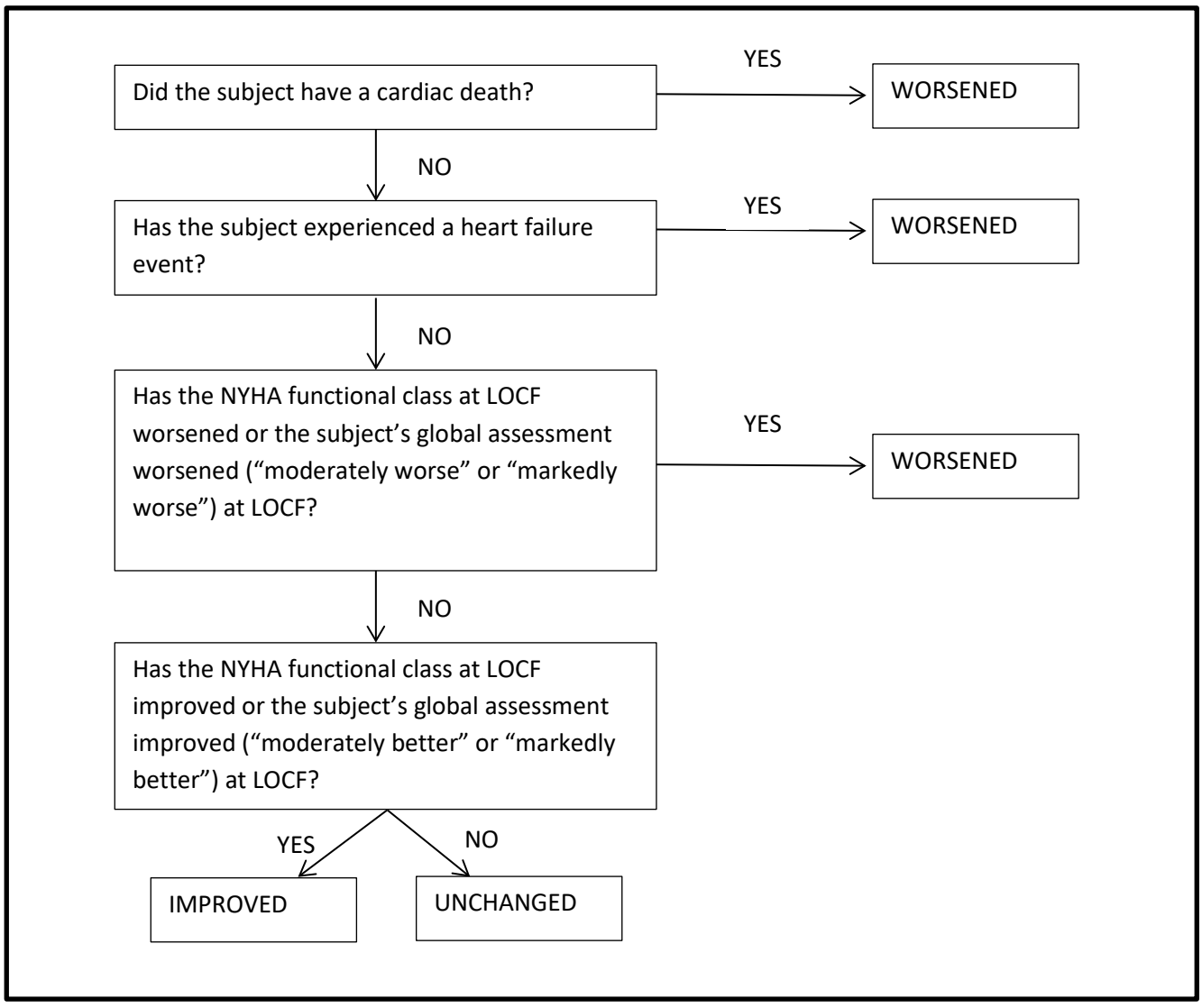
- No HF events as described in CIP

  AND

- No cardiac death

- "Unchanged" – subjects who have non-missing NYHA at LOCF or non-missing PGA at LOCF and are neither "Improved" nor "Worsened".

If both NYHA and PGA are missing based on LOCF and doesn't have HF event and cardiac death, they will be excluded from the analysis.


Did the subject have a cardiac death?
YES
WORSENED
NO
Has the subject experienced a heart failure event?
YES
WORSENED
NO
Has the NYHA functional class at LOCF worsened or the subject's global assessment worsened ("moderately worse" or "markedly worse") at LOCF?
YES
WORSENED
NO
Has the NYHA functional class at LOCF improved or the subject's global assessment improved ("moderately better" or "markedly better") at LOCF?
YES
NO
IMPROVED
UNCHANGED

5.2.3 Reverse LV remodeling, measured as % changes in LVESV, [redacted] and LVEF

- [redacted]

5.2.4 NYHA Class changes

- [redacted]

5.2.5 6-minute walk test changes

- [redacted]

- [redacted]

5.2.6 Quality of Life (MLWHF and EQ-5D) changes

- [redacted]

- [redacted]

5.3 Overall Sample Size

A total number of up to 6896 subjects will be enrolled (see section 5.1.1.4).

5.4 Trial Success

[redacted]

5.5 Multiplicity Adjustment

No multiplicity adjustment is planned in this study.

6.0 ADDITIONAL DATA

6.1 Baseline and Demographic Characteristics

Descriptive statistics of continuous variables will be presented by treatment group and include sample size, mean median, standard deviation, minimum and maximum. For categorical variables, the number and percentage of subjects in each category will be presented by treatment group. Baseline characteristics will be tabulated and compared between the two treatment groups. Categorical variables will be tested using Fisher's exact test and continuous variables will be tested using two sample t-test.

6.2 Mortality

Kaplan-Meier survival curves will be used to summarize freedom from all-cause mortality and freedom from cardiovascular mortality by treatment groups. Randomization will be considered day 0.

6.3 Adverse Events

Adverse events, serious adverse events and unanticipated adverse device effects (UADE) will be summarized in terms of number of events, the percentage of subjects with events, and event rate estimated as # event/patient-years.

6.4 Withdrawals

Withdrawals will be summarized for subjects who have withdrawn from the trial.

6.5 Protocol Deviations

Protocol deviations will be summarized for subjects in whom a protocol deviation was reported.

7.0 DOCUMENTATION AND OHER CONSIDERATIONS

7.1 Software

All analyses will be performed using SAS® for Windows, version 9.3 or higher.

7.2 Rationale of SAP Revision

The following table provide the rationale of changes from SAP [redacted]