Rationale and design of a randomized clinical trial to assess the safety and efficacy of multipoint pacing therapy MOre REsponse on Cardiac Resynchronization Therapy with MultiPoint Pacing (MORE-CRT MPP-PHASE II)

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ABSTRACT

Background: Although cardiac resynchronization therapy (CRT) is beneficial in most heart failure patients, up to 40% do not respond to CRT. Data from the MultiPoint™ Pacing (MPP) IDE trial and MORE-CRT MPP PHASE I study suggest improved response in subjects in the MPP arm –programmed with wide LV electrode anatomical separation (≥30 mm) and shortest timing delays of 5 ms (MPP-AS) –compared with quadripolar biventricular (BiV) pacing.

Study design: The MORE-CRT MPP PHASE II trial is a prospective, randomized, multicenter study to assess the 6-month impact of MPP programmed to mandated MPP-AS settings in subjects who do not respond to six months of BiV pacing (MPP OFF). Approximately 5,000 subjects with a standard CRT indication will be enrolled and implanted with a quadripolar CRT system (Abbott) capable of delivering MPP. Only BiV pacing is activated at implant. At six months, subjects classified as CRT non-responders (<15% reduction in left ventricular end-systolic volume [LVESV]) are randomized (1:1) to MPP or continued BiV pacing. The mandated MPP parameters (e.g., MPP-AS) are programmed to subjects randomized to the MPP arm. At 12 months, the two groups will be compared to determine if there is a difference in CRT response rate.

Conclusions: This trial will evaluate whether MPP programmed to mandated MPP-AS settings improves LV reverse remodeling and clinical response to CRT in patients who fail to respond to six months of BiV pacing (www.clinicaltrials.gov identifier NCT02006069).

Key words: multipoint pacing, heart failure, left ventricular lead, biventricular pacing, cardiac resynchronization, heart failure, randomized trial

INTRODUCTION

Cardiac resynchronization is a well-established therapy for heart failure and has been shown to produce significant clinical benefits, including reduced mortality, fewer heart failure hospitalizations, and improved symptoms and quality of life.[1-6] Conventional CRT with the Quartet quadripolar LV lead (e.g., quadripolar biventricular (BiV) pacing) has demonstrated significantly lower LV-lead related event and improved clinical response rates compared with that with a bipolar or unipolar lead, possibly because the quadripolar lead design allows more pacing configurations and pacing from a more basal pacing site in a higher proportion of patients.[7-9]

However, the proportion of patients who fail to respond to cardiac resynchronization therapy (CRT) remains significant.[10] The cause of CRT non-response is not completely understood and involves multiple inter-related factors; in those patients with atrial fibrillation (AF) there is limited evidence (retrospective and observational data) for the benefits of CRT in the absence of sinus rhythm, which may suggest CRT patients with AF who undergo atrial ventricular junctional (AVJ) ablation respond similarly as to those patients in normal sinus rhythm. However, there is a general consensus that suboptimal left ventricular (LV) lead placement is one of the main contributing reasons to non-response.[11]

In an effort to improve CRT response rate, clinicians have proposed the implantation of multiple LV leads to improve LV synchrony. While technically feasibile, this approach can increase CRT implant procedure time, fluoroscopic exposure and procedure-related adverse events.[12-14] An alternative approach is to use a quadripolar lead (Figure 1) for multipoint pacing (MPP) of the LV from two of ten possible vectors in a CRT-D or from two of fourteen possible vectors in a CRT-P (Table 1). In addition, a programmable delay (5-80 ms) can be introduced

between the two LV pacing pulses, thereby delivering sequential pacing either before or after the right ventricular stimulation.

Small prospective studies have shown CRT with MPP results in acute improvements in contractility, hemodynamics, and dyssynchrony compared with quadripolar BiV pacing.[15-19] A recent study demonstrated both mid-term (3 months) and long-term (12 months) LV reverse remodeling and an improved CRT response rate with MPP compared with quadripolar BiV pacing.[20] In addition, an ad-hoc analysis of the MPP IDE study has shown an 87% CRT response rate by programming two MPP vectors with wide two cathode anatomic spacing (≥ 30mm) and minimal timing delay (5ms) i.e., MPP-AS programming .[21, 22] Data from the MOre REsponse on Cardiac Resynchronization Therapy with MultiPoint™ Pacing Phase I trial have been recently published.[23] MPP-AS elicited a significantly higher non-responder conversion rate compared to MPP-Other (45.6% vs. 26.2%, p=0.006) and a trend in a higher conversion rate compared to biventricular pacing (45.6% vs. 33.8%, p=0.10).

However, there is still a need for larger trials to confirm the long-term efficacy of CRT with MPP and to prospectively evaluate the impact of MPP programming. Moreover, it is important to specifically evaluate the effects of MPP in patients who do not respond to quadripolar BiV pacing. Therefore, the objective of the present report is to describe the design of the MOre REsponse on Cardiac Resynchronization Therapy with MultiPoint™ Pacing Phase II (MORE-CRT MPP – PHASE II) trial. This is a prospective, randomized, multicenter trial to assess the impact of MPP programmed with MPP-AS in subjects who do not respond after an initial six months of BiV pacing.

METHODS

Patient Selection

The trial will enroll approximately 5,000 subjects at up to 250 centers worldwide. Subjects are eligible for enrollment if they meet the current Class I or IIa criteria of the ESC or ACCF/AHA/HRS guidelines for CRT device implantation (including upgrades from single or dual chamber ICDs or pacemakers). A complete list of the MORE CRT MPP Phase II trial inclusion and exclusion criteria appears in Table 2. Subjects are considered enrolled in the study after giving informed consent; sites then assess the subject's cardiac performance – via 2-dimensional echocardiography – and other clinical and demographic variables at a Baseline visit (Table 3).

Implant Procedure

Within 30 days following enrollment, the clinician implants the subject with a regulatory-approved Abbott CRT-D or CRT-P device with the MPP feature and an Abbott quadripolar LV lead. Any commercially-available right atrial and right ventricular leads may be implanted. The clinicians activate BiV pacing at implant and programs the subject's device – including atrioventricular and interventricular delays – based on their discretion. Clinical sites must obtain post-implant fluoroscopic images in two views (LAO 45 ± 10° and RAO 45 ± 10°) to document lead location (Table 3). Subjects enrolled in the trial but who do not have a successful implant of the MPP CRT device terminate their participation in the trial.

Subject Classification

Within seven days of the implant procedure, all subjects have a Classification visit (Table 3) at clinical sites to evaluate the success of the implant procedure, and to perform the required MPP vector test. The MPP vector test consists of measuring pacing thresholds using each of the four electrodes on the quadripolar lead as the cathode and various other electrode combinations as the anode (Table 1). The test is considered successful if at least any two of the four LV cathodes are free from phrenic nerve stimulation at 1 V above the pacing capture threshold, and high capture threshold, defined as > 4.5V at the device default pulse width. Subjects implanted with an appropriate device but who do not have a successful MPP vector test at a Classification visit terminate their participation in the trial. All subjects with a successful MPP vector test are considered "qualified" subjects and continue in the trial.

Subject Follow-up and Randomization

During the first six months following implant, all subjects receive quadripolar BiV pacing (MPP OFF). At the 6-month follow-up visit, clinical sites perform a 2-dimensional echocardiogram on qualified subjects and evaluate CRT response, defined as a reduction of at least 15% in left ventricular end systolic volume (LVESV) compared with baseline. An independent echocardiogram core lab (Cardialysis, The Netherlands) provides a final, blinded evaluation of CRT response via changes in LVESV using the modified Simpson method in the apical 4- and 2-chamber views according to standard methods recommendations of the American Society of Echocardiography.[24] If the bi-plane method is not feasible, a single view is analyzed. Contrast LV opacification is used when indicated for subjects with poorly defined endocardial borders.

Subjects who have an LVESV reduction of at least 15% compared with baseline by both the site and the core lab are classified as responders, and these subjects terminate their participation in the trial. If the core lab assesses a subject as a responder, but the clinical site assesses the same subject as a non-responder, the subject will continue follow-up until 12 months; data from these subjects are excluded from the primary endpoint analysis. Subjects who have an LVESV reduction of less than 15% as assessed by the core lab are classified as non-responders.

Subjects classified as non-responders at the 6-month visit undergo acute testing to determine if their device can be programmed to protocol-mandated MPP settings. The mandated MPP-AS settings are defined as follows,

- MPP vector combination: Two programmable MPP vectors with wide spacing (≥30 mm between two cathodes, corresponding to D1-M3/P4 of any Quartet lead, or of M2-P4 of the 1458QL lead, see Figure 1)
- LV1-LV2 timing delay: 5 ms
- LV2-RV timing delay: 5 ms

Subjects unable to have their device programmed with the mandated MPP settings terminate their participation in the trial. Subjects with a successful acute MPP test at 6 months are randomized in a one-to-one ratio to a group with MPP (MPP arm) or a group with continued BiV pacing (BiV arm) for an additional 6 months of follow-up. Subjects randomized to the BiV arm will receive BiV pacing per the clinician's discretion; subjects randomized to the MPP arm receive MPP with the mandated parameters.

During the 12-month visit, clinical sites perform a final 2-dimensional echocardiogram and evaluate CRT response compared with baseline. The independent core lab again provides a

final, blinded assessment of CRT response at 12 months. The study will be terminated after all qualified subjects complete the 12-month follow-up visit (Figure 2).

Primary and Secondary Endpoints

The primary endpoint of the trial is the percentage of non-responder subjects converted to responders after six months of CRT with MPP or BiV pacing. A response to CRT is a reduction in LVESV of at least 15% at 12 months compared with baseline. Subjects who die due to cardiac reasons post randomization are considered a non-responder. Assuming 34% of subjects in the BiV arm versus 43.9% of subjects in the MPP arm will become responders at 12 months compared to baseline, at least 380 subjects with analyzable data at 12 months are required in each arm (using a one-sided significance level of 2.5% and a power of 80%). Assuming a dropout rate of 21% after randomization, at least 482 randomized subjects are required in each arm. Further, assuming 37% of qualified subjects are non-responders at six months post-implant – with a dropout rate of 6.4% during the first six months following the Classification visit – and considering approximately 35% of qualified subjects are unable to receive protocol-mandated MPP settings due to phrenic nerve stimulation or high thresholds, the trial is required to include at least 4,286 qualified subjects. In order to obtain 4,286 qualified subjects and taking into account implant failures (7.3%), drop-out before implant (2.4%), and MPP activation failure following implant (5%), the trial requires enrollment of approximately 5,000 subjects.

The primary endpoint analysis will be carried out on an "As-Treated" basis – subjects will be analyzed accordingly to their programming (MPP or BiV) at 12 months or at the last follow-up before 12 months. The analysis population for the primary endpoint will include all 6-month non-responders randomized at six months and who complete the trial with analyzable

data, or who die due to cardiac reasons prior to 12 months. In addition, for the MPP arm, the subjects programmed with the protocol-mandated MPP settings will be included in the primary endpoint analysis. The number and proportion of responders will be reported, as well as comparisons between the samples using the Chi-squared test.

In addition to the primary analyses, subgroup analyses on the primary endpoint will be performed by gender, cardiomyopathy classification (ischemic or non-ischemic), device type (CRT-P or CRT-D), conduction delay types (LBBB or Non-LBBB), QRS width ≥ 150 or < 150, left ventricular ejection fraction (LVEF) ≥ 25 or < 25, left ventricular end diastolic volume (LVEDV) $\geq$ median or $<$ median, and by NYHA Class (III/IV or II).

Secondary endpoint analyses will be performed once all subjects have completed or crossed the 12-month visit window. For the MPP arm, subjects programmed with the protocol-mandated MPP settings will be included. Changes in the following outcomes will be compared between baseline and 12 months, and between the 6- and 12-month visits: reduction of LVESV; Packer's Clinical Composite Score (CCS);[25] reverse LV remodeling – measured as percent changes in LVESV, left ventricular end-diastolic dimension (LVEDD) and LVEF; NYHA class; 6-minute hall walk test; and quality of life (Minnesota Living with Heart Failure and EQ-5D).

Statistical analysis

The trial hypothesis will be tested at the one-sided 2.5% significance level for the primary endpoint. 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 arm (MPP) and the proportion of subjects who are responders in the control arm (BiV) – P_{MPP}-P_{BiV} – is greater than 0. The 97.5% LCB will be calculated using the Wald asymptotic confidence limits

with continuity correction method for difference of binomial proportions. Subjects with missing responder status will be excluded from analysis.

DISCUSSION

Newer CRT pacing strategies have been developed to address the inconsistent response to CRT in a substantial number of patients. One such strategy is the use of multiple LV pacing leads to activate larger areas of the myocardium.[12-14, 26] Previous experimental and clinical work has shown that simultaneously activating a larger volume of ventricular tissue results in an increased depolarization velocity and shorter interventricular conduction times.[20, 27] In addition, by capturing a larger volume of ventricular muscle, the site of latest LV intrinsic activation may undergo earlier activation, resulting in better synchronization and improved cardiac output. Multisite LV pacing using multiple leads has been evaluated in numerous small trials, but the results have been inconsistent.[12, 14, 26, 28] Furthermore, the use of multiple LV leads significantly increases the complexity, duration, and risk of the procedure. Thus, MPP using a single quadripolar lead is an attractive alternative to the use of multiple LV leads.

Compared with traditional BiV pacing, several small studies have shown MPP delivered through a quadripolar LV lead improves LV dP/dtmax (maximum rate of rise of LV pressure),[17] LV dyssynchrony,[16, 29] LV peak radial strain,[19] LV pressure-volume loop parameters,[18] and LV electrical activation.[26] Studies also demonstrated MPP provides effective stimulation of the LV and results in both mid-term and long-term LV reverse remodeling and improvements in LV function compared with quadripolar BiV pacing.[20, 30]

Although these previous studies indicate MPP may offer advantages over BiV pacing in patients who need CRT, the long-term clinical effects of MPP and the impact of MPP programming have not yet been evaluated in large randomized, prospective trials. The MORE-CRT MPP trial is the first large, randomized, multicenter trial to evaluate the long-term effects of MPP. Given the trial design, the results should provide more definitive information on whether

there is a clinical benefit of CRT with MPP at 12 months, when MPP is activated at six months in patients who have failed to respond to BiV pacing.

Because the patient population eligible for inclusion into the trial includes patients who receive CRT via defibrillators and pacemakers, this enables observation of potential effectiveness of the MPP feature in a wider audience. Response is assessed after a 6-month period, and is defined using an echocardiographic measure which is objective in nature (LVESV reduction ≥15%) and will moreover be validated by an independent core lab blinded to the site's assessment of the patient's response. One limitation in determining response to CRT is that the LVESV measure used to determine response is most likely a continuum and may not necessarily be a simple "cut off" point. The randomization aspect of the trial should produce comparable groups of non-responders who will either have MPP or BiV pacing. Randomization should also reduce effects of potential confounding factors and result in a more unbiased testing of treatment efficacy.

A post-hoc analysis from the MPP IDE study showed that patients programmed with a distance between LV1 and LV2 ≥ 30 mm and a minimal programmable delay of 5 ms (MPP-AS) had a significantly higher responder rate and non-responder to responder conversion rate compared to other MPP configurations.[21] Furthermore, the results from the recent MORE CRT MPP – PHASE I study were consistent with a two-fold response in conversion rate with MPP-AS compared to MPP-other based on LV reverse remodeling, and a trend in a higher conversion rate with MPP-AS compared to BiV pacing (46% versus 34%).[23] The finding from the Phase I study underscores the importance of proper MPP programming and significance of assessing the impact of mandated MPP-AS programming compared with BiV pacing in converting non-responders to responders in the Phase II study.

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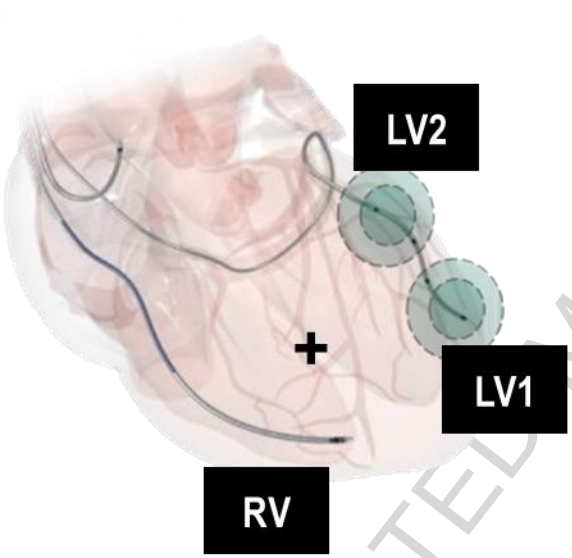
FIGURE LEGENDS

FIGURE 1 Diagram of Quartet™ Family of LV quadripolar leads The diagram shows electrode location and spacing.

FIGURE 2 Study Flow Diagram The diagram outlines patient flow of screening, implant, randomization, and follow-up in the MORE-CRT MPP PHASE II trial. BiV = biventricular; MPP = multipoint pacing; LVESV = left ventricular end-systolic volume.

Table 1. The pacing configurations available in the Abbott Quadripolar CRT-D system (10) and Quadripolar CRT-P system (14). D1 = Distal tip, M2 = middle ring 2, M3 = middle ring 3, P4 = proximal ring



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

Table 2. Inclusion and exclusion criteria

Inclusion criteria (all must be present)

- 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

Exclusion criteria (all must be absent)

- 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

Table 3. Summary of the All Scheduled Evaluations and Procedures

	Enroll	Baseline	Implant Procedure	Patient Classification	6 Month Follow-up	12 Month Follow-up
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

(X*): If performed as Standard of care at the site, X[$]: Testing of mandated MPP settings before randomization, X[§]: can be performed at any time from 3 months prior CRT implant (by an echo qualified study center), †CRT device-based test that measures the conduction delay between the right and left ventricles.

BNP, brain natriuretic peptide; EQ-5D, European Quality of Life-5 Dimensions; LVESV, left ventricular end-systolic volume; LAO, left anterior oblique; MLWHF, Minnesota Living with Heart Failure; MPP, MultiPoint pacing; NYHA, New York Heart Association; RAO, right anterior oblique

Figure 1

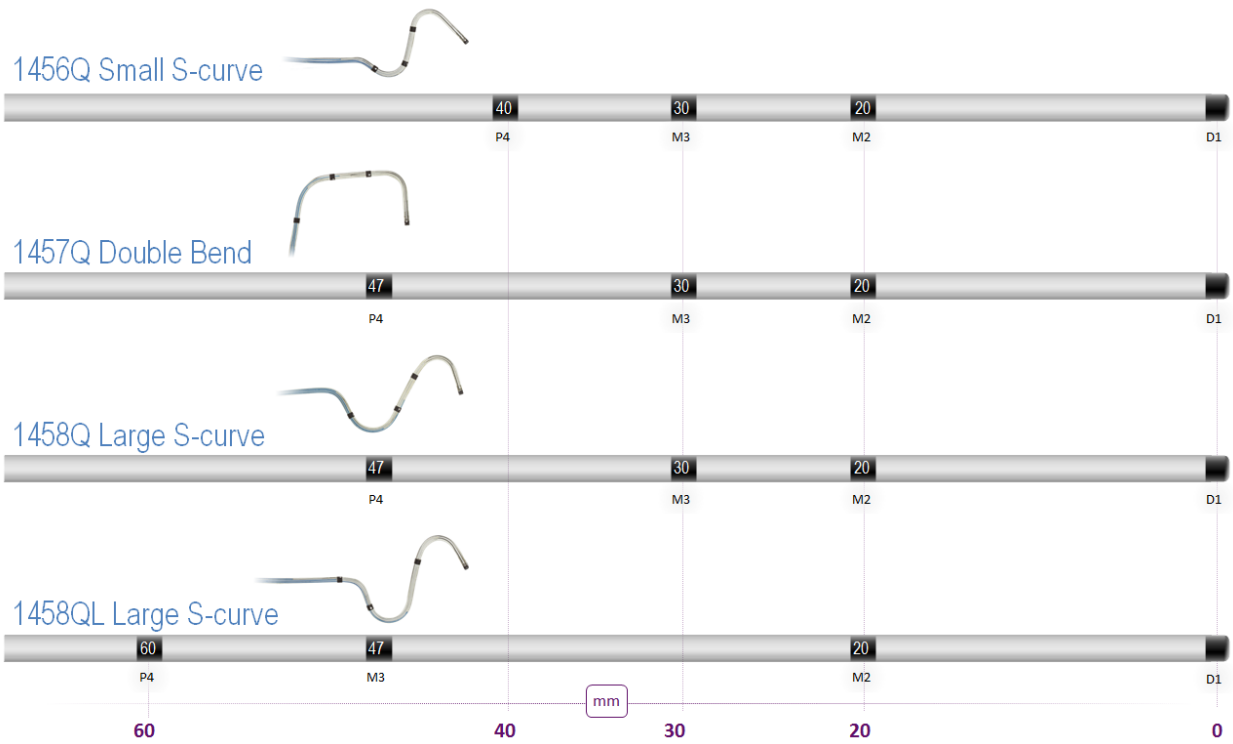
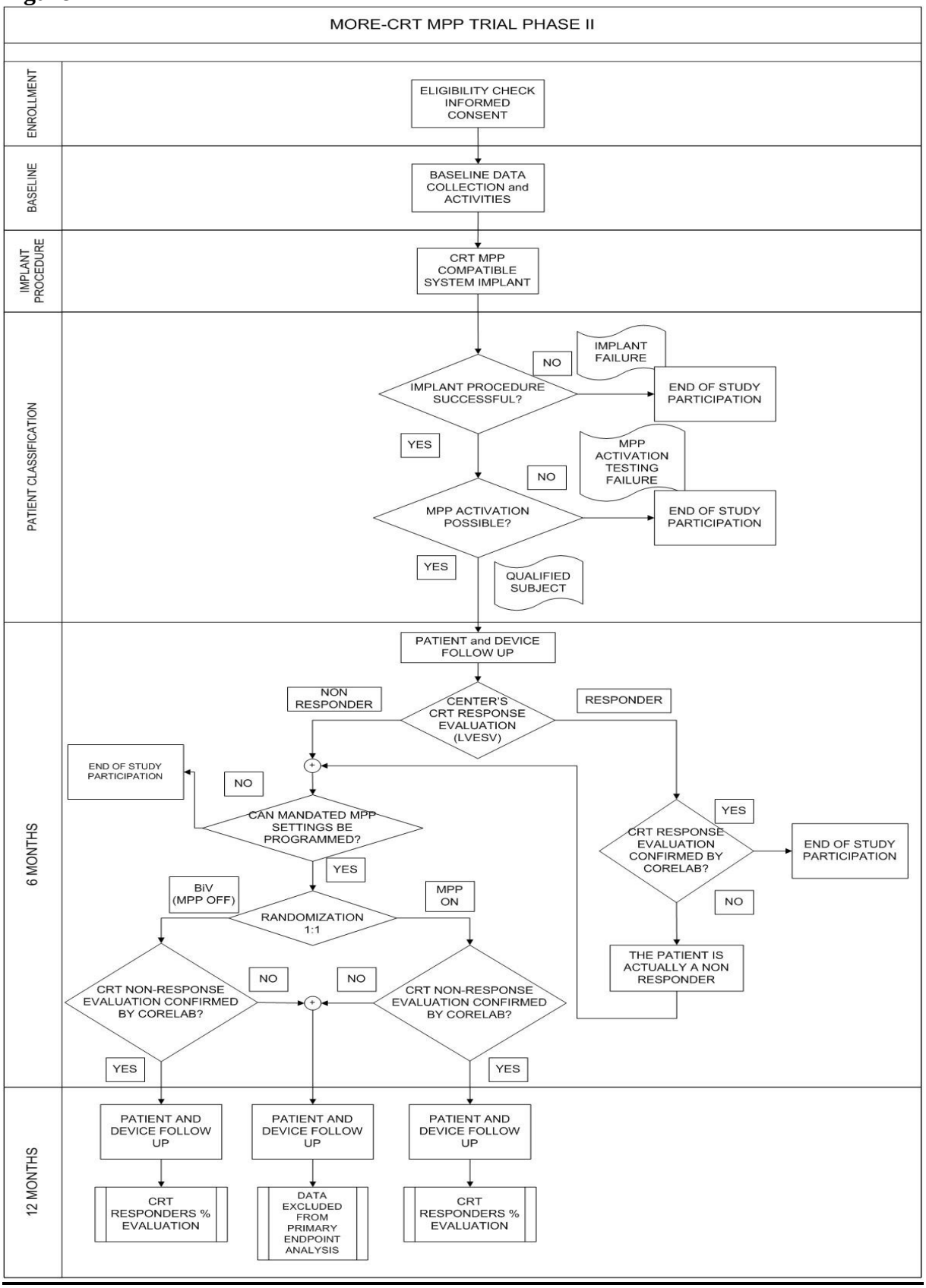


Figure 2



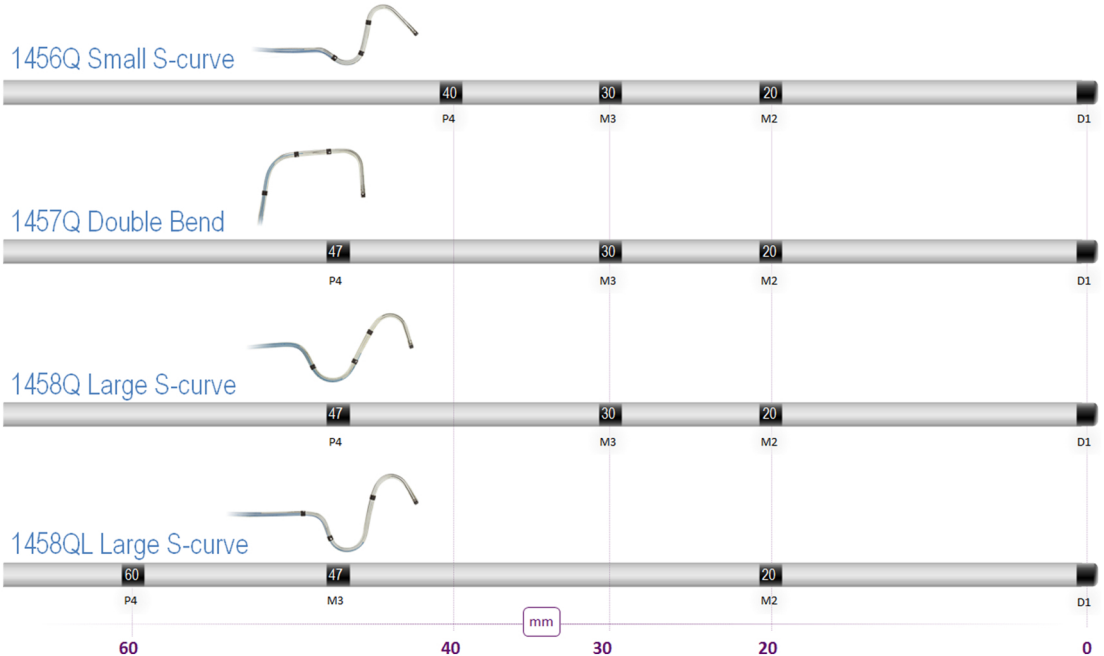

1456Q Small S-curve
40
30
20
P4
M3
M2
D1
1457Q Double Bend
47
30
20
P4
M3
M2
D1
1458Q Large S-curve
47
30
20
P4
M3
M2
D1
1458QL Large S-curve
60
47
20
P4
M3
M2
D1
mm
60
40
30
20
0

Figure 1

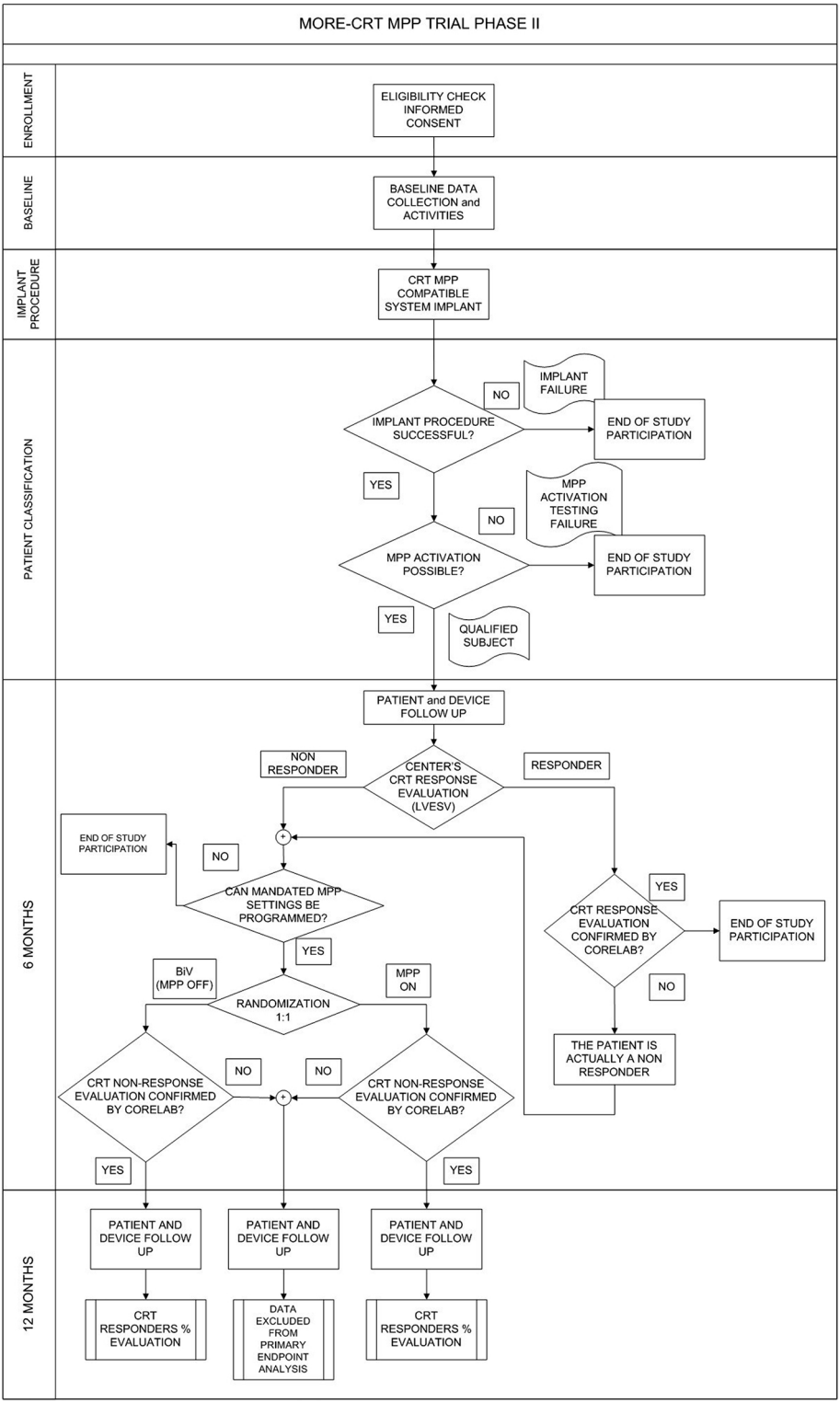

MORE-CRT MPP TRIAL PHASE II
ENROLLMENT
ELIGIBILITY CHECK INFORMED CONSENT
BASELINE
BASELINE DATA COLLECTION and ACTIVITIES
IMPLANT PROCEDURE
CRT MPP COMPATIBLE SYSTEM IMPLANT
PATIENT CLASSIFICATION
IMPLANT PROCEDURE SUCCESSFUL?
NO
IMPLANT FAILURE
END OF STUDY PARTICIPATION
YES
MPP ACTIVATION POSSIBLE?
NO
MPP ACTIVATION TESTING FAILURE
END OF STUDY PARTICIPATION
YES
QUALIFIED SUBJECT
6 MONTHS
PATIENT and DEVICE FOLLOW UP
CENTER'S CRT RESPONSE EVALUATION (LVESV)
NON RESPONDER
RESPONDER
END OF STUDY PARTICIPATION
NO
CAN MANDATED MPP SETTINGS BE PROGRAMMED?
YES
BiV (MPP OFF)
RANDOMIZATION 1:1
MPP ON
CRT NON-RESPONSE EVALUATION CONFIRMED BY CORELAB?
NO
NO
CRT NON-RESPONSE EVALUATION CONFIRMED BY CORELAB?
YES
YES
CRT RESPONSE EVALUATION CONFIRMED BY CORELAB?
YES
END OF STUDY PARTICIPATION
NO
THE PATIENT IS ACTUALLY A NON RESPONDER
12 MONTHS
PATIENT AND DEVICE FOLLOW UP
PATIENT AND DEVICE FOLLOW UP
PATIENT AND DEVICE FOLLOW UP
CRT RESPONDERS % EVALUATION
DATA EXCLUDED FROM PRIMARY ENDPOINT ANALYSIS
CRT RESPONDERS % EVALUATION

Figure 2