Clinical Investigation Plan for

QP ExCELs U.S.

Sentus QP – Extended CRT Evaluation with Quadripolar Left Ventricular Leads

EP PASSION/MPP Sub-Study Amendment

NCT03155724

September 6, 2019

BIOTRONIK, Inc.
6024 Jean Road, Lake Oswego, OR 97035

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PROTOCOL SIGNATURE PAGE

The signature below documents receipt and review of the QP ExCELs study protocol and any attachments, and provides assurance that this study will be conducted according to all stipulations of the protocol, including all statements regarding confidentiality, and according to local legal and regulatory requirements and applicable guidelines.

Principal Investigator:

_____

Name (please print)

_____ _____

Signature Date

Summary

Title	Sentus **QP** – **Ex**tended **C**RT **E**valuation with Quadripolar Left Ventricular **L**ead**s** EP PASSION/MPP Sub-Study Amendment
Acronym	QP ExCELs
Subject collective	Heart failure subjects with standard CRT-D indication according to clinical routine.
Design	Single-arm, multi-center, and prospective trial. The MPP sub-study is designed to fulfill the FDA required post-aproval study for the US market released BIOTRONIK MultiPole Pacing (MPP) feature (PMA P050023/S107) of the Ilivia HF-T QP family CRT-D system (PMA P050023/S103),or Acticor/Rivacor HF-T QP family CRT-D system (PMA P050023/S125).
Objectives	The primary objective of this clinical investigation is to convert a percentage of CRT non-reponders to responders using the MultiPole Pacing (MPP) feature.
Primary Endpoint	Evaluation of the CRT responder status with the MPP feature
Secondary Endpoints	1. Freedom from MPP system-related complications at 6 months post MPP enrollment. 2. Clinical composite score + patient global assessment responder status 3. Clinical composite score responder status utilizing a modified responder classification
Sample Size	QP ExCELs study: up to 1,754 subjects enrolled in U.S. MPP sub-study: up to 110 subjects within the U.S. who are participating in the QP ExCELs study.
Investigational Sites	Up to 75 sites within the United States
Follow-up period	All subjects will be followed up to 6 months for screening into the MPP sub-study. If the MPP inclusion/exclusion criteria are met at screening, the subject will be followed an additional 6 months.
Sponsor	BIOTRONIK, Inc. Clinical Studies Department 6024 Jean Road Lake Oswego, Oregon 97035

1. INTRODUCTION

1.1 Study Overview

The QP ExCELs study protocol was designed to support a pre-market study phase and an FDA required post-approval registry phase for BIOTRONIK's Sentus QP lead. In addition, the QP ExCELs protocol supports an FDA required post-approval MultiPole Pacing (MPP) sub-study to demonstrate the MPP feature can effectively convert a percentage of CRT non-responders to responders.

Upon completion of the pre-market analysis and approval of the Sentus QP LV lead (P070008/S079, approved May 4, 2017), enrollment into the QP ExCELs study was continued to fulfill the post-approval study requirements. On September 24th, 2019, BIOTRONIK received FDA approval to transition the QP ExCELs Study protocol to the Sentus QP EP PASSION Post-Approval Study Protocol. The purpose of this clinical study protocol amendment is to support the continuation of the MPP sub-study while the QP ExCELs Post-Approval Study protocol is transitioned to the Sentus QP EP PASSION Post-Approval Study protocol.

Subjects eligible for the study are receiving or have recently received a new (*de novo*) implant or undergoing an upgrade from an existing ICD or pacemaker implant with no prior attempt at LV lead placement. Prior to enrollment, eligible subjects will be identified and will provide written informed consent, which will include consent to participate in the QP ExCELs study and the MPP sub-study. Subjects will be screened for the MPP sub-study at the 6 month in-office follow-up, or between 3 months and 6 months post-implant if the patient has a heart failure hospitalization. Those subjects satisfying the MPP sub-study inclusion and exclusion criteria will continue into the MPP sub-study and be seen for additional follow-up visits at 3 months and 6 months after MPP sub-study enrollment (See Section 3.3 for details). No further study visits will be completed for subjects that do not qualify for the MPP sub-study.

All devices utilized in conjunction with this study are U.S. market approved and prescribed by physicians according to approved indications for use.

1.2 Background

Heart failure (HF) is a major public health issue with a current prevalence of 2-3% in the total and 10-20% in the aged population (Lloyd-Jones et al., 2010). The overall prevalence for heart failure is increasing due to aging population. Additional factors are the success of the modern therapies in prolongation of survival of patients suffering from coronary events and the effective prevention of death for patients being at high risk.

The overall mortality for the population is 50% in the first 4 years and 40% of the patients with HF-related hospitalizations have to be readmitted to hospital or die within one year (Dickstein et al., 2008).

Cardiac Resynchronization Therapy (CRT) is used in order to synchronize interventricular and intraventricular contraction pattern of the heart in patients with heart failure in whom there is evidence of electrical dyssynchrony (QRS width ≥120 ms). CRT with defibrillator function (CRT-D) is recommended to reduce morbidity and mortality in patients in NYHA class III-IV who are symptomatic despite optimal medical therapy and suffer from a reduced left ventricular ejection fraction (LVEF ≤ 35%, (Dickstein et al., 2008)). This indication has been recently extended to patients in NYHA class II (Dickstein et al., 2010).

Despite the proven benefit of CRT in the indicated population, up to one-third of patients do not respond to the therapy (Rinaldi et al., 2015). The combination of the BIOTRONIK left ventricular lead family Sentus QP with the corresponding Cardiac Resynchronization Therapy devices (CRT) provides additional pacing options to optimize cardiac resynchronization therapy, based on the individual anatomy and needs of heart failure patients as well as the ability of stimulating more than one LV pacing site within one cardiac cycle.

Studies have shown that multiple point LV pacing via a QP LV lead may be an alternative approach to improve CRT response by delivering multiple LV pacing pulses, simultaneously recruiting a larger volume of myocardium (Forleo et al., 2016). A recent IDE study from St. Jude Medical showed that quadripolar multiple point LV pacing (MultiPoint™ Pacing algorithm) was non-inferior to standard quadripolar biventricular (BiV) pacing (Tomassoni et al., 2016).

The current protocol is designed to demonstrate the effectiveness of the MPP feature in BIOTRONIK CRT-D systems by converting a percentage of CRT non-responders to responders.

1.2.1 Published Results for Multipoint LV Pacing

Forleo et al., 2016 evaluated the experience of the St. Jude Medical MPP-capable CRT-D devices (Unify Quadra MP or Quadra Assura MP) connected to a quadripolar LV lead (Quartet™). A total of 507 patients in whom these devices had been successfully implanted were enrolled between August 2013 and May 2015. The analyses included: (i) current clinical practices for the management of such patients, and (ii) the impact of MPP on heart failure clinical composite response and on the absolute change in ejection fraction (EF) at 6 months. Multipoint pacing was programmed to ‘ON’ in 46% of patients before discharge. Methods of optimizing MPP programming were most commonly based on either the greatest narrowing of the QRS complex (38%) or the electrical delays between the electrodes (34%). Clinical and echocardiographic follow-up data were evaluated in 232 patients whom data were available both at the baseline and the 6-month follow-up examination. These patients were divided into two groups according to whether MPP was programmed to ‘ON’ (n = 94) or ‘OFF’ (n = 138) at the time of discharge. At 6 months, EF was significantly higher in the MPP group than in the biventricular-pacing group (39.1 ± 9.6 vs. 34.7 ± 7.6%; P < 0.001). Even after adjustments, early MPP activation remained an independent predictor of absolute increase in LVEF of ≥5% (odds ratio 2.5; P = 0.001). At 6

months, an improvement in clinical composite score was recorded in a greater proportion of patients with MPP-ON than in controls (56 vs. 38%; P = 0.009). On comparing optimal MPP and conventional vectors, QRS was also seen to have decreased significantly (P < 0.001) (Forleo et al., 2016).

The recent MultiPoint™ Pacing (MPP) IDE Study from St. Jude Medical showed that quadripolar multiple point LV pacing (MultiPointTM Pacing algorithm) was non-inferior to standard quadripolar biventricular pacing. The multicenter study enrolled and followed 506 subjects with a standard CRT-D indication who were implanted with a CRT-D system (Quartet™ LV lead with a Quadra CRT-D) capable of delivering either quadripolar biventricular pacing or MPP. Quadripolar Bi-V pacing was activated at implant. At 3 months post-implant, patients' responder status was assessed, both responders and non-responders were randomized, and 1:1 randomization (Bi-V or MPP) was stratified by responder status. The primary efficacy endpoint (freedom from system-related complications through 9 months) was 93.2%, (97.5% lower confidence bound 90.4%) was greater than the objective performance criterion of 75%. The primary efficacy endpoint was met for both intention-to-treat and as-treated populations in 381 randomized patients (ITT, p=0.013 and as-treated, p=0.008, respectively). For patients in the MPP arm programmed with wide cathode spacing and the shortest intraventricular timing delay (5ms), MPP provided significantly higher clinical responder rate (between 3 and 9 months) up to 87% (p=0.003 vs <30mm) and converted 100% non-responders to responders (p=0.006 vs <30mm).

1.3 Devices

This study utilizes the Ilivia 7 HF-T QP family and the Acticor/Rivacor HF-T QP family CRT-D systems with an IS4 port for connection to a Sentus OTW left ventricular lead. The Sentus OTW QP L, Sentus OTW QP S, Sentus OTW QP S/49, and Sentus OTW QP L/49 will be further referred to as Sentus QP leads throughout this protocol.

1.3.1 Sentus QP Lead

The Sentus QP leads are 4.8 F transvenous, steroid-eluting, quadripolar coronary sinus leads intended for permanent pacing and sensing of the left ventricle during cardiac resynchronization therapy. The development of the Sentus QP lead is based on the predecessor product Corox OTW BP. The new elements of the development include two additional ring electrodes along the distal portion of the lead, a standard IS4 quadripolar lead connector and a small diameter.

A single steroid collar with 0.5 mg dexamethasone acetate (DXA) is located proximal to the lead tip. In the Sentus OTW QP L and Sentus OTW QP S models the distance between LV1-tip and LV2-ring is 21 mm, between LV2-ring and LV3-ring 20 mm and between LV3-ring and LV4-ring 20 mm. The Sentus OTW QP S/49 and Sentus OTW QP L/49 models have shorter pole spacing for short target vein anatomies with a distance of 21 mm between LV1-tip and LV2-ring, 15 mm

between LV2-ring and LV3-ring, and 10 mm between LV3-ring and LV4-ring. The tip and ring electrodes are coated with fractal iridium. The tantalum and platinum/iridium conductor coil is insulated with silicone, and then externally coated with polyurethane. Polyurethane improves the gliding capabilities of the lead when advanced through a left ventricular lead delivery catheter and through the coronary vasculature. The Sentus QP leads can be positioned in the target vein by using a guide wire via the over-the-wire technique or by using a stylet.

The Sentus QP has an outer diameter of 4.8 F and can be implanted with a CS lead delivery system.

Four Sentus QP lead models are available:

- Sentus OTW QP L and L/49 models are passive fixation leads utilizing a 2D dual-curve to achieve a stable position within the target vein.
- Sentus OTW QP S and S/49 models utilize a bend in the distal end enhanced with a silicone screw to provide passive fixation within the target vein.

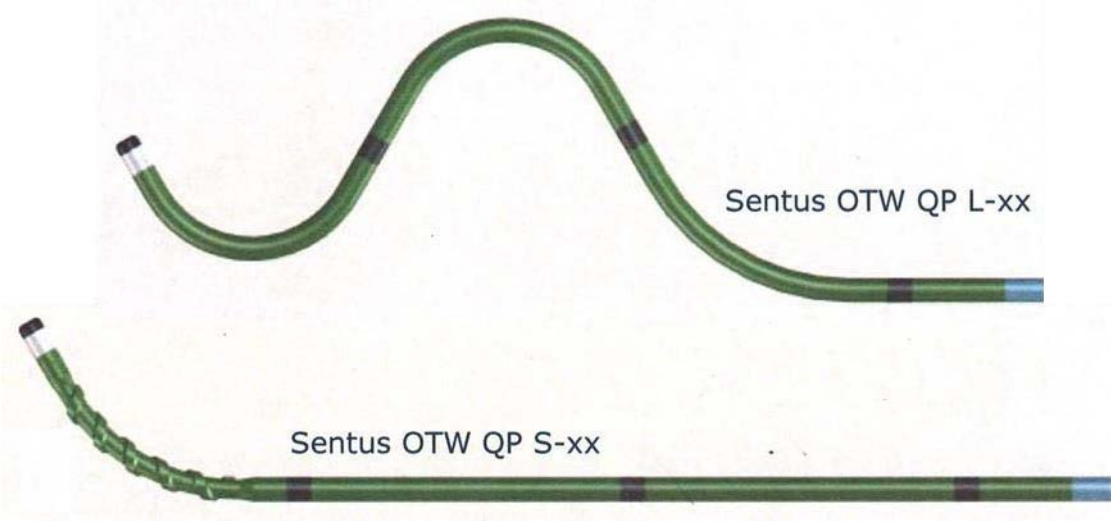


Figure 1: Sentus QP Lead Tip Design

The Sentus OTW QP is available in three lengths; L-75 (77 cm), L-85 (87 cm), and L-95 (97 cm). All three length variants carry a green marker ring to identify them as left ventricular CRT leads.

1.3.2 Pacing and Sensing Vector Options

When connected to a CRT-D device with an IS4 LV port, the Sentus QP leads offer more options in pacing and sensing configurations as compared with conventional bipolar systems.

The vectors are built between a cathode (From -) to an anode electrode (To +). Besides the four consecutively numbered LV electrodes of the quadripolar LV

lead (LV1 tip, LV2 ring, LV3 ring, LV4 ring) the distal shock coil of the RV lead (RV coil) or the ICD housing (CRT-D) can be used as additional anode electrodes for the LV pacing and sensing configuration. This gives the Sentus QP leads a total of 12 LV pacing and 7 LV sensing vector options as described in Table 1. When implanted with an Acticor/Rivacor family device, the Sentus QP LV lead offers 20 programmable pacing configurations.

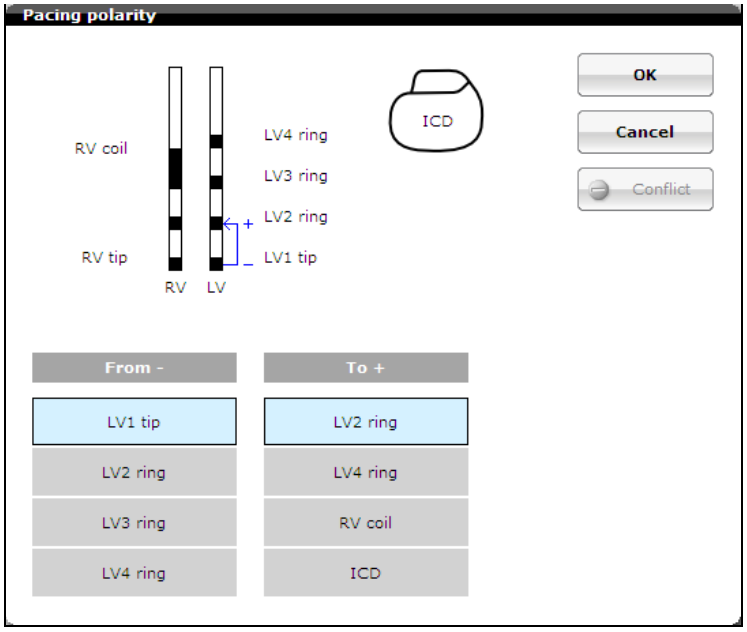
Table 1: LV Pacing and Sensing Configurations

Pacing Vectors			**Sensing Vectors**		
#	From (-) →	To (+)	#	From (-) →	To (+)
1	LV1 tip →	LV2 ring	1	LV1 tip →	LV2 ring
2	LV1 tip →	LV4 ring	2	LV1 tip →	ICD
3	LV1 tip →	RV coil	3	LV2 ring →	LV3 ring
4	LV1 tip →	ICD	4	LV2 ring →	ICD
5	LV2 ring →	LV1 tip	5	LV3 ring →	LV4 ring
6	LV2 ring →	LV4 ring	6	LV3 ring →	ICD
7	LV2 ring →	RV coil	7	LV4 ring →	ICD
8	LV3 ring →	LV2 ring			
9	LV3 ring →	LV4 ring			
10	LV3 ring →	RV coil			
11	LV4 ring →	LV2 ring			
12	LV4 ring →	RV coil			
13	LV3 ring →	LV1 tip*			
14	LV4 ring →	LV1 tip*			
15	LV1 tip →	LV3 ring*			
16	LV2 ring →	LV3 ring*			
17	LV4 ring →	LV3 ring*			
18	LV2 ring →	ICD*			
19	LV3 ring →	ICD*			
20	LV4 ring →	ICD*			

*Pacing vectors are only available in the Acticor/Rivacor family devices.

The vectors are chosen by selecting a cathode (From -) and an anode electrode (To +) during device interrogation and programming (Figure 2).

Figure 2: Programmer Display of LV Pacing Polarity



1.3.3 MultiPole Pacing (MPP) Description

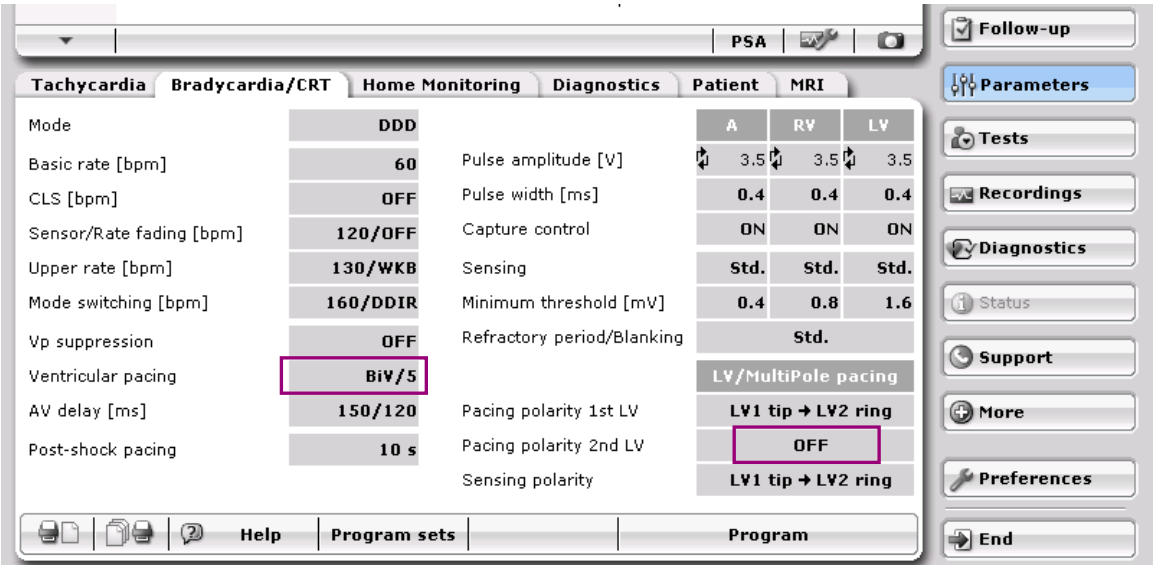
The MultiPole Pacing feature of the Ilivia and Acticor/Rivacor HF-T QP family allows left ventricular pacing in two different vectors within a single cardiac cycle using the same quadripolar lead in order to improve synchronization of the contraction pattern. Both left ventricular stimuli will either be before the right ventricular pace (1st LV – 2nd LV - RV) or after the right ventricular pace (RV-1st LV – 2nd LV). The second LV stimulus will only be capable of delivering the second pacing stimulus in the left ventricle; sensing and timing will not be affected by 2nd LV. The delay between the two left ventricular paces is programmable between 0 ms and 50 ms in 5 ms steps. All 20 currently approved pacing configurations are available for both pacing stimuli. However, the same pacing vector cannot be used for both stimuli. Pacing output and interventricular delays can be programmed independently. There is no change to the same parameter ranges available for pacing amplitude and pulse width (0.5 to 7.5 V and 0.4 to 1.5 ms, respectively). The programmable parameters for the MultiPole Pacing feature are listed in Table 2.

Table 2: Programmable Parameters for MultiPole Pacing

Parameter	Programmable range
LV MultiPole stimulation	OFF, 1st LV-2nd LV-RV, RV-1st LV-2nd LV
LV stimulation amplitude (1st LV and 2nd LV)	0.5 to 7.5 V
LV stimulation width (1st LV and 2nd LV)	0.4 to 1.5 ms
Interval 1st LV – 2nd LV	0 to 50 ms
Stimulation configuration (1st LV and 2nd LV)	Any available pacing vector (Table 1)

MultiPole Pacing is programmable using programmer software that can be used with one of BIOTRONIK's programmers, either the ICS 3000 (P950037/S035, dated May 18, 2005) or the Renamic (P950037/S089, dated April 15, 2011). The user accesses the feature from the Bradycardia/CRT parameters tab (Figure 3).

Figure 3: Programming MultiPole Pacing



As shown in Figure 4 and Figure 5 the polarity, pulse amplitude, and pulse width for the two LV stimuli can be programmed independently.

Figure 4: Programming 1st LV Stimulus

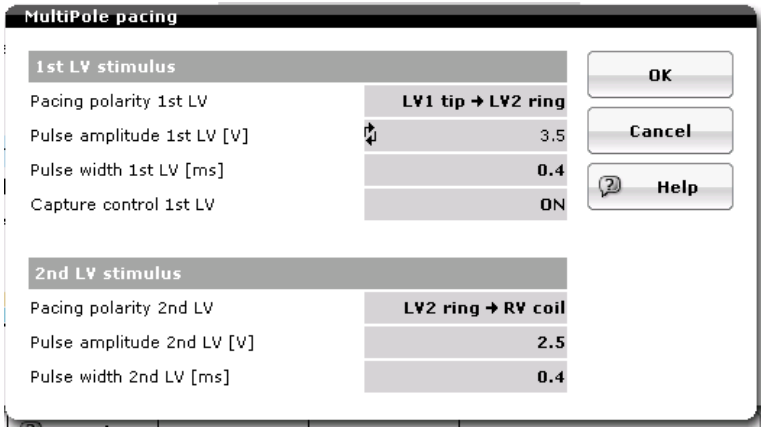


Figure 5: Programming 2nd LV Stimulus

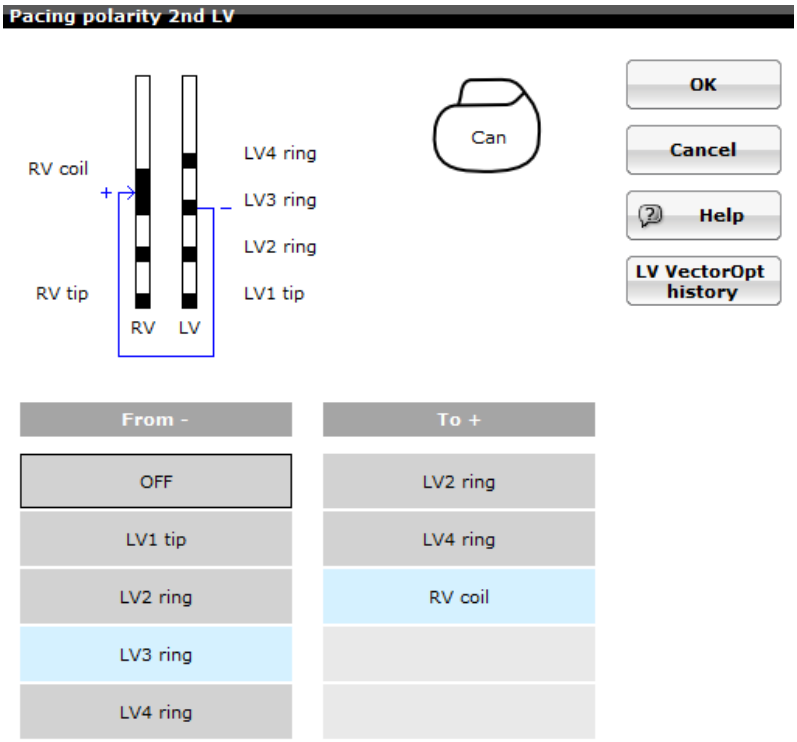


Figure 6 and Figure 7 compare the timing of the ventricular stimuli depending on which chamber is selected to be initially paced. When the right ventricle is paced first, the LV-LV delay starts after the V-V delay, whereas the V-V and LV-LV delays start simultaneously when the left ventricle is paced first.

Figure 6: V-V Delay, LV First

Initially paced chamber	**LV**
VV delay after Vp [ms]	**5**
	MultiPole pacing
Pacing polarity 2nd LV	**LV3 ring → LV4 ring**
LV-LV delay [ms]	**0**
Pacing sequence	1st LV – 2nd LV – RVp

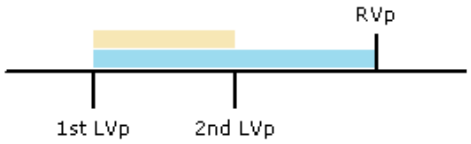
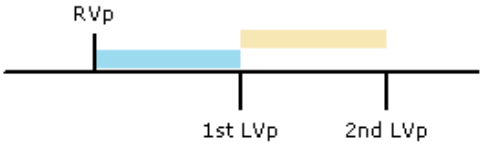


Figure 7: V-V Delay, RV First

Initially paced chamber	**RV**
VV delay after Vp [ms]	**0**
	MultiPole pacing
Pacing polarity 2nd LV	**LV3 ring → LV4 ring**
LV-LV delay [ms]	**0**
Pacing sequence	RVp □- 1st LV -□ 2nd LV



2. STUDY DESIGN

The QP ExCELs Study is a multi-center, prospective, non-randomized clinical investigation that includes a sub-study to satisfy an FDA required post-approval study of the MultiPole Pacing feature (PMA P050023/S107) of the Ilivia HF-T QP family CRT-D system (PMA P050023/S103) or Acticor/Rivacor HF-T QP family CRT-D system (PMA P050023/S125).

Subjects enrolled into the QP ExCELs study are 'provisionally enrolled' in the MPP sub-study upon signing the Informed Consent Form. Once the subject meets all of the MPP sub-study inclusion and none of the exclusion criteria at the QP ExCELs 6 month follow-up visit, or if a heart failure hospitalization has occurred, the subject may continue into the MPP sub-study, at which point they are 'fully enrolled' (as defined in Table 3). No additional subject follow-up is required once the QP ExCELs 6 month follow-up visit is completed, unless the subject is enrolled into the MPP sub-study.

As part of the MPP sub-study inclusion and exclusion criteria, a CRT responder status will be determined for all QP ExCELs subjects. The CRT Responder Classification at QP ExCELs 6-month follow-up will be evaluated by comparing the subject status at the QP ExCELs Enrollment Visit and classified as documented below:

- "Improved":
    - No HF hospitalization has occurred, AND
    - NYHA class is improved
- "Unchanged":
    - No HF hospitalization has occurred, AND
    - NYHA class is unchanged
- "Worsened":
    - HF hospitalization has occurred, OR
    - NYHA class is worsened

Those subjects determined to have a CRT Responder Classification of "Worsened" or "Unchanged" at the MPP enrollment visit may continue into the MPP sub-study if all other inclusion and exclusion criteria are met. After enrollment into the MPP sub-study, the MPP feature will be programmed ON and an MPP optimization procedure may be performed for all subjects according to the site's preferred optimization method.

Evaluation at the 3-month MPP follow-up (90 ± 30 days post-MPP enrollment) and 6-month MPP follow-up (180 ± 30 days post-MPP enrollment) will include NYHA classification, Patient Global Assessment (PGA), and HF hospitalization status, in addition to collection of the MPP programming. After completion of the 6-month MPP follow-up, subjects may be programmed to MPP or standard BiV pacing, per

physician discretion. Subjects participating in the MPP sub-study will be exited once the MPP sub-study 6 month visit has been completed.

2.1 Objectives

The primary objective of this clinical investigation is to demonstrate that the MPP feature is effective by converting a percentage of CRT non-responders to responders. Each subject's responder status will be assessed using a Clinical Composite Score (CCS) including three components: NYHA Class, heart failure (HF) hospitalizations, and cardiovascular death (Packer et al., 2001).

The MPP sub-study also includes three secondary endpoints.

2.1.1 Primary Endpoint 1

The purpose of primary endpoint 1 is to evaluate the CRT responder status with the MPP feature within the Ilivia 7 HF-T QP family CRT-D or Acticor/Rivacor 7 HF-T QP family CRT-D system, compared to a pre-specified performance goal.

The associated hypothesis is evaluated based on a CCS determining a responder classification based on changes in NYHA class, HF hospitalization, and cardiovascular death.

A responder status will be derived classifying these subjects as "Improved", "Worsened", or "Unchanged" using the following definitions.

Responder Classification at the 6-Month MPP Follow-up (evaluated compared to MPP enrollment visit):

- "Improved":
  - No HF hospitalization or cardiovascular death, AND
  - NYHA class is improved
- "Unchanged":
  - No HF hospitalization or cardiovascular death, AND
  - NYHA class is unchanged
- "Worsened":
  - HF hospitalization or cardiovascular death has occurred, OR
  - NYHA class is worsened

Ho: The proportion of subjects (P) who are classified as "Improved" is not superior to a performance goal (PG) of 3%.

$PG \geq P$

Ha: The proportion of subjects who are classified as "Improved" is superior to a performance goal of 3%.

$PG < P$

A rejection of the null hypothesis would indicate that the proportion of subjects classified as “Improved” is superior to 3%.

2.1.2 Secondary Endpoint 1

The purpose of Secondary Endpoint 1 is to evaluate adverse events that require additional invasive intervention to resolve, specifically related to the MPP feature of the Ilivia or Acticor/Rivacor HF-T QP family. These adverse events include any software issues related to MPP programming or any adverse event that occurs while MPP is enabled and that may be attributed to the use of the MPP feature.

2.1.3 Secondary Endpoint 2

The purpose of Secondary Endpoint 2 is to evaluate a modified CCS, determining a responder classification based on changes in NYHA class, Patient Global Assessment (PGA), HF hospitalization, and cardiovascular death, where the PGA will ask subjects to assess how their overall status has changed since prior to receiving CRT therapy (markedly better, better, unchanged, worse, markedly worse).

Modified Responder Classification (CCS + PGA) at the 6-Month MPP Follow-Up (evaluated compared to MPP enrollment visit):

- “Improved”:
  - No HF hospitalization or cardiovascular death, AND
  - Neither NYHA class is worsened or PGA is worsened (“worse” or “markedly worse”), AND
  - NYHA class is improved or PGA is improved (“better” or “markedly better”)
- “Unchanged”:
  - No HF hospitalization or cardiovascular death, AND
  - NYHA class is unchanged, AND
  - PGA is unchanged (“unchanged”)
- “Worsened”:
  - HF hospitalization or cardiovascular death has occurred, OR
  - NYHA class is worsened or PGA is worsened (“worse” or “markedly worse”)

2.1.4 Secondary Endpoint 3

The purpose of Secondary Endpoint 3 is to evaluate the Responder Classification (as defined in Section 2.1.1) in which both “Improved” and “Unchanged” subjects will be classified as responders. At the time of enrollment into the MPP sub-study, MPP sub-study subjects have already been found to have no change or worsening in their HF status with BiV pacing. Since HF is a chronic and progressive condition,

these subjects may be expected to continue to worsen during the MPP follow-up period or remain stable with careful management. In this secondary endpoint, a status of “Unchanged” (in addition to “Improved”) during the MPP follow-up period will be considered a responder to MPP.

2.1.5 Additional Data of Interest

Additional information will be collected to characterize the study population, implanted system, and progress of the clinical investigation. The data will be statistically analyzed, where appropriate. Further data of interest will include:

- Demographics, including age and gender
- Baseline New York Heart Association (NYHA) class
- Historical left ventricular ejection fraction (LVEF), if obtained within 6 months prior to enrollment
- Implanted devices, including pulse generator and other leads
- Implantation site and, if available, implant approach
- Sentus QP lead performance up to 6 months post-implant including R-wave sensing, pacing impedance, and pacing threshold
- Patient Global Assessment (PGA) at each visit
- MPP programmed settings
- Adverse events attributed to MPP feature
- Device initial and final programmed settings
- Methods utilized to optimize MPP, AV and/or V-V timing
- Adverse events related to implant procedure, pulse generator, or implanted leads
- Revisions to implanted system and reason for revision
- Compliance to protocol requirements and study visit schedule

2.2 Subject Status Definitions

The subject status definitions utilized in this study are provided in Table 3.

Table 3: Subject Status Definitions

Subject Status	Definition
Provisionally enrolled	Subject has provided written informed consent but has not yet been screened against the MPP sub-study specific inclusion and exclusion criteria. Provisionally enrolled subjects will become fully enrolled if they meet the MPP sub-study specific inclusion and exclusion criteria, and complete the MPP Enrollment visit. Provisionally enrolled subjects will not be included in the analysis population for the study objectives; however, they may be included in analysis of additional data of interest.
Screen Failure	Subject has signed consent, but at the time of consent it was identified the subject does not meet all inclusion/exclusion criteria, OR Subject consented prior to implant, but prior to implant the subject status changes. Subject will be exited and will not be included in the analysis population or count toward the enrollment maximum.
Fully Enrolled	Subject meets all of the MPP sub-study specific inclusion criteria and none of the exclusion criteria, and completes the MPP Enrollment visit. Fully enrolled subjects will be included in the analysis population for the study objectives, as well as in the analysis of the additional data of interest.

2.3 Study Size and Duration

The MPP sub-study will enroll up to 110 subjects at up to 75 sites within the United States who are participating in the QP ExCELs study. Based on the previous sample size analysis for the post-approval QP ExCELs cohort, the sample size for the QP ExCELs study is 1754 and will remain unchanged to support continuation of the MPP sub-study (QP ExCELs protocol version February 1, 2017 provides the justification and sample size analysis).

Subjects that enroll in the MPP sub-study will be followed 12 months post-implant, while subjects that do not continue in the MPP sub-study will be followed for 6 months post-implant.

2.3.1 MPP Sub-Study Sample Size Analysis

The investigation is designed to limit the number of patients involved while still exposing the device to a sufficiently large patient population in order to ensure a representative and statistically meaningful sample.

2.3.1.1 Primary Endpoint 1 Sample Size

The estimated sample size requirements are based on a superiority comparison of the proportion of responders to a performance goal of 3%, chosen based on the assumption that any conversion of non-responders to responders is clinically relevant. A performance goal of 3% was chosen rather than 0% to account for variability ("noise") around 0%, for example, due to infrequent subjects who are late responders to CRT or improve regardless of MPP. The expected result is estimated at a 10% conversion of non-responders to responders.

There is limited published data available for mid- to long-term follow-up CRT response with multiple point LV pacing in any population. The St. Jude Medical MultiPoint Pacing IDE Study ("St. Jude IDE study", NCT01786993) evaluated CRT response based on a Clinical Composite Score (CCS) after 3 months of BiV pacing (Tomassoni et al., 2016; System Help Manual, St. Jude Medical). Subjects were then randomized to the MultiPoint™ Pacing treatment arm or to continue on with BiV pacing. The study showed that 70.1% of subjects were responders to MultiPoint™ Pacing. However, both responders and non-responders after 3 months of BiV pacing were included in the MultiPoint™ Pacing treatment arm. Additionally, the St. Jude IDE study only randomized subjects with acute "equal or better" EA velocity time integral (VTI) with MultiPoint™ Pacing vs. BiV pacing per echocardiogram at the 3-Month Visit. There were 52 subjects that did not meet this criterion and were not randomized. Thus, subjects that may likely have not responded to multiple point LV pacing therapy were not randomized which certainly led to a higher response rate to MultiPoint™ Pacing.

BIOTRONIK proposes to allow enrollment of any QP ExCELs subject meeting non-responder criteria ("all-comer non-responders") at the 6-Month Follow-up into the MPP sub-study as it is not standard of care to perform echocardiograms on CRT subjects to determine if they are responding to standard CRT therapy. As such, we estimate that the proportion of non-responders at 6-months that will be converted to responders at 12-months post-implant will be less than that observed in the St. Jude IDE study. There are three additional studies which have published results for CRT response with MPP measured via CCS or NYHA improvement with mid- to long-term follow-up (6 to 12 months) (Forleo et al., 2016; Pappone et al., 2015; Zanon et al., 2016). However, these studies also did not limit multiple point LV pacing treatment to non-responders, thus the results are not directly applicable to the proposed BIOTRONIK study design.

Assumptions:

- Study Design: Superiority Trial
- Type I error (alpha): 0.025 (one-sided)

- Statistical power: 80%
- Performance Goal: 3%
- Expected: 10%

A total of 90 evaluable subjects would be required to demonstrate superiority to a performance goal of 3%.

2.4 Interim Analysis

An interim analysis will be performed on the primary endpoint when 50% (n = 45) of subjects have completed participation in the MPP sub-study. An alpha spending function (DeMets et al., 1994) will be incorporated to make adjustments on alpha for the interim and final analyses. Boundaries will be computed based on the O'Brien-Fleming method. The MPP sub-study will be terminated early and a final report will be prepared if the evidence of benefit reaches significance of P<0.0026 at the 50% interim analysis.

Due to the conservative alpha spending for the interim analysis, the threshold for determining significance at the final analysis is impacted minimally, with a final nominal p-value required for significance being 0.0224. The required sample size is not affected to any meaningful extent by the interim analysis and the sample size for primary endpoint 1 remains unchanged (n = 90).

Interim Analysis (50%), significance level, alpha=0.0026

Type I Error, Final adjusted significance level, alpha = 0.0224

2.5 Adjustments to Overall Sample Size

Due to the inclusion of interim analyses, a total of 90 evaluable subjects are required to demonstrate superiority to a performance goal of 3%. Assuming a 10% loss to follow-up rate during the study for reasons unrelated to the study outcomes, a total enrollment of 100 subjects would be required to achieve an evaluable study population of 90 subjects.

2.6 Data Analyses

Descriptive statistics will be used to present and summarize the data collected in the clinical study. Frequency distributions and cross tabulations will be presented for discrete variables. Means, standard errors, and ranges will be presented for continuous variables.

Classification of "HF hospitalization" and "cardiovascular death" events for use in primary endpoint 1, secondary endpoint 2, and secondary endpoint 3 analyses will be determined by a Clinical Events Committee (Section 5.1.1.).

For primary endpoint 1, the lower, one-sided, exact 97.5% bound for the observed proportion of responders ("improved") would have to exceed 3% for rejection of the null hypothesis. Additionally, descriptive statistics will be provided for observed

changes in NYHA class and frequency tabulations provided for the other components of the Clinical Composite Score.

The AE-free rate calculated for secondary endpoint 1 will be based on the total number of subjects with at least one MPP related adverse event requiring additional invasive intervention to resolve. For the secondary endpoint analysis, the AE classification, category, resolution, and relation to the MPP feature for each individual event will be determined by the Clinical Events Committee (CEC) (Section 5.1.1). All adverse events which the CEC determines the event is related or possibly related to the MPP feature will be included in the secondary endpoint 1 analysis. Adverse events with a final CEC adjudicated relation of not related or unknown will not contribute to or be included in the evaluation of the secondary endpoint.

2.6.1 Replacement of Missing Data

The last observation carried forward (LOCF) principle will be utilized for the analysis of NYHA Classification and Patient Global Assessment for primary endpoint 1 and secondary endpoints 2 and 3.

Missing NYHA and patient global assessment data at either the enrollment or follow-up visits affects the number of subjects that can be included in the analysis. It is possible that subjects or study personnel may either forget or choose not to answer one or more of the questions related to NYHA classification or patient global assessment.

2.6.2 MPP Sub-Study Analysis Population

The primary and secondary endpoint analyses will be conducted according to the intention-to-treat principle (IIT) utilizing all available data from fully enrolled subjects. Subjects are expected to remain programmed with the MPP feature ON from MPP enrollment through the completion of the sub-study. Subjects who have the MPP feature permanently turned OFF prior to completion of the sub-study will be required to report a protocol violation; however, these subjects will be included in the analysis population. All available data from subjects that undergo a pulse generator change and no longer have an MPP eligible device will be included in the analysis. Subjects may have the MPP feature temporarily turned OFF due to a lead revision procedure and these short durations with MPP will not be reported as a protocol violation.

Any QP ExCELs subject that does not enroll into the MPP sub-study but receives MPP due to the physician’s determination will not be analyzed towards the MPP study endpoints.

3. PROTOCOL REQUIREMENTS

3.1 Subject Population

The subject population consists of heart failure subjects with CRT-D indication according to clinical routine.

Up to 1754 subjects will be enrolled in the clinical investigation. The investigator is responsible for screening all potential subjects and selecting those who are appropriate candidates for enrollment in the QP ExCELs clinical study. The subjects selected for participation should be from the investigator's general patient population with documented evidence of an indication for implantation of a BIOTRONIK CRT-D system according to clinical routine and according to the inclusion and exclusion criteria described below. Decision for implantation of the respective BIOTRONIK devices is based on medical decisions alone and should not be influenced by the possible enrollment to this clinical trial.

The implanting physician is responsible for choosing the fixation and length variant. For the indications, we recommend following the respective current guidelines of the Heart Rhythm Society (HRS), the American College of Cardiology (ACC), and the American Heart Association (AHA), as well as those of other national cardiology associations.

Investigators are strongly encouraged to seek equal enrollment between men and women at their site. This will help ensure women are adequately represented in the study population and enable meaningful analyses of results by gender.

3.1.1 Indications for Use

The Sentus OTW QP left ventricular pacing lead is a 4.8 French (5 F introducer) quadripolar steroid-eluting lead intended for permanent implantation in the left ventricle via the coronary veins to provide pacing and/or sensing when used in conjunction with a compatible IS4 pulse generator.

3.1.2 Contraindications

Implantation of this lead is contraindicated in the following cases:

- Coronary sinus anomalies
- Tissue in the coronary sinus area that has been damaged by an infarction
- Any anomalies of the venous system that preclude transvenous implantation of the lead
- Patient cannot tolerate a single systemic dose of up to 0.5 mg of dexamethasone acetate (DXA)

3.1.3 Inclusion Criteria

All of the following inclusion criteria have to be fulfilled for participation in the QP ExCELs Study:

- Standard CRT-D indication according to clinical routine
- *De novo* implantation or upgrade from existing ICD or pacemaker implant utilizing a BIOTRONIK Ilivia 7 HF-T QP family CRT-D system or Acticor/Rivacor HF-T QP family CRT-D system. feature with IS4 LV port and Sentus QP LV lead, that meets one of the following criteria:
    - Implant planned to occur after enrollment
    - Enrollment occurs within 30 days after implant and NYHA from within 30 days prior to implant is documented in subject medical record
- Patient is able to understand the nature of the clinical investigation and provide written informed consent
- Patient is able and willing to complete all routine study visits at the investigational site up to 12 months of follow-up
- Able to understand the nature of the study and give informed consent
- Available for follow-up visits at the investigational site, including those specific to the MPP sub-study
- Age ≥ 18 years

At the time of MPP screening for inclusion into the MPP sub-study, additional inclusion criteria have to be fulfilled for participation:

- Successfully implanted with a BIOTRONIK Ilivia 7 HF-T QP family CRT-D system or Acticor/Rivacor HF-T QP family CRT-D system. Successful implantation is defined as having at least two LV pacing vectors with a measured pacing threshold of ≤ 5.0 V @ any pulse width (allowing for a minimum 2.5 V safety margin) without phrenic nerve stimulation at the final programmed pacing output at the time of enrollment into the MPP sub-study.
- CRT Responder Assessment classification as “Worsened” or “Unchanged”
- Standard continuous biventricular (BiV) pacing from implant until MPP enrollment

3.1.4 Exclusion Criteria

None of the following exclusion criteria can be fulfilled for QP ExCELs study participation:

- Chronic atrial fibrillation
- Contraindication to CRT-D therapy
- Currently implanted with an endocardial or epicardial left ventricular lead or had prior attempt to place a left ventricular lead
- Cardiac surgical procedure, such as coronary artery bypass graft or valve surgery that is planned to occur within 6 months after implant or ablation that is planned to occur within 90 days after implant (ablations planned to occur prior to or at implant are not exclusionary)

- Expected to receive a heart transplant or ventricular assist device within 12 months
- Life expectancy less than 12 months
- Participation in any other investigational cardiac clinical investigation during the course of the study
- Presence of another life-threatening, underlying illness separate from their cardiac disorder
- Pregnant or breast-feeding at time of enrollment

At the time of MPP screening for inclusion into the MPP sub-study none of the following exclusion criteria can be fulfilled:

- Development of chronic atrial fibrillation since QP ExCELs enrollment
- Received MPP pacing prior to MPP sub-study enrollment

3.2 Methods

3.2.1 eCRFs

During the course of the clinical investigation all clinical procedures are performed according to clinical routine. All parameters and measurements that are recorded within the clinical investigation are described in this section and are documented on the appropriate electronic Case Report Forms (eCRFs). Information from electronically delivered source data (e.g. programmer interrogations, adverse event documentation) will be uploaded to the appropriate eCRF, then captured and stored in a validated environment until the end of the study. The investigator will be required to use an electronic signature to approve the content of the data reported in the eCRFs.

A QP ExCELs Study Termination eCRF should only be completed for early study termination. A QP ExCELs Study Termination eCRF is not required for subjects who complete the 6 month QP ExCELs visit and who are not enrolled into the MPP sub-study. For subjects enrolled into the MPP sub-study, an MPP sub-study specific termination eCRF is required to record a study exit; however, a QP ExCELs Termination eCRF is not required.

BIOTRONIK, Inc. will audit and monitor the content of the eCRFs as described in Section 9. The required procedures and corresponding time schedule for eCRF completion is described in Section 3.3

All data have to be available for source data verification during monitoring conducted by the sponsor. Subjects have to consent to the use of their medical data prior to enrollment by signing the informed consent form.

3.2.2 Subject Demographics, Comorbidities and Medications

After the informed consent has been obtained, demographic information including year of birth, gender, height and weight should be gathered for all subjects.

Furthermore, details regarding illnesses, ECG diagnostics (if obtained within 6 months prior to enrollment), most recent LVEF, the assessment of the current NYHA class, the device therapy indication, comorbidities and current cardiovascular medication should be collected.

3.2.3 Device Settings

The device programming must be medically reasonable. Recommended device settings for participation in this clinical trial are summarized in Table 4:

Table 4: Recommended Device Settings

Parameter	Recommended device settings
BIOTRONIK Home Monitoring®	ON
Capture control LV lead	ON or ATM
Pacing configuration	BiV
LV MultiPole Pacing	OFF*

*In order to support the CRT responder assessment for enrollment into the MPP sub-study, the MPP feature should not be programmed ON prior to enrollment in the MPP sub-study.

3.2.4 CRT Based Lead Measurements

Documentation of the mean sensing amplitude, the pacing threshold and the impedance is required for the LV channel at beginning of device interrogation at implantation and the required 6 month follow-up post-implant. The pacing threshold can be measured either manually or triggered automatically.

The LV pacing threshold is considered **elevated** if the threshold is greater than 2.5 V at 0.4 ms. The LV lead impedance is considered '**out of range**' if a measurement is < 200 Ohms or > 3000 Ohms. The LV sensing threshold is considered '**out of range**' if a measurement is lower than 2 mV.

The electronic programmer file with the stored measurements is used for source data verification.

3.2.5 New York Heart Association (NYHA) Classification

During the course of the study, the NYHA classification will be utilized for evaluation of the specific level of cardiac disease. The NYHA will be evaluated at all protocol-defined follow-ups. The following bullets provide the definitions for each class:

- Class I: Subjects with cardiac disease, but without resulting limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnea, or anginal pain.

- Class II: Subjects with cardiac disease resulting in slight limitation of physical activity. They are comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnea, or anginal pain.
- Class III: Subjects with cardiac disease resulting in marked limitation of physical activity. They are comfortable at rest. Less than ordinary activity causes fatigue, palpitation, dyspnea, or anginal pain.
- Class IV: Subjects with cardiac disease resulting in inability to carry on any physical activity without discomfort. Symptoms of cardiac insufficiency or of anginal syndrome may be present even at rest. If any physical activity is undertaken, discomfort is increased.

The description for each of the classes was taken from the ACC/AHA Guidelines for Implantation of Cardiac Pacemakers and Antiarrhythmia Devices (Gregoratos et al., 1998).

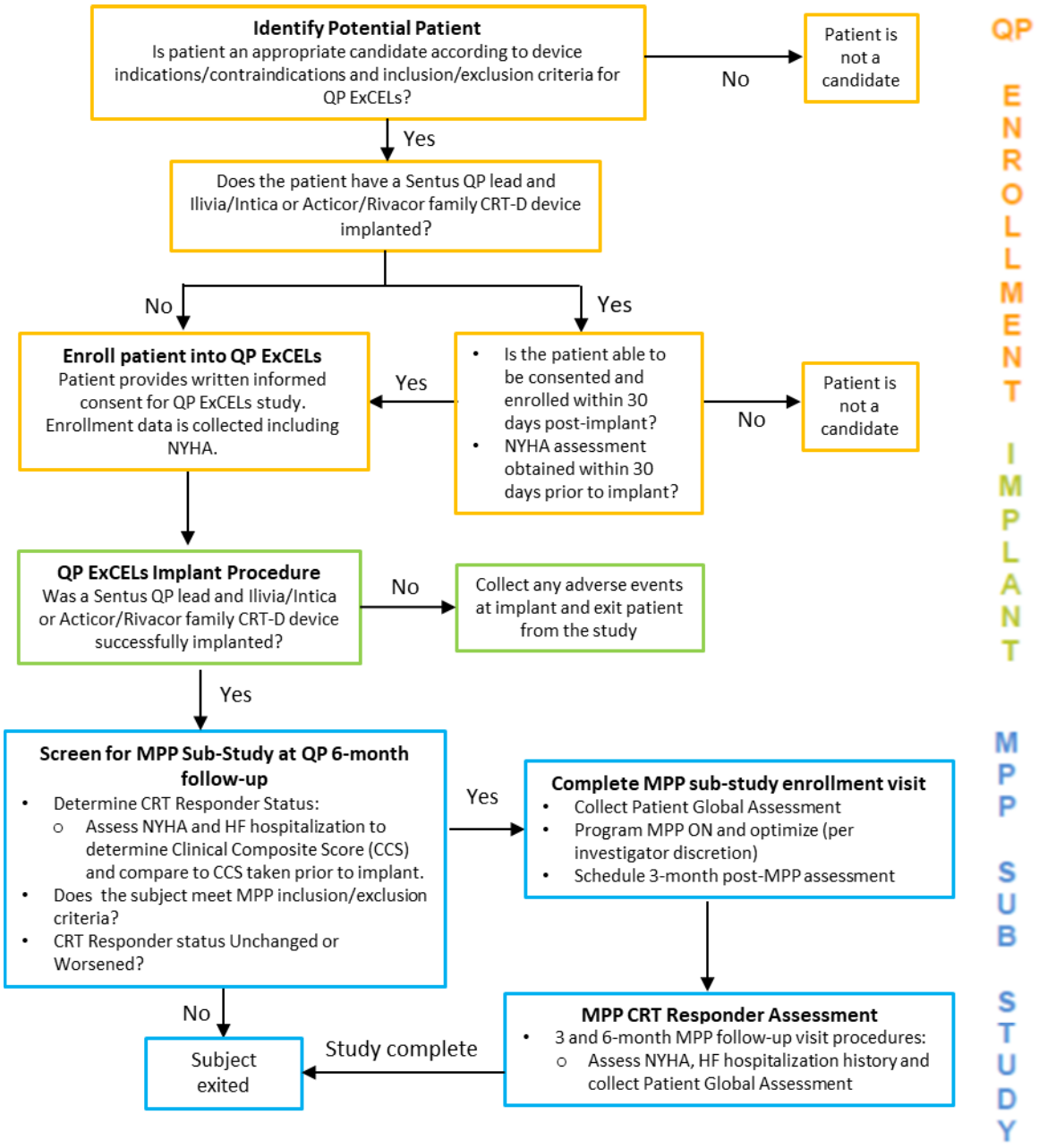
3.2.6 Patient Global Assessment (PGA)

During the course of the MPP sub-study a PGA will be given to assess how the subject's overall status has changed since prior to receiving CRT therapy (markedly better, better, unchanged, worse, markedly worse). It is important to minimize the influence on the respondent by limiting their interaction and verbal exchanges with spouses or other individuals who may affect results while the assessment form is being completed.

3.3 Study Procedures

Figure 8 provides an overview of the clinical study design. Details of subject eligibility requirements are noted in Sections 3.1.3 and 3.1.4. Details of other specific study procedures and collected data are noted in Section 3.2.

Figure 8: Clinical Study Design



Assessments of the lead performance are required at the QP ExCELs implant and 6 months follow-up visits. If circumstances prevent the presence of the subject at the in-office follow-up visit, the reason for the missed follow-up has to be indicated on the eCRF. In addition, interim evaluations related to adverse events, system revisions, or heart failure hospitalizations for inclusion into the MPP sub-study will be performed.

Table 5: Required Visit Windows for MPP Sub-Study

Visit Type	Window	Days post-implant
QP ExCELs 6 month follow-up/ MPP Enrollment*	+ 30 days	137 to 227
3 month MPP follow-up	± 30 days	198 to 228
6 month MPP follow-up	± 30 days	288 to 318

*MPP Enrollment may also occur after 3 months post-implant (90 days post-implant) if the subject has a heart failure hospitalization.

3.3.1 Overview of Study Procedures

Table 6 displays an overview about the study procedures at the different visits which are described in detail afterwards.

Table 6: Procedures by Visit Type

Procedures	Enrollment	Implant	QP ExCELs and MPP sub-study Follow-up	Interim Follow-up†
Informed consent	x			
Verification of inclusion and exclusion criteria	x			
Demographic data and comorbidities	x			
NYHA class and heart failure symptoms	x*		x	x
ECG and ECHO values (if performed routinely)	x			
Co-morbidities	x			
Cardiovascular medication	x			
CRT-D implantation		x		
Implantation information		x		
Programming of device settings		x	x	x
Standard device evaluation		x	x	x
Adverse event reporting	x	x	x	x
Completion of eCRFs	x	x	x	x

† Interim follow-ups may be collected when related to an AE, system revision or for a heart failure hospitalization for enrolment into the MPP sub-study. Implant information only needs to be collected if a system revision has occurred.

* NYHA collected within 30 days prior to implant if enrolled after implantation.

3.3.2 QP ExCELs Enrollment

Prior to enrollment, the physician selects potential candidates which are eligible for the clinical study. If the potential subject meets all inclusion and exclusion criteria (Sections 3.1.3 and 3.1.4), the potential subject is asked to read and sign an Informed Consent Form. The potential subject should be provided with sufficient time to consider participation in the trial.

Subjects are 'provisionally enrolled' into the MPP sub-study upon signing the Informed Consent Form and meeting the inclusion/exclusion criteria at time of consent. All subjects enrolled in the study must be entered in the subject enrollment log. The consent process should be documented within the subject's medical record.

After informed consent has been obtained, the following data should be collected for baseline evaluation:

1. Demographic characteristics (year of birth, gender, height, weight)
2. Device therapy indication
3. ECG diagnosis, if routinely performed
4. NYHA class
    a) For subjects enrolled prior to implant, current NYHA class as assessed by study personnel at the time of enrollment

       or

    b) NYHA class obtained within 30 days prior to implant for subjects enrolled after implant.
5. Most recent LVEF, obtained prior to implant
6. Comorbidities and cardiac medications

The Enrollment eCRF needs to be completed using the data collected during the enrollment visit.

3.3.3 Implantation

Implantation may occur after enrollment of the subject or may occur prior to enrollment if an NYHA assessment within 30 days prior to the implant date is available in the subject's medical record. For subjects implanted prior to enrollment, implant details and device data will be collected retrospectively.

At implantation, the following data is collected:

1. Implanted devices (manufacturer, model, serial number), plus date of implant
2. Implantation site, and if available, implant approach
3. Sentus QP lead implant success
5. Activation of the recommended device settings as listed in Section 3.2.3
6. Sentus QP lead evaluation from implant procedure:

- Determine LV lead impedance
- Determine LV mean R-wave sensing amplitudes
- Determine LV pacing threshold at 0.4 ms pulse width for the pacing vector programmed at the end of implantation

7. Device programming and settings at end of implantation procedure
8. Store the electronic procedure data (including final device settings, measurements, episodes) from the BIOTRONIK programmer
9. Complete the Implantation eCRF using data collected during implant and information from the end of procedure device evaluation
10. Document any reportable adverse event (e.g. phrenic nerve stimulation, high LV pacing threshold, etc.) during the procedure on the respective eCRF.

Please note:

1. If the BIOTRONIK Ilivia 7 or Acticor/Rivacor HF-T QP family CRT-D and/or Sentus QP LV lead were not implanted, the subject will be exited from the clinical investigation using a Study Termination eCRF.
2. In order to support the CRT responder assessment for enrollment into the MPP sub-study, the MPP feature should not be programmed ON prior to the MPP sub-study enrollment.

3.3.4 QP ExCELs 6-month Follow-up

Six (6) months (± 45 days) after implantation, subjects return to the investigational site for an in-office assessment of their implanted system. To support CRT Responder Assessment at 6-months post-implant, QP ExCELs 6-month follow-ups occurring prior to the visit window or more than 30 days after the visit window will not be allowed.

The following data should be collected:

1. Perform device interrogation:
   - Determine LV lead impedance
   - Determine LV lead R-wave sensing amplitude
   - Determine the LV pacing threshold at 0.4 ms pulse width for the programmed pacing vector
   - Determine LV pacing threshold @ any pulse width (allowing for a minimum 2.5 V safety margin) and document occurrence of phrenic nerve stimulation for additional LV pacing vectors.
2. Obtain NYHA classification and HF hospitalization status to determine CRT Responder Assessment classification

3. Screen subject for MPP sub-study by confirming subject meets all of the MPP sub-study specific inclusion criteria and none of the MPP sub-study specific exclusion criteria (Sections 3.1.3 and 3.1.4). If the subject qualifies for the MPP sub-study, complete MPP sub-study enrollment procedures in Section 3.3.5.
4. Device programming and settings at end of follow-up.
5. Store the electronic procedure data (including final device settings, measurements, episodes) of the BIOTRONIK programmer on an appropriate USB flash drive.
6. Complete the appropriate Follow-Up eCRF.
7. Document any reportable adverse event (e.g. phrenic nerve stimulation, high LV pacing threshold, etc.) using the respective eCRF.

If subject does not qualify for the MPP sub-study, no further follow-up visits are required. A study termination eCRF is not required.

3.3.5 MPP Sub-Study Enrollment

MPP sub-study enrollment occurs after a subject has been screened and determined to meet all MPP sub-study specific inclusion criteria and none of the exclusion criteria. QP ExCELs subjects with a heart failure hospitalization will be considered to have a CRT Responder Assessment classification of worsened and are eligible for the MPP sub-study. Subjects with a heart failure hospitalization occurring prior to the 6 month post-implant follow-up visit may be enrolled between 3 and 6 months post-implant by completing an interim follow-up eCRF (Section 3.3.8.1) or be enrolled at the QP ExCELs 6 month follow-up visit (Section 3.3.4).

MPP optimization may be performed or not performed per investigator discretion at the time of enrollment into the MPP sub-study. The investigator will determine if MPP optimization will be performed for each subject and which method will be used (e.g. QRS width, electrical delay, echocardiography, etc.). MPP programmed parameters may be adjusted as needed during the follow-up period for MPP sub-study subjects.

After a patient has been screened and determined to be eligible for the MPP sub-study, the following data will be collected:

1. Turn MPP ON and collect MPP programmed settings
2. Document MPP optimization method
3. Obtain Patient Global Assessment
4. Document any reportable Adverse Events
5. Review and complete the appropriate eCRFs

The MPP feature must be programmed ON from MPP enrollment until the subject exits the sub-study. Subjects who have the MPP feature permanently turned OFF prior to completion of the sub-study will be required to report a protocol violation.

3.3.6 3-Month MPP Follow-up

At a 3-month MPP follow-up (90 ± 30 days post-MPP enrollment), subjects return to the investigational site for an in-office assessment of their heart failure status and implanted system.

The following data should be collected:

1. Collect MPP programmed settings
2. Obtain NYHA classification and HF hospitalization status
3. Obtain Patient Global Assessment
4. Collect device initial and final programmed settings
5. Document any reportable Adverse Events
6. Review and complete the appropriate eCRFs

3.3.7 6-Month MPP Follow-up

At the 6-month follow-up (180 ± 30 days post-MPP enrollment), subjects return to the investigational site for an in-office assessment of their heart failure status and implanted system.

1. Collect MPP programmed settings
2. Obtain NYHA classification and HF hospitalization status
3. Obtain Patient Global Assessment
4. Collect device initial and final programmed settings
5. Document any reportable Adverse Events
6. Review and complete the appropriate eCRFs
7. Complete a study termination eCRF documenting MPP sub-study completion

Following the 6-month MPP follow-up, all subjects may be programmed to MPP or standard BiV pacing, per physician discretion.

3.3.8 Interim Follow-up

Interim follow-ups may occur anytime during the clinical investigation; however, only those interim evaluations in support of MPP sub-study enrollment due to a heart failure hospitalization between 3 and 6 months post-implant and those related to adverse events or system revisions may be collected in the clinical investigation. Interim follow-ups can be visits scheduled by physicians according to clinical routine, visits scheduled by the physician due to BIOTRONIK Home Monitoring® alerts or trends, or visits initiated by the subject.

3.3.8.1 MPP Sub-Study Heart Failure Hospitalization

Subjects with a heart failure hospitalization meeting the definition in Section 6.1.4 may be enrolled into the MPP sub-study between 3 and 6 months post-implant by completing an interim visit eCRF. The following procedures are required:

1. Obtain NYHA classification and HF hospitalization status to determine CRT Responder Assessment classification
2. Perform device interrogation:
   - Determine LV lead impedance
   - Determine LV lead R-wave sensing amplitude
   - Determine the LV pacing threshold at 0.4 ms pulse width for the programmed pacing vector

   Determine LV pacing threshold @ any pulse width (allowing for a minimum 2.5 V safety margin) and document occurrence of phrenic nerve stimulation for additional LV pacing vectors.
3. Screen subject for MPP sub-study by confirming subject meets all of the MPP sub-study specific inclusion criteria and none of the MPP sub-study specific exclusion criteria (Sections 3.1.3 and 3.1.4). If the subject qualifies for the MPP sub-study, complete MPP sub-study enrollment procedures in Section 3.3.5

3.3.8.2 Adverse event related interim follow-up

For interim follow-ups related to an adverse event, the data collected on the Interim Follow-up eCRF is the same as the 6 and 12 month evaluations (Section 3.3.4).

3.3.8.3 System Revision

For interim evaluations that involve a system revision (even if the Sentus QP lead is not directly affected), the following data is required:

1. Implantation procedure information (date of intervention, information about new implanted devices).
2 Revised device (manufacturer, model, serial number).
3. Sentus QP lead measurements during procedure:
   - Determine LV lead impedance
   - Determine LV lead R-wave sensing amplitudes
   - Determine LV pacing threshold at 0.4 ms pulse width for the pacing vector programmed at the end of intervention.
4. Device programming and settings at end of intervention.

5. Store the electronic procedure data (including final device settings, measurements, episodes) of the BIOTRONIK programmer on an appropriate USB flash drive.
6. Complete the electronic System Revision eCRF.
7. Document any reportable adverse event (e.g. phrenic nerve stimulation, high LV pacing threshold, etc.) during the procedure by using the respective eCRF.

Please note:

1. If prior to MPP sub-study enrollment, the BIOTRONIK Ilivia 7 HF-T QP family CRT-D system or Acticor/Rivacor HF-T QP family CRT-D and/or Sentus QP LV lead were explanted and not replaced with an MPP sub-study eligible system, the subject will be exited from the clinical investigation using a Study Termination eCRF.
2. Whenever possible, BIOTRONIK devices that are explanted must be returned to BIOTRONIK, Inc. for analysis.

3.3.9 Study Termination

A QP ExCELs Study Termination eCRF should only be completed for early study termination. Reasons for early study termination are described in Section 3.4.2. A QP ExCELs Study Termination eCRF is not required for subjects who complete the 6 month QP ExCELs visit and who are not enrolled into the MPP sub-study. For subjects enrolled into the MPP sub-study, an MPP sub-study specific termination eCRF is required to record a study exit; however a QP ExCELs Study Termination eCRF is not required.

3.4 Study Participation Expectations

3.4.1 Point of Enrollment

Subjects are ‘provisionally enrolled’ into the MPP sub-study upon signing the Informed Consent Form and meeting the inclusion/exclusion criteria at time of consent.

3.4.2 Reasons for Study Termination

Once a subject is enrolled and successfully implanted, every effort should be made to continue to follow the subject in the clinical investigation. However, it is inevitable that some subjects will decline to participate further, change geographic location, or become non-compliant with the visit schedule.

3.4.2.1 No implant attempt

If BIOTRONIK Ilivia 7 HF-T QP family CRT-D system or Acticor/Rivacor HF-T QP family CRT-D system and/or Sentus QP LV lead was not implanted, the subject is exited. The reason for study termination must be provided.

3.4.2.2 Withdrawal of subject consent

Subjects may withdraw their consent for study participation at any time without stating the reason and without any unfavorable consequences. All data, which are collected until the date of withdrawal will be used for analysis. A Study Termination eCRF has to be completed by the investigator in which the reasons for withdrawal should be documented if willingly provided by the subject.

3.4.2.3 Subject death

Personnel at the investigational site should notify BIOTRONIK as soon as possible concerning any subject death during the investigation. This notification should include a completed study termination eCRF, death certificate, and a copy of the notification of the death sent to the IRB. If a death certificate is not available, a detailed statement (death report) signed by the investigator should be written in addition to the termination eCRF. The death report should include all of the following, if available:

- date and time of death
- place death occurred
- identification of the rhythm at the time of death, if known (include any available documentation)
- immediate cause of death
- any other circumstances surrounding the death
- whether it was device or procedure related

All implanted devices that are involved with the investigational study should be removed and returned to BIOTRONIK.

All deaths occurring while enrolled in the MPP study will be reviewed by the CEC.

3.4.2.4 Sentus QP lead or BIOTRONIK CRT-D extraction

If prior to MPP enrollment , any subject who has the BIOTRONIK Ilivia 7 HF-T QP family CRT-D system or Acticor/Rivacor HF-T QP family CRT-D system and/or Sentus QP LV lead explanted and not replaced with an MPP sub-study eligible system will be withdrawn from the clinical investigation. After documentation of the system revision procedure (Section 3.3.8.3), a Study Termination eCRF should be completed.

Whenever possible, devices that are explanted must be returned to BIOTRONIK, Inc. for analysis.

3.4.2.5 Lost to follow-up

Subjects lost to follow-up are those for whom contact is lost despite the investigator's best efforts to locate the subject. Study sites should attempt to contact these subjects in order to maintain study visit compliance and all contact

attempts should be documented. At a minimum, the site should make two attempts to contact the subject by phone and one attempt by certified mail.

In the event the subject cannot be contacted using the above methods, the subject is terminated from the clinical investigation by completing a Study Termination eCRF.

3.4.2.6 MPP Sub-Study Completion

Subjects who complete the MPP 6 month follow-up visit will be exited with reason of MPP sub-study completion selected on the Study Termination eCRF; however a QP ExCELs Study Termination eCRF is not required.

3.4.3 Date of Study Termination

The expected study termination for all subjects should not be earlier than the 6 month follow-up visit.

For all early study terminations, the following rules apply:

- In case of withdrawal of consent, date of study termination is the date of withdrawal of consent.
- In case of subject death, the date of study termination is the date of death.
- If subject is lost to follow-up, date of termination is the date of last documented contact with the subject.
- If BIOTRONIK Ilivia 7 HF-T QP family CRT-D system or Acticor/Rivacor HF-T QP family CRT-D system and/or Sentus QP LV lead was not implanted, the date of termination is the date of decision not to implant.
- If prior to MPP enrollment, the BIOTRONIK Ilivia 7 HF-T QP family CRT-D system or Acticor/Rivacor HF-T QP family CRT-D system and/or Sentus QP LV lead was explanted and not replaced with an MPP sub-study eligible system, the date of study termination is the date of system revision.

Study related procedures and documentation should end at the day of study termination for the respective subject.

4. ADDITIONAL STUDY CONDITIONS

4.1 IRB Approval

Institutional Review Board (IRB) approval is required for each study site according to local requirements and investigator prior to participation in this clinical study. Subject enrollment may not begin until both the IRB and BIOTRONIK, Inc. have granted approval for the study site. IRB approval is also required throughout the duration of this clinical investigation. If IRB approval is withdrawn, BIOTRONIK, Inc. must be notified by the investigator within 5 working days.

4.2 Subject Consent

Subject participation in this study is voluntary. All subjects must sign an IRB approved Informed Consent Form (ICF) prior to participation in the study. Subject informed consent must be obtained prior to enrollment or any protocol related procedures. Informed consent should be obtained in accordance with the FDA regulations (21CFR, Part 50). The investigator is required to inform BIOTRONIK and the reviewing IRB within 5 days if any subject was not appropriately consented to participate in the study. In order to assist with the consent process, BIOTRONIK will provide a template patient consent form to investigational sites participating in the study.

4.3 Data Collection

4.3.1 Electronic Data Capture (EDC)

MedNet Solutions Incorporated is a privately-held company that specializes in web-based clinical data management technology. MedNet will host the EDC system and provide a secure environment that is accessible to authorized individuals through the internet. BIOTRONIK, Inc. will implement a study specific configuration using this software to meet the data collection requirements of the protocol. It is the platform for electronic case report form (eCRF) data entry, query management, and access to clinical data for parties authorized by BIOTRONIK, Inc.

4.3.2 Electronic Case Report Forms (eCRFs)

Original data will be collected from each investigational site and recorded into the EDC system via completion of eCRFs. The investigator will be required to use an electronic signature to approve the content of the data reported in the eCRFs. BIOTRONIK, Inc. will audit and monitor the content of the eCRFs as described in Section 9.

Information from electronically delivered source data (e.g. programmers) will be captured and stored in a validated environment until the end of the study.

4.3.3 BIOTRONIK Home Monitoring® Data

In the QP ExCELs study, data of the study subjects will be accessible to the sponsor via transfer from the Home Monitoring Service Center during the course of study participation of the respective subject. BIOTRONIK Home Monitoring® data might be used for evaluation and publication if desired by the sponsor.

All data are transferred to the sponsor in a pseudonymized form. Data includes all information transmitted from the device (e.g. IEGMs, statistics, lead information).

4.4 Confidentiality of Subject Data

Information sent to BIOTRONIK, Inc. pertaining to study subjects will be kept confidential at BIOTRONIK, Inc. and is subject to audit by IRB and other regulatory authorities. For reporting purposes, data collected from U.S. sites will be shared with BIOTRONIK SE & Co. KG. Information shared with BIOTRONIK SE & Co. KG will be kept confidential. Reports submitted to physicians and data presented in publications of study results will not make any reference to subject name.

In order to verify the study data and ensure study integrity, monitors from BIOTRONIK, Inc., authorized personnel from BIOTRONIK SE & Co. KG, regulatory authorities, and the reviewing IRB may review and/or copy the study records.

4.5 Data Quality Control

BIOTRONIK, Inc. will regularly review study data. At any time, reports can be generated on entered or missing data by BIOTRONIK, Inc. or by approved research personnel at each investigational site. The EDC system will be used to track received and expected visit data and eCRFs for each subject. This system also provides the capability to monitor the status, volume, and disposition of data. In addition, all study data will undergo extensive automatic edit and plausibility checks that provide information to the investigational sites to help improve and maintain data quality control procedures designed to detect inaccuracies and inconsistencies.

4.6 Deviations from Clinical Investigation Plan

The investigator is required to conduct this study in accordance with the signed investigator agreement and clinical protocol. The investigator shall notify BIOTRONIK, Inc. and reviewing IRB in writing no later than 5 working days after any significant deviation from the clinical protocol that has occurred to protect the life or physical well-being of a subject in an emergency. Except in such emergency situations, prior approval by BIOTRONIK, Inc. is required for significant deviations from the clinical protocol.

BIOTRONIK, Inc. categorizes protocol non-compliance instances as either protocol violations or protocol deviations. Both protocol violations and deviations will be reported in the interim and final clinical progress reports.

4.6.1 Protocol Violations

Protocol violations are defined as instances where the protocol requirements and/or regulatory guidelines were not followed, and are generally more serious in nature. Protocol violations are considered to potentially affect the scientific soundness of the study and/or the rights, safety, or welfare of subjects. Protocol violations include, but are not limited to, failure to obtain consent, and subject inclusion/exclusion violations.

4.6.2 Protocol Deviations

Protocol deviations are defined as instances where the requirements of the protocol were not followed in such a manner whereby data is unusable or unavailable. Protocol deviations are less serious in nature and may not require IRB notification as long as they do not affect the rights, safety, or welfare of the study subject.

Informed Consent documentation issues are also considered protocol deviations. These include but are not limited to incomplete ICF, missing dates for signature(s), missing initials or illegible information, subject signature date completed by someone other than subject, utilization of an outdated or non-IRB approved ICF, or incomplete associated forms required at time of consent, etc. (this is not an exclusive list).

4.6.3 IRB Reporting of Non-Compliance

The study site must notify the reviewing IRB of all non-compliance issues per the IRB and protocol reporting requirements. At a minimum, all violations and non-compliance issues related to informed consent and informed consent documentation should be reported to the IRB.

In some instances, such as failure to obtain consent, the study site should also seek guidance from the IRB to ensure the subject received appropriate information to consider her or his participation in the study.

The site should provide a copy of the IRB protocol noncompliance notification (as applicable) to BIOTRONIK.

4.7 Subject Retention

BIOTRONIK, Inc. will provide additional tools to the sites in an effort to minimize the number of subjects that are lost to follow-up. This includes an overview of each subject's visit schedule, including the windows for each visit as they become due. The visit schedule reporting allows research personnel to become alerted to and track all study subjects that should be scheduled for upcoming study evaluations.

In addition, BIOTRONIK, Inc. monitors will review subjects, including those that may be lost to follow-up, to ensure protocol and study visit compliance.

4.8 Study Completion

BIOTRONIK, Inc. will notify the U.S. study site upon completion or termination of the clinical investigation or of the investigator's participation. BIOTRONIK, Inc. will provide a Clinical Investigation Report to each investigational site. BIOTRONIK, Inc. will also determine which sites will have an on-site close out visit and provide details on closure activities to all investigators to ensure the investigator understands any applicable regulatory requirements, including those related to record retention.

5. STUDY OVERSIGHT

5.1 Clinical Events Committee

A Clinical Events Committee (CEC) consisting of at least 3 independent Electrophysiologists or Cardiologists (with CRT experience) will be established to review and adjudicate all MPP sub-study related events (Section 5.1). Protocol defined adverse events that are not MPP sub-study related will be included in the clinical report based on site-reported information.

The CEC will be blinded to the investigational site and subject identity, and to minimize bias members will not participate as investigators. The CEC will create a study specific charter defining the adverse event adjudication process, specifically detailing review guidelines along with appropriate response timelines.

The Clinical Events Committee is responsible for:

- Endpoint adjudication of adverse events meeting the criteria above
- Adjudication meetings, as needed, via telephone conference or face-to-face
- Regular reporting of adjudication results to the sponsor

The Clinical Events Committee will be supported by members of the sponsor in pre-selection of device complications from non-device related adverse events (e.g. broken leg, headache, cancer) and in organizational tasks.

5.1.1 Clinical Events Committee – MPP Sub-Study Events

The QP ExCELs Clinical Events Committee (CEC) described in Section 5.1 will adjudicate all adverse events that require additional invasive intervention to resolve which may be related to the MPP feature. These events include any software issues related to MPP programming or any adverse event that occurs while MPP is enabled and that may be attributed to the use of the MPP feature. The CEC will indicate whether the adverse event is related, possibly related, not related, or has an unknown relation to the MPP feature.

In addition, the CEC will adjudicate all deaths reported while participating in the MPP sub-study and classify each death as cardiovascular, vascular, non-cardiovascular/vascular, or unknown.

The CEC will adjudicate all reported protocol-defined hospitalizations while a subject is enrolled in the MPP sub-study. Hospitalization events will be classified as cardiovascular, vascular, non-cardiovascular/vascular, or unknown. Additionally, hospitalizations classified as cardiovascular will be further classified as a HF hospitalization, non-HF hospitalization, or unknown. Hospitalization events reported by the investigator as part of the initial responder classification for enrollment into the MPP sub-study will not be adjudicated by the CEC.

6. ADVERSE EVENTS

In the course of the clinical investigation, undesired medical events can occur in participating subjects, which are called adverse events (AEs). All AEs shall be assessed by the investigator and shall be documented and reported throughout the clinical investigation.

The investigator shall submit to the sponsor all reportable events using the respective eCRFs provided within the EDC system.

Based on literature research, the adverse events listed in Appendix B may possibly occur as medical complications of a cardiac rhythm management system implant.

6.1 Definitions

6.1.1 Definition of Adverse Event

An AE is defined as 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 includes:

- Events related to the medical device or the comparator
- Events related to the procedures involved
- For users or other persons, this definition is restricted to events related to the medical devices.

6.1.2 Definition of Adverse Device Effect

An adverse device effect (ADE) is an AE that is related to the use of a medical device. This includes any AE resulting from insufficient or inadequate instructions for use or the deployment, implantation, installation, or operation, or any malfunctioning of a device and any event resulting from use error or from unintentional misuse of the device.

Adverse events, which result from the required medical procedures involved, when implanting, using or testing the respective device, even if not directly related to the device (e.g. anesthetic complications, wound healing disturbances, lead perforation, etc.) are considered ADEs.

Three categories for classification of relationship to the device and/or procedure are available:

- Clearly not related: A relationship of the AE to the device and / or procedure can be excluded.
- Possibly related: It cannot be excluded that there is a connection with the device under investigation and / or the procedure.
- Clearly related: A relationship of the AE to the device and/or procedure is likely/sure.

6.1.3 Serious AEs, ADEs

AEs and ADEs are classified as serious if one or more of the following consequences are fulfilled:

- led to death
- led to serious deterioration in the health of the subject, that either resulted in
  - a life-threatening illness or injury, or
  - a permanent impairment of a body structure or a body function, or
  - in-patient or prolonged hospitalization, or
  - medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function.
- led to fetal distress, fetal death or a congenital abnormality or birth defect.

Note: Planned hospitalization for a pre-existing condition, or a procedure required by the protocol, without serious deterioration in health, is not considered a serious adverse event.

In-patient hospitalization is defined as at least one overnight stay (change of date) in a hospital. Events for which subjects are hospitalized for less than 24 hours without change of date will not be documented as serious, unless one or more of the other seriousness criteria are fulfilled.

6.1.4 Definition of Heart Failure Hospitalization

Hospitalization for worsening heart failure is defined as a hospitalization that includes increased signs and/or symptoms of worsening heart failure requiring the administration or augmentation of intravenous or oral heart failure therapy (e.g., inotropes, diuretics, and/or vasodilators).

A hospitalization classification will be based on the primary admission diagnosis, not on the development of new events that occur during the hospitalization.

For each hospital admission, the investigator will be requested to state whether or not the subject experienced worsening heart failure at the time of admission or during the admission, and if so, whether or not this was the primary reason for admission or secondary to an obvious precipitating factor such as atrial fibrillation. The investigator will also be asked to state whether or not the subject received an intravenous medication for heart failure including diuretics, vasodilators or inotropic agents or a substantial increase in oral diuretic therapy for heart failure.

6.2 Reporting Adverse Events

The investigator has to record any reportable adverse event which occurs during study duration. The adverse event will be classified according to the seriousness, the relation to the implanted devices, and to the procedure. The investigator shall

report to the sponsor, by completing the appropriate eCRF, the following types of events:

- all adverse events related to or possibly related to the implanted system
- any major adverse events related to procedures involved with implanting, using, or testing the implanted system (examples are provided in Section 6.3.1 and definitions are provided in Appendix A: Definition of Terms)
- any adverse device effects, regardless of severity
- any cardiovascular hospitalizations and any other hospitalizations in which cardiovascular symptoms occur during participation in the MPP sub-study (Section 6.3.2 provides definitions)
- most recent heart failure hospitalization that occurs after eligible system implant and before MPP sub-study enrollment (if subject participates in the MPP sub-study; Section 6.1.4 provides definition)
- all adverse events that require additional invasive intervention to resolve, specifically related to the MPP feature of the CRT-D that occur during participation in the MPP sub-study (examples are provided in Section 6.3.3)

Events will be reported on an Adverse Event eCRF. Events should be reported as information is available, even if this results in an incomplete eCRF. The investigator must follow-up all ongoing reportable events either as long as the subject participates in the clinical investigation, the clinical investigation is terminated, or until the event has been resolved, whatever comes first.

The investigator must characterize each event by a single primary diagnosis. The primary diagnosis may describe an event consisting of several clinically recognizable features, symptoms or secondary diagnoses. Note: The observed symptoms and secondary diagnoses must be properly documented in the respective eCRF.

Multiple events may occur simultaneously in one subject. For each medically independent event with a primary diagnosis an individual report must be provided.

In addition, the action taken/treatment should also be provided with any supportive documentation available.

The investigator has to ensure that all relevant information is available. This also includes information from other parties (family, other hospitals, etc.).

If a patient dies during the clinical investigation, the investigator shall document the cause of death, circumstances and place of death (as defined in Section 3.4.2.3). All actions taken, which were initiated to gain further information must be documented in writing and provided to BIOTRONIK, Inc.

Investigators are required to adhere to applicable regulations and reviewing IRB reporting requirements for adverse events.

6.3 Reportable Adverse Events

6.3.1 Lead, System, and Procedure Related Event Examples

The following are examples of potential reportable adverse events and do not limit the required adverse event reporting as defined in Section 6.2.

Examples of reportable lead related events

- Ablation sequelae (such as lead dislodgement or damage during an ablation)
- Cardiac perforation occurring post implant
- Clinical lead failure
- High pacing threshold
- Extracardiac stimulation (e.g. phrenic nerve stimulation)
- Electrical lead failure
- Intermittent capture
- Lead abrasion
- Lead dislodgement or migration (not occurring during a procedure)
- Lead impedance out of range, high impedance
- Lead impedance out of range, low impedance
- Lead fracture or insulation damage
- Lead undersensing
- Lead-related thrombosis
- Loss of sensing
- No capture
- Mechanical lead failure
- Muscle or nerve stimulation
- Twiddler's syndrome
- Unsuccessful Sentus QP lead implant
- Lead repositioned, explanted, or replaced for any other reason

Examples of reportable system or pulse generator related events

- Device extrusion
- Device migration
- Inappropriate detection of arrhythmias
- Inappropriate therapy or shocks
- Inability to defibrillate or pace
- Myopotential sensing
- Pacemaker mediated tachycardia
- Premature battery depletion
- Pulse generator failure
- Shunting current or insulating myocardium during defibrillation with internal or external paddles
- Skin erosion
- Pulse generator repositioned, explanted, or replaced for any other reason

Examples of reportable major implant related events

- Air embolism
- Anesthetic complications
- Allergic reaction to components used at implant or during lead testing,
- or to components of the lead
- Arrhythmias associated with implant
- Arteriovenous fistula
- Body rejection phenomena
- Cardiac perforation with or without tamponade associated with lead implant
- Chronic nerve damage
- Coronary sinus dissection
- Damage to lead during a procedure
- Fluid accumulation
- Heart valve damage
- Major Hematoma
- Infection
- Keloid formation/fibrotic tissue formation
- Lead dislodgement of chronic leads that occurs during a procedure
- Loose set-screw
- Myocardial damage
- Non-healing pocket dehiscence or other wound healing disturbance
- Pericardial effusion
- Pericarditis
- Phlebitis
- Pleural effusion
- Pneumothorax associated with lead implant
- Pulmonary embolism associated with the implant procedure
- Respiratory arrest
- Venous occlusion associated with the

- Hemothorax
- Incorrect lead connection with pulse generator

implant procedure

Please note: Phrenic nerve stimulation is an expected event during left ventricular threshold testing. As the Sentus QP lead allows for measurements in up to 20 different vectors, phrenic nerve stimulation might be a common observation in this study. Therefore phrenic nerve stimulation during threshold testing is only considered a reportable adverse event if serious medical symptoms occur.

6.3.2 Reporting Hospitalizations

To eliminate possible bias at the site level related to possible endpoint events of the MPP sub-study, adverse events requiring hospitalization for any cardiovascular hospitalizations and any other hospitalizations in which cardiovascular symptoms occur will be collected while subjects are enrolled in the MPP sub-study. Each hospitalization will be adjudicated to determine whether it meets the MPP sub-study endpoint criteria as a heart failure hospitalization by the Clinical Events Committee (CEC).

BIOTRONIK will be responsible for verifying completeness of the initial reported event and coordinating with sites to obtain any missing or additional source documentation required by the CEC to adjudicate the case. Additional documentation will be requested from the enrolling site as needed. The hospital report should include the following, if available:

- Discharge summary
- History and physical and admission summary
- Diagnostic and laboratory test results
- Chest X-ray, echocardiography, ultrasound or other imaging test results, as appropriate
- Consultations, operation reports, progress notes and discharge summaries from the subject medical records
- Investigator description and assessment of the event

6.3.3 MPP Feature Related Adverse Events

All adverse events that required additional invasive intervention to resolve, specifically related to the MPP feature of the CRT-D will be reported. These adverse events include any software issues related to MPP programming for any adverse event that occurs while MPP is enabled and that may be attributed to the use of the MPP feature.

6.4 Sponsor Reporting

To ensure reporting requirements are met during the study, adverse event information reported for all study sites will be reviewed by BIOTRONIK to ensure specific reporting requirements are met.

7. OTHER INSTITUTIONS AND PHYSICIANS

This clinical study is not transferable to other institutions attended by the investigator unless prior approval is obtained from both BIOTRONIK, Inc. and the appropriate IRB. Only approved investigators are authorized to participate in the clinical investigation. However, there are certain situations where an investigator might not be immediately available to provide the necessary medical care for a subject enrolled in the clinical investigation (such as a subject emergency room visit for medical treatment) in these instances a protocol deviation will not be issued and all available data will be utilized.

In case technical support is needed the service hotline of BIOTRONIK, Inc. is available 24 hours a day. Phone: 1-800-547-0394.

8. RISKS AND BENEFITS

8.1.1 Potential Benefits

The clinical benefit of the Ilivia 7 HF-T QP family or Acticor/Rivacor HF-T QP family CRT-D system, is similar to that of standard CRT-Ds. Subjects taking part in this study may receive additional examinations of their CRT system.

Although the participating study subjects might benefit from the new CRT-D system with MPP feature, currently there is only limited benefit for enrolled study subjects. Studies have shown that multiple point LV pacing via a QP LV lead may be an alternative approach to improve CRT response by delivering multiple LV pacing pulses, simultaneously recruiting a larger volume of myocardium (Forleo et al., 2016). A recent IDE study showed that quadripolar multiple point LV pacing was non-inferior to standard quadripolar biventricular pacing (Tomassoni et al., 2016). The medical community, as well as future subjects, may benefit from these study results, which will enable a better understanding of the safety and efficacy of the MPP feature.

8.1.2 Potential Risks

All devices, device leads, device programmers, and Home Monitoring® systems included in the QP ExCELs study are legally marketed and being prescribed by physicians according to FDA approved indications for use. There are no new known risks associated with participation in this study. Please refer to the product manuals for risks associated with the implanted leads or CRT-Ds.

During the course of this study subjects may experience potential adverse the evaluation of the relation between the adverse event and the MPP feature. The date of the adverse event and resolution must be recorded. When an adverse event is noted in the EDC system, corrective action will also be provided with any supportive documentation available. Corrective actions may include, for example: drug therapy changes, programming changes, lead repositioning, new lead implants, or CRT-D explant.

Study sites may report adverse events through MedWatch, FDA's adverse event reporting tool for market-released devices. As defined in BIOTRONIK's internal procedures, these adverse events may be reported by BIOTRONIK through manufacturer's MedWatch reports.

Another research related risk is the potential loss of confidentiality that is minimized by PHI redaction in the study.

9. MONITORING

9.1 Summary

The responsibility of BIOTRONIK, Inc. as sponsor is to ensure protocol and regulatory compliance through proper monitoring of the clinical investigation in sites. As the investigator, the physician is responsible for conducting the clinical investigation in accordance with the signed Investigator Agreement, the study protocol, applicable laws, and FDA and/or local regulations and any conditions of approval imposed by the reviewing IRB. The principal investigator must also accept responsibility for all aspects of the clinical investigation including the actions of any sub-investigators participating in the clinical investigation at the site.

BIOTRONIK utilizes a risk-based monitoring strategy consistent with FDA's Guidance for Industry: Oversight of Clinical Investigations – A Risk-Based Approach to Monitoring, August 2013. Risk-based monitoring starts with performing a study risk assessment of the identified critical data and processes. The resulting monitoring plan focuses on targeted source data verification and trend analyses to improve oversight and data quality, while integrating predefined triggers for additional on-site monitoring. The detailed QP ExCELs risk-based monitoring plan developed by BIOTORNIK, Inc. focuses on a combination of monitoring visits and centralized monitoring.

Monitors will conduct monitoring visits periodically during the clinical investigation in accordance with the monitoring plan. Sites are required to support these monitoring visits and the study monitoring effort. Monitoring visits will also provide an assessment of the continued acceptability of the facilities to continue participation in the study.

Centralized monitoring is conducted via investigator signed electronic case report forms (eCRFs) through the source data verification of source documents uploaded to the eCRF. Some examples of data that may be monitored remotely include: informed consent forms, enrollment, eligibility, implant, study termination, device data and adverse events reported in the EDC system. Sites are required to support centralized monitoring by providing source documents to BIOTRONIK in order to source data verify data reported in the EDC system and resolving queries in a timely manner. Uploaded source documents should meet ALCOA-C principles of attributable, legible, contemporaneous, original, accurate, and complete. It is critical that the fully executed informed consent form and all necessary source documentation are uploaded to the EDC in a timely manner.

The entries in the eCRF will be reviewed and source data verified by monitors (authorized BIOTRONIK, Inc. personnel, or by authorized BIOTRONIK, Inc. designees) to ensure that the investigator and the clinical investigation team conducts the clinical investigation in accordance with the clinical investigation protocol and applicable FDA and local laws and regulations to ensure adequate protection of the rights, safety and wellbeing of subjects and the quality and integrity of the resulting data. In addition, BIOTRONIK, Inc. may require the

presence of personnel from BIOTRONIK, Inc. at implant and/or follow-up visits outlined in this protocol in order to assist the investigator and other site personnel.

9.2 Monitors

Monitors are trained, qualified, and designated by BIOTRONIK, Inc. management to oversee the progress of a study at the clinical site. Additional monitors may be appointed as necessary.

If a monitor becomes aware that an investigator is not complying with the signed Investigator Agreement, the study protocol, applicable laws, and FDA and/or local regulations and any conditions of approval imposed by the reviewing IRB, the monitor is obliged to notify BIOTRONIK, Inc. study management. BIOTRONIK, Inc. will evaluate the non-compliance and issue corrective actions, discontinue enrollment or as a last measure close the clinical investigation site.

10. RECORDS AND REPORTS

10.1 Investigator Records

Investigators are required to maintain the following accurate, complete and current records relating to this study:

- All correspondence relating to the study with another investigator, an IRB, BIOTRONIK, Inc., a monitor, or any regulatory agency (e.g., a letter sent from the investigator to the IRB)
- All clinical forms and documentation, including:
    - A copy of all signed Informed Consent Forms
    - All procedure and visit report forms, including supporting documents
    - Records of any adverse device effect, including supporting documentation
    - Records pertaining to subject deaths during the study
    - Protocol with documentation and rationale for any deviations from the clinical protocol
    - Any other records required by BIOTRONIK, Inc.

The investigator must retain records related to the study according to FDA regulations and IRB requirements.

10.2 Investigator Reports

Investigators are required to prepare and submit to BIOTRONIK, Inc. the following complete, accurate and timely reports on this study, when necessary:

- Notification of a subject death during the study
- Notification of the withdrawal of IRB approval
- Annual progress reports prepared for the IRB
- Notification that informed consent was not obtained from a subject
- Final summary report prepared for the IRB
- Any other information upon the request of an IRB, regulatory authority, or BIOTRONIK, Inc.

Table 7 outlines the responsibilities, including time constraints, for submitting the above reports.

Table 7: Investigator Reports

Type of Report	Prepared by Investigator for:	Time Constraints of Notification
Subject death during study	BIOTRONIK, Inc., IRB	As soon as possible and as required by reviewing IRB
Subject withdrawal	BIOTRONIK, Inc.	Within 5 working days after notification of withdrawal
Withdrawal of IRB approval	BIOTRONIK, Inc.	Within 5 working days of receipt of notice of withdrawal of approval
Progress report(s)	BIOTRONIK, Inc., IRB	Submitted no less than yearly
Significant deviations from study plan	BIOTRONIK, Inc., IRB	Within 5 working days after emergency to protect life or physical well-being of subject, otherwise prior approval by BIOTRONIK, Inc. is required
Informed consent not obtained	BIOTRONIK, Inc., IRB	Within 5 working days of occurrence
Final summary report	BIOTRONIK, Inc., IRB	Within 3 months after completion or termination of the study

10.3 Sponsor Records and Reports

BIOTRONIK, Inc. will maintain the following records:

- All correspondence with the investigator(s), IRBs, and FDA that pertains to the study
- Investigator agreements, financial disclosures, and current curriculum vitae
- Name and address of each investigator and each IRB that is involved with the investigation
- Adverse events
- Adverse device effects
- Electronic Case Report Form data
- Confirmation of completed subject informed consent forms
- Clinical investigation protocol and report of prior investigations
- Screening visit reports
- Monitoring reports
- Clinical progress reports
- Statement of the extent to which the good manufacturing practice regulation in part 21 CFR 820 will be followed in manufacturing the device

BIOTRONIK, Inc. is responsible for preparing the following reports, when necessary:

Table 8: Sponsor Reporting Responsibilities

Type of Report	Prepared by BIOTRONIK for	Time Constraints of Notification
Withdrawal of IRB approval	FDA, all reviewing IRBs, participating investigators	Within 5 working days of receipt of notice of withdrawal of approval
Withdrawal of FDA approval	Reviewing IRBs, participating investigators	Within 5 working days
Progress report	FDA, all reviewing IRBs	Submitted at least annually
Final report	FDA, all reviewing IRBs, participating investigators	Notification within 30 working days of the completion or termination of the investigation. A final report will be submitted within 6 months after completion or termination of the study.

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12. APPENDIX A: DEFINITION OF TERMS

Abnormal Defibrillation Impedance – Defibrillation impedance is typically considered abnormal if a measurement is < 25 Ω or > 150 Ω (based on lead model and measurement range of the device). Includes high or low shock impedance when attempting to deliver a shock.

Abnormal Pacing Impedance – Pacing impedance is typically considered abnormal if a measurement is <200 Ω or >3000 Ω (based on lead model and measurement range of the device).

Cardiac Perforation associated with a lead – Penetration of the lead tip through the myocardium (including microperforation), clinically suspected and confirmed by chest x-ray, fluoroscopy, echocardiogram, intracardiac electrogram and/or visually.

Clinical Lead Failure – Inability of the lead to correctly sense or pace in the heart, not attributable to a mechanical or electrical failure of the lead or pulse generator and that remains unresolved despite reprogramming and/or repositioning.

Coronary Sinus Dissection – A tear that occurs in the wall of the coronary sinus.

Electrical Lead Failure – Confirmed or suspected lead issue that is due to an electrical failure of the lead, such as electrical noise not attributable to other causes, and that leads to loss of pacing and/or sensing. Specific types of confirmed or suspected electrical lead failures, such as high impedance values, no capture, and loss of sensing, are separate adverse event categories and should only be reported once. Confirmed or suspected electrical lead failures caused by induced malfunctions, such as lead damage caused during a procedure, are excluded.

Elevated Pacing Threshold – Either of the following is considered an elevated pacing threshold for the Sentus QP lead:

- At implant: pacing threshold > 3.0 V at 0.4 ms or 0.5 ms
- At routine evaluation: pacing threshold > 2.5 V at 0.4 ms or 0.5 ms

These thresholds are less than half of the maximum output in BIOTRONIK CRT devices and allow for an adequate safety margin.

Extracardiac Stimulation – Clinical observation of inadvertent nerve/muscle stimulation other than cardiac muscle, such as phrenic nerve stimulation.

Failure to Capture or Intermittent Capture – Intermittent or complete failure to achieve cardiac stimulation at programmed output delivered outside of the cardiac refractory period. This will be considered an AE if invasive intervention is taken. In absence of invasive intervention, this will only be considered an AE if there is failure to capture at the permanently programmed output with a minimum 2:1 safety margin. Sudden and significant increase in the pacing threshold value (elevated threshold compared to previous measured value) at which 2:1 safety margin can no longer be achieved.

Failure to Sense or Undersensing – Intermittent or complete loss of sensing or failure to detect intended intrinsic cardiac signals (atrial or ventricular) during non-refractory periods at programmed sensitivity settings. In absence of additional invasive intervention, this will only be considered an AE if the loss of sensing is not due to a medical reason and cannot be resolved with reprogramming.

Hematoma – A localized collection of extravasated blood, usually clotted, in an organ, space, or tissue. A hematoma is not considered a protocol defined AE unless it is a major hematoma related to the implant procedure. See major hematoma.

High Pacing Threshold – High lead pacing threshold resulting in invasive intervention. In absence of invasive intervention, at follow-up, lead threshold that has increased two fold from the chronic threshold value, and is unable to achieve a 2:1 safety margin.

Incorrect Lead/Header Connection – Lead connector pin connected to wrong header port, such as swapping leads or reversing connector pins, that is not identified and corrected prior to the end of the implant/revision procedure.

Infection – An invasion and multiplication of microorganisms in body tissues causing local cellular injury and requiring intravenous antibiotics and or system removal/extraction.

Lead Conductor Fracture – A mechanical break within the lead conductor (includes connectors, coils and / or electrodes) observed visually, electrically, or radiographically.

Lead Dislodgment – Radiographic, electrical or electrocardiographic evidence of electrode displacement from the original implant site or electrode displacement that adversely affects pacing, and/or lead performance.

Lead Explant – Surgical removal of a lead either by simple traction (such as occurs during the acute implant stage) or using manipulation and tools (as can be required for chronically implanted leads).

Lead Insulation Breach or Insulation Break – A disruption or break in lead insulation observed visually, electrically, or radiographically.

Loose Set Screw – Header set screw not properly tightened prior to end of implant/revision procedure.

Major Hematoma – Hematoma requiring evacuation, drainage, blood transfusion, hospitalization or extension of hospital stay to treat hematoma.

Mechanical Failure – Malfunction of the lead through a break in the conductor, insulation, or connector pin leading to loss of pacing / sensing observed visually, electrically, or radiographically. Confirmed or suspected mechanical failures induced by intervention, such as lead damage caused during a procedure, are not protocol defined adverse events.

New York Heart Association (NYHA) Functional Classification – A recognized system of classifying the extent of heart failure.

NYHA Class	Symptoms
I	Subjects with cardiac disease, but without resulting limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnea, or anginal pain.
II	Subjects with cardiac disease resulting in slight limitation of physical activity. They are comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnea, or anginal pain.
III	Subjects with cardiac disease resulting in marked limitation of physical activity. They are comfortable at rest. Less than ordinary activity causes fatigue, palpitation, dyspnea, or anginal pain.
IV	Subjects with cardiac disease resulting in inability to carry on any physical activity without discomfort. Symptoms of cardiac insufficiency or of anginal syndrome may be present even at rest. If any physical activity is undertaken, discomfort is increased.

Non-healing Pocket Dehiscence – Separation of wound edges around the pocket of the implanted pulse generator that have not healed.

Pneumothorax – Air or fluid in the pleural space surrounding the lung leading to collapse or partial collapse of the lung requiring observation or chest tube placement

Premature Battery Depletion – Reaching elective replacement indicator (ERI) before the predicted date.

Pulmonary Embolism – Blockage of the main artery of the lung or one of its branches by a substance that has travelled from elsewhere in the body through the bloodstream.

Pulse Generator Failure – Confirmed or suspected pulse generator issue that is due to a mechanical failure or electrical malfunction, such as inability to communicate with pulse generator, electrical circuit failure, or inability to deliver therapy, that is not attributable to another component of the system or caused by an external source.

Skin Erosion – Deterioration of tissue over an implanted device or the movement of a lead toward or through the skin.

Tamponade – Compression of the heart caused by blood accumulation in the space between the myocardium and the pericardium.

Thrombosis – The development of a blood clot in a vein or artery that leads to the obstruction of blood flow.

Twiddler's Syndrome – A condition where the pulse generator leads are dislodged by the subject unwittingly rotating or otherwise moving the subcutaneous pulse generator.

Venous Occlusion – Blockage of a vein causing a reduction of blood supply and associated symptoms.

13. APPENDIX B: PREVIOUSLY IDENTIFIED ADVERSE EVENTS

Based on literature research, the following adverse events may possibly occur as medical complications of a cardiac rhythm management system implant. The most common adverse events related to the implantation procedure are listed in Table 9a. Expected adverse events related to the left ventricular pacing threshold test in the novel vectors are listed in Table 9d. All references used for this chapter refer to the list at the end of this section.

Adverse events listed below are considered expected unless not previously identified in nature, severity or degree of incidence.

Table 9a: Expected Perioperative Events

Frequency	Percent (%)	Risk
Very frequent >1 out of 10 patients	7-19[45]	LV lead exchange due to unsuccessful positioning
	3-27[32]	Atelectasis (when thoracotomy necessary)
	3-27[32]	Pleural effusion (when thoracotomy necessary)
	3-27[32]	Pneumonia (when thoracotomy necessary)
	Up to 17[32]	VT/VF exacerbation[8,32]
Frequent 1 to 10 patients out of 100	1-7[32]	Infection (general)
	5.2[55,56] - 6[32]	Lead perforation
	3-4[32]	Pericarditis (when patch lead placement necessary)
	Up to 3[32]	Embolism
	Up to 3[49]	Phrenic nerve stimulation
	0.6 – 2.0[49]	Infection requiring reoperation
	0.07*-3[32,54]	Pericardial tamponade (2-3% during patch lead placement)
	0.93[31]-10.6[2,49]	Lead dislodgement
	0.12[31]–3.4[49]	Coronary sinus dissection
Occasionally 1 to 10 patients out of 1.000	0.93[31]	Hematoma
	0.7[54]	Loosening of set screw
	0.02[31] -1[30]	Myocardial infarction
	0.06[31]-2[32]	Cerebrovascular accident, stroke (1-2% during thoracotomy)
	0.6[30]	Lead dysfunction
	0.5[30] – 0.7[57]	Mortality
	0.5[30]	Severe pocket hematoma
	0.5[54]	Pericardial tamponade (2-3% during patch lead

		placement)
	0.42[31] -1[30]	Pneumothorax
	0.3[31] – 0.4[49]	Cardiac arrest
	0.2[30]	Arrhythmia
	0.2 – 0.3[49]	Respiratory arrest
	0.2[49]	Tamponade
	0.1 - 0.4[51]	Allergic reaction to ionic contrast material
	0.14[50]	Air embolism
	0.1[49]	Lead fracture/ insulation failure
	0.1[59]	Ventricular fibrillation
Rare 1 to 10 patients out of 10.000	0.09[31]	Drug reaction
	0.08[31]	Hemothorax
	0.07[31]	Cardiac perforation
	0.04[31]	Phlebitis, superficial
	0.03[31]	Conduction block
	0.03[31]	Infection related to device
	0.03[31]	Peripheral embolus
	0.02[52]– 0.04[53]	Allergic reaction to non-ionic contrast material
	0.02[31]	Phlebitis, deep
	0.02[31]	Transient ischemic attack
Very rare <1 patient out of 10.000	<0.01[31]	Cardiac valve injury
	<0.01[31]	Peripheral nerve injury
	<0.01[31]	AV-fistula
Not known Frequency not assessable on the basis of the available data		Allergic reaction to dexamethasone acetate, bleeding[32], brachial plexus injury[32], device migration[30,41], diaphragmatic stimulation[32], discomfort, erosion, exit block[32], failure to insulate set screw[32], hemoptysis[32], injury to vagus nerve[32], lead malpositioning[32], lead microdislocation[32], local tissue reaction[30], muscle stimulation[30], nerve stimulation (general) [30], myocardial lesion[30], pocket seroma[32], subclavian artery puncture[32], higher x-ray load due to extended fluoroscopy times[34], failing of shock test[40], injury due to implantation accessories[42,44]

Table 9b: Expected Postoperative Events

Frequency	Percentage (%)	Risk
	9.7[20] -37[23]	Lead failure[20,22,23]
Very frequent	2.9[7]–25.4[24]	Inappropriate shocks[7,24,25,54]

>1 out of 10 patients	Up to 13[29]	Device explantation (manufacturers` advisory: 4%[29], electronic failure: 2%[29], housing defects: 1%[29])
	0.3[1] – 13.6[4]	Phrenic nerve stimulation
	12[6,21]	Lead dysfunction
	1.2[19] –10.6[2]	Lead dislodgement
Frequent 1 to 10 patients out of 100	1.7[2] – 9.5[2]	Formation of clinical significant hematomas
	7.6[15] – 9.5[1]	Hematoma[1,3,15,16,17]
	7[46]	Subclavian vein occlusion ≥ 75%
	0.1[5] - 7[1]	Infections[1,5,14] (CRT-D related: 1.9[1,4,13] - 1.9%[1,4]; in-hospital infections: 0.7%[12]; infections after replacement: 1.9%[13])
	0.1 – 4.2[60]	Lead fracture
	1.6[7] – 3.9[4]	Elevated pacing threshold/ loss of capture/ failure to capture
	2.4[30]	Aggregate perforation
	3.4[30]	Pocket erosion
	0[2] – 1.5[7]	Mortality within 30 days after implant (0.4% related to implant procedure[7])
	1.5[30]	Premature depletion of battery
	1.4[7]	Diaphragmatic muscular stimulation
	0.3[2] – 1.3[5]	Lead perforation
	1.3[1]	Pericarditis requiring anti-inflammatory agents
	0.05[7] – 1,2[12,57,61]	Pneumothorax
	0.9[1]	High LV threshold
	0.7[5]	Oversensing
	0.6[7]	Discomfort
	0.6[7]	Pain at device pocket
	0.6[1]	Pericardial effusion requiring intervention
	0.6[7]	Seroma
	0.6[7]	Shoulder pain
	0.5[4]	Lead conductor fracture
	0.5[30]	M. pectoralis tremor
	0.3[5] – 0.5[18]	Post-operative perforation
	0.7[54]	Thrombosis of brachial, subclavian or jugular veins
	0.3[12]	Acute renal failure requiring hemodialysis
	0.3[1]	Ipsilateral venous thrombosis

	0.3[7]	System- or lead-related arrhythmia
	0.2[4]	Elevated lead impedance
	0.2[63]	Site pain
	0.2[54]	Thrombosis of deep femoral vein
Rare 1 to 10 patients out of 10.000	0.09[35]	Fluid accumulation due to heart perforation
	0.1[7]	Cardiac/ cardiac vein/ coronary sinus dissection
	0.1[7]	Hypotension
	0.07[39]	Twiddlers syndrome
Not known Frequency not assessable on the basis of the available data		Farfield sensing or crosstalk leading to pacemaker malfunction[30], Pacemaker Mediated Tachycardia[30], isolation deficiency[30], connector deficiency[30], undersensing[30], chronic nerve damage[30], fibrotic tissue formation[30], keloid formation[30], formation of cysts[30], sensing of myopotentials[30], pulse generator failures[26], device extrusion[36, 43], vein occlusion[37], occlusion of coronary sinus[38]

Table 9c: Expected Psychological Events

Frequency	Percentage (%)	Risk
Very frequent >1 out of 10 patients	25[9,10] - 50[9]	Anxiety or depression[9,10,11,27]
Occasionally 1 to 10 patients out of 1,000	Up to 1[6]	Psychological intolerance
		Psychosomatic impairment
Not known Frequency not assessable on the basis of the available data		Decreased energy levels[28], sleep disturbances[28], loss of libido[28], fatigue[28], reduced physical capacity[28], change in body perception[28], decreased activity level[28], sense of impending danger and uncertainty about the future[28], sensation of losing control[28], sensation of isolation[28], cognitive impairment[28], decline in social interaction[28], fear of shock delivery[28], fear of death[28], fear of device malfunction[28], alteration of social relationships[28], obsessive thinking about shocks[28]

Tale 9d: Expected Events due to Pacing Threshold Test of the LV Lead

Frequency	Percentage (%)	Risk
Very frequent >1 out of 10 patients	32[47]- 41[48]	Phrenic nerve stimulation in 1 or more pacing vectors
Not known Frequency not assessable based on the available data		palpitations

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