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Statistical Analysis Plan

Clinical Investigation Plan Title	SYNSEQ study Left Ventricular Synchronous versus Sequential MultiSpot Pacing for CRT
Clinical Investigation Plan Version	Version 1
Sponsor/Local Sponsor	Medtronic, Bakken Research Center BV Endepolsdomein 5 6229 GW Maastricht, The Netherlands
Document Version	Version 1.0

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1. Version History

Version	Summary of Changes	Author(s)/Title
1.0	Not Applicable, New Document	Baerbel Maus, Senior Statistician

2. List of Abbreviations and Definitions of Terms

Abbreviation	Definition
AE	Adverse Event
AEAC	Adverse Event Advisory Committee
AHA	American Heart Association
AV	Atrioventricular
BiV	Biventricular
BMI	Body Mass Index
CIP	Clinical Investigational Plan
CRF	Case Report Form
CRT	Cardiac Resynchronization Therapy
CRT-D	Cardiac Resynchronization Therapy - Defibrillator
CRT-P	Cardiac Resynchronization Therapy – Pacemaker
CV	Cardiovascular
ECG	Electrocardiogram
eCRF	electronic Case Report Form
EP	Electrophysiology
ESC	European Society of Cardiology

HF	Heart Failure
LBBB	Left Bundle Branch Block
LV	Left Ventricular/Ventricle
LVEF	Left Ventricular Ejection Fraction
MedDRA	Medical Dictionary for Regulatory Activities
MRI	Magnetic Resonance Imaging
RA	Right Atrium
RBBB	Right Bundle Branch Block
RV	Right Ventricular/Ventricle
SAP	Statistical Analysis Plan
SOP	Standard Operating Procedure

3. Introduction

Cardiac Resynchronization Therapy (CRT) has been one of the most important advancements in the past decade for patients with systolic heart failure (HF) and a wide QRS. Several clinical trials have shown improvements in mortality, exercise capacity, clinical symptoms, and quality of life. However, a considerable amount of CRT patients show only limited benefit from the therapy. One possible reason for a low responder rate is non-optimal left ventricular lead position.

The purpose of the SYNSEQ (Left Ventricular Synchronous versus Sequential MultiSpot Pacing for CRT) study is to assess the positive left ventricular (LV) dP/dt max achieved by multipoint LV pacing (either simultaneously or sequentially) in comparison to the response achieved by the current (standard) BiV pacing configuration in patients indicated/recommended for cardiac resynchronization therapy.

The study will also evaluate the feasibility of non-invasive sensors to assist with optimal lead placement and pacing sequence. Additionally, it is anticipated that this study will provide data that can be used to design future studies.

This Statistical Analysis Plan (SAP) will be used to support the final report and analysis of the SYNSEQ study. The Statistical Analysis Plan has been designed to document, before data is analyzed, the planned analyses for the final report. This SAP does not limit the analysis in reports, and additional analyses of the study data beyond this plan are expected. However, this document provides the basis for the statistical sections of the final report. Analyses not planned in the SAP and incorporated into the final report will be referred to as "Additional Analysis".

The following documents were used to create this Statistical Analysis Plan (SAP):

- CIP SYNSEQ Version 1, dated 22/OCT/2015

- SAP iSPOT Version 1, dated 07/MAR/2014
- Safety Plan SYNSEQ Version 1, dated 25/FEB/2016

4. Study Objectives

4.1. Primary objective 1

Compare the hemodynamic response of a MultiSpot-SYN Left Ventricular pacing configuration (simultaneous LV pacing) to a single spot LV pacing configuration in patients undergoing a research study, an EP exploratory procedure or CRT implant using the contractility parameter positive LV dP/dt max.

4.2. Primary objective 2

Compare the hemodynamic response of a MultiSpot-SEQ Left Ventricular pacing configuration (sequential LV pacing) to a single spot LV pacing configuration in patients undergoing a research study, an EP exploratory procedure or CRT implant using the contractility parameter positive LV dP/dt max.

4.3. Secondary objective 1

Compare the positive LV dP/dt max from a MultiSpot-SEQ LV pacing configuration to a MultiSpot-SYN LV pacing configuration in patients undergoing a research study, an EP exploratory procedure or CRT-implant using the contractility parameter positive LV dP/dt max.

4.4. Secondary objective 2

Correlate the (non)invasive measures (blood pressure, electrocardiographic mapping and RV/LV EGM timings and QRS width) obtained during the different pacing configurations to the positive LV dP/dt max measures obtained.

4.5. Secondary objective 3

Evaluate the (non)invasive measures ability to identify the pacing configuration with the highest positive LV dP/dt max.

5. Investigation Plan

5.1. Study Design

This clinical trial is a prospective, interventional, non-randomized, multi-center research study designed to assess augmentation of contractility as measured by positive LV dP/dt max across LV pacing site(s) in patients indicated/recommended for CRT. There is no control group. Subjects will serve as their own control since each pacing configuration is planned to be applied in each subject during the electrophysiological (EP) visit. No blinding will be performed. No interim analysis is planned. The study will enroll up to 40 subjects who fulfill the eligibility criteria and who have completed the EP study procedure.
One limitation of the study is that there is no follow-up data being collected to identify long-term response to CRT. The focus is on acute measurements during the EP study visit. The intent of this study was further to evaluate the benefit of MultiSpot pacing versus BiV pacing in a patient population which is

less likely to respond to CRT therapy. The results of this study might not extend to other patient populations. The sample size is small but comparable with previous studies.

5.2. Eligibility

5.2.1. Inclusion Criteria

- Subject is indicated or recommended for CRT-P or CRT-D device according to the current ESC/AHA guidelines
- Subject is in sinus rhythm
- Subject receives optimal heart failure oral medical therapy
- Subject is willing to sign the informed consent form
- Subject is 18 years or older

5.2.2. Exclusion Criteria

- Subject has permanent atrial fibrillation/flutter or tachycardia
- Subject has pure right bundle branch block (= no additional left ventricular conduction delays)
- Subject has left bundle branch block **and** QRS-duration of > 150 ms **and** no sign of myocardial scar indicated by late gadolinium enhancement MRI
- Subject experienced recent myocardial infarction, within 40 days prior to enrollment
- Subject underwent valve surgery, within 90 days prior to enrollment
- Subject is post heart transplantation, or is actively listed on the transplantation list
- Subject is implanted with a left ventricular assist device
- Subject has severe renal disease (up to physicians discretion)
- Subject is on continuous or uninterrupted infusion (inotropic) therapy for heart failure (≥ 2 stable infusions per week)
- Subject has severe aortic stenosis (with a valve area of <1.0 cm^2 or significant valve disease expected to be operated within study period)
- Subject has complex and uncorrected congenital heart disease
- Subject has a mechanical heart valve
- Pregnant or breastfeeding women, or women of child bearing potential and who are not on a reliable form of birth control
- Subject is enrolled in another study that could confound the results of this study without documented pre-approval from Medtronic study manager

5.3. Treatment and Study Procedures

5.3.1. Treatment

The following pacing configurations will be evaluated at the EP visit (pacing protocol):

Biventricular pacing

Pacing will be performed on one LV electrode pair (at 3 different longitudinal locations), and on the tip of the RV-lead. In total, three different pacing locations will be evaluated:

Configuration 1: RV + LV lateral Apex

Configuration 2: RV + LV lateral Mid

Configuration 3: RV+ LV lateral Base **(Reference: Standard CRT)**

MultiSpot simultaneous LV-ventricular pacing (MultiSpot-SYN)

Pacing will be performed on 3 electrodes on the LV wall, placed at different longitudinal locations, and on the tip of the RV-lead simultaneously.

Configuration 4: RV + LV lateral Apex + LV lateral Mid + LV lateral Base

MultiSpot sequential LV-ventricular pacing (MultiSpot-SEQ)
Three electrodes on the LV wall will be paced sequentially. The RV electrode will be paced simultaneously with the last paced LV electrode. The timing-sequence and the amount of spots will depend on the electrical delays measured during the experiments.

Configuration 5: LV lateral Apex → LV lateral Mid → LV lateral Base + RV

For each pacing configuration, the evaluation of the effect of CRT will be performed approximately 4 times (repetition) in order to increase signal to noise ratio. Each setting lasts about 20 beats (10-15 sec) interspersed with baseline (AAI; also 20 beats, 10-15 sec) pacing.
Optimal AV-delay will be calculated using CardioSync™ formulas (PAV_{ECG}=min (Ap-Pend + 30 ms, Ap-RVs – 50 ms)) derived from a correlation study between electrocardiographic measures such as the intrinsic AV interval and P-wave duration. PAV denotes here the optimal paced AV delay. Ap-Pend indicates the time between atrial pacing (Ap) and end of the P-wave. Ap-RVs denotes the time interval between atrial pacing (Ap) and right ventricular sensing (RVs). Up to five different AV-delays will be evaluated in this study (i.e. the optimal AV-delay and optimal AV-delay ± 30 and ± 60 ms).
Each of the five pacing configuration will be combined with each of the five AV delays. Each combination of configuration and AV delay will be repeated four times interspersed with baseline pacing.

5.3.2. Visits and Data Collection

CRF data will be entered and collected in Oracle Clinical. The SYNSEQ study consists of the following study visits: baseline and EP study procedure. The baseline visit can be a standalone visit or occur on the same day as the EP study. At baseline a magnetic resonance image (MRI) will be collected.

Electrophysiological data from the EP study (e.g., surface ECGs, (non-)invasive blood pressure, LV pressure, electrograms) will be collected by the scientists using a data acquisition system. The raw data will be processed by the scientists/engineers after the EP procedure, e.g., calculations of first time derivative of the LV pressure, and timing differences between electrodes on the heart or on the chest. The processed data will be provided by the scientists/engineers to the statistician(s) in Excel sheets.

6. Determination of Sample Size

6.1. Primary Objective #1

The sample size calculation is based on the primary objective 1 and the primary endpoint, i.e., % change LV dP/dt max from baseline (AAI setting). This study is powered to show superiority of MultiSpot SYN pacing to BiV pacing (standard CRT) for the primary endpoint % change + LV dP/dt max from baseline (AAI pacing). Assuming an expected difference in % change between MultiSpot and BiV pacing of 3.5% and standard deviation of 7%, 34 patients would have 80% power to demonstrate superiority. The total sample size is increased to 40 patients to accommodate for data collection problems during the EP

procedure. The following null-hypothesis H_0 and alternative hypothesis H_1 will be evaluated at a significance level of 0.05:

$$H_0: \Delta_{MultiSpot\ SYN} - \Delta_{BiV} = 0\%$$
$$H_1: \Delta_{MultiSpot\ SYN} - \Delta_{BiV} \neq 0\%,$$

where Δ indicates percentage change from baseline for the corresponding configuration. Previous literature and results from the iSPOT study suggests that the average difference in percentage change between MultiSpot SYN and BiV pacing is 2.5% in a normal HF population (iSPOT study, Sohal, et al., 2015; Thibault, et al., 2013). For the standard deviation of the difference in % change between MultiSpot and BiV pacing we assume 7% based on previous literature and the iSPOT study.

Not much literature is available for the difference in % change between MultiSpot and BiV pacing for the study population targeted in this study. This study selects "difficult" CRT patients in order to adequately address the potential benefit of MultiSpot Pacing in this patient population. The term "difficult" represent those patients with an increased likelihood of non-response to conventional cardiac resynchronization therapy (e.g. ischemic patients or non-LBBB left ventricular dyssynchrony patients). Based on few small subgroup analyses (iSPOT study, Sohal, et al., 2015), we expect that the difference in % change between MultiSpot SYN and BiV pacing will be slightly higher in the targeted study population, namely 3.5%. The sample size calculation is based on this difference of 3.5% and a standard deviation of 7%.

6.2. Primary Objective #2

For the primary objective 2, previous literature suggests that the average difference in % change LV dP/dt max between MultiSpot SEQ and BiV pacing is 3% (Pappone, et al., 2014; Shetty, et al., 2014) in a normal HF population. Assuming an increased difference between MultiSpot SEQ pacing and BiV pacing within the targeted study population similar to the increase for the difference between MultiSpot SYN pacing, i.e., 1 %, the expected difference between MultiSpot SEQ pacing and BiV pacing is 4%. Assuming this difference and a standard deviation of 7%, a sample size of 34 patients has 90 % power to demonstrate superiority.

6.3. Secondary Objective #1

For the secondary objective 1, a power of 80% is achieved with 34 patients. Based on previous research (iSPOT study, Sohal, et al., 2015), we assume that the lower border of the 95 % confidence interval for % change MultiSpot SYN to baseline (AAI mode) in the targeted patient population is 12.6. In this study we consider MultiSpot SEQ non-inferior to MultiSpot SYN if the difference in their means is less than a quarter of the difference between MultiSpot SYN pacing and baseline. The non-inferiority margin is thus chosen to be – 3%. Assuming the expected difference in percentage change dP/dt max between MultiSpot SEQ and MultiSpot SYN pacing is 0.5% and a standard deviation in differences of 7%, 34 patients would have 80% power to demonstrate non-inferiority of MultiSpot SEQ to MultiSpot SYN.

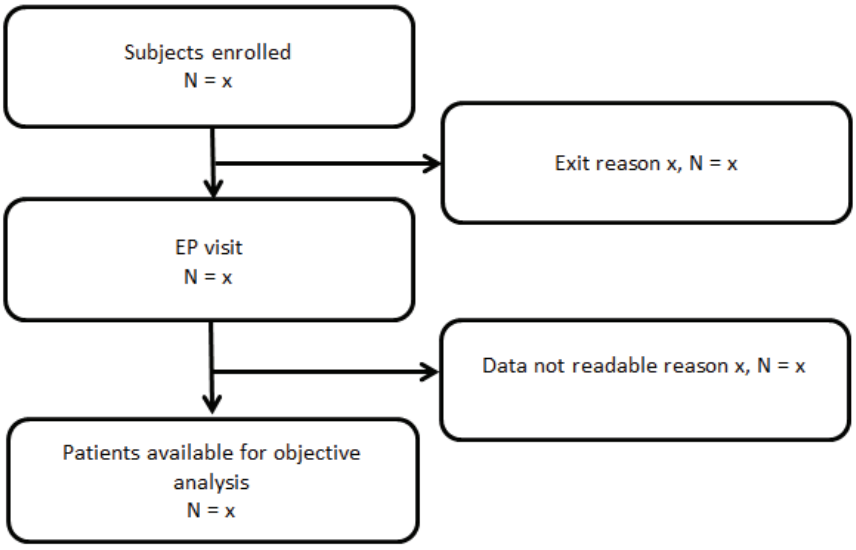
7. Statistical Methods

7.1. Study Subjects

7.1.1. Disposition of Subjects

A subject is enrolled in the study when he/she signs and dates the Patient Informed Consent. The study will enroll up to 40 subjects who fulfill the eligibility criteria and who have completed the EP study procedure. It is anticipated that this study will require approximately 12 to 18 months for subject enrollment. Patients' participation in this study is expected to last approximately between 1 day and 3 months, depending on the time between enrollment and the EP study and the duration of hospital stay after the research study, or EP related procedure, or the CRT-implant. Subjects will be exited from the study just before the moment of hospital discharge. There will be no further follow-up required for subjects that are exited from the study. A flow chart similar to Figure 1 will be created to describe patient disposition.

Figure 1: Patient Disposition Flow Chart



Study exits will be summarized according to exit reason. Violation of inclusion and exclusion criteria at baseline will be summarized for all enrolled patients.

The following tables will be considered to summarize patient disposition:

1. Number (%) of patients per center
2. Number (%) of patients by visit/procedure
3. Follow-up time

Follow-up time will be determined as the time between date of enrollment and date of study exit or date of last contact with subject if the subject was lost to follow-up.

7.1.2. Clinical Investigation Plan (CIP) Deviations

Deviations from the clinical investigation plan will be collected as deviations on the Study Deviation eCRF. Deviations will be summarized in the final report in a table by coded category. Deviation coding will be performed by Medtronic, and the coding will be collected on the MDT Deviation eCRF. The number of deviations per category, the number and percentage of subjects with a deviation in this category will be reported.

7.1.3. Analysis Sets

This statistical analysis plan is created to support the final analysis of the SYNSEQ study. Study manager, scientists/engineers, data manager and statistician will determine the visit cut-off date and received data cut-off date for the final data base lock as suitable.

All patients who signed the informed consent document will be defined as the enrolled population. The Analysis Population is defined as patients who are enrolled, have no inclusion or exclusion criteria violation regarding the most important criteria, i.e., inclusion criteria 1 and 2 and exclusion criterion 3, and have less than 3 months between MRI and EP visit.

The EP study visit should take place within 3 months (less than or equal to 92 days) after the MRI has been obtained. Subjects should be exited if the EP visit cannot be done within 3 months after the MRI. In the case that the subject has not been exited and EP visit data has been obtained, this data cannot be included in the analysis since it might influence the validity of results.

Patients, who are not part of the Analysis Population, will not be included in the primary analysis of the primary objectives, but will be reported in the patient disposition table (number of patients per center). A secondary analysis might be performed including patients who were excluded of the analysis cohort. Safety will be reported on the All Enrolled Population and the primary objectives will be reported on the Analysis Population.

Table 1: Definition of Analysis Sets

Cohort	**Definition**
All Enrolled	All patients that signed informed consent (i.e. informed consent date not blank)
Analysis	Enrolled Patients who have no inclusion or exclusion criteria violation regarding the most important criteria (i.e., inclusion criteria 1 and 2 and exclusion criterion 3) and who have less than three months between MRI and EP visit
Safety	All patients that signed informed consent

Table 2: Use of Analysis Sets

Analysis Item	**Analysis set**
Baseline summary	Analysis
Attrition and follow up summary	Analysis
Primary Objective #1	Analysis
Primary Objective #2	Analysis
Secondary Objective #1	Analysis
Secondary Objective #2	Analysis
Secondary Objective #3	Analysis
Adverse Event summary	Safety
Device Deficiency summary	Safety
Deviation summary	All Enrolled

7.2. General Methodology

Data summaries for categorical data will be summarized as count, e.g., number of patients, and/or number of events, and a percentage relative to the total number of patients/events. The denominator will be explicitly identified when not clear from the context. Continuous variables will be represented by mean and standard deviation, except when the distribution of the variable is highly skewed in which case median and quartiles will be reported.

P-values for hypothesis testing will be evaluated based on two-sided testing using significance level of 0.05 except for the non-inferiority testing (secondary objective 1) which is evaluated using one sided testing and a significance level of 0.025. Confidence intervals will be reported as two-sided 95% confidence intervals.

7.3. Center Pooling

The study is expected to be conducted in approximately 10 centers in Europe. The data from all centers will be pooled. There will be no minimum limit that each investigator must enroll. The maximum number of enrolled subjects per center is 15 subjects.

7.4. Handling of Missing Data and Dropouts

No imputation of missing data is planned. Study attrition of subjects will be summarized (see Section 7.1.1). For the EP study data, it can happen that a configuration cannot be applied for a certain subject or that the data collected cannot be used for analysis. For each configuration, the number of patients with this configuration available will be summarized in a table similar to Table 3. For each objective and comparison between configurations, the number of patients effectively contributing to the analysis will be reported.

Table 3: Number of Patients per Pacing Configuration

Configuration	Available Patients
BiV distal	N
BiV mid	N
BiV apical	N
MultiSpot SYN	N
Multispot SEQ	N

7.5. Adjustments for Multiple Comparisons

Besides the comparisons between MultiSpot SEQ/SYN pacing and BiV pacing (primary objectives), there is also interest in comparing the BiV pacing configuration directly to each other. In total, ten comparison are being planned (3 for primary objective #1, 3 for primary objective #2, 1 for secondary objective #1, and three comparisons directly between the BiV pacing configurations).

No adjustment for multiple comparisons is planned due to the exploratory nature of the study.

7.6. Demographic and Other Baseline Characteristics

The following characteristics will be collected at baseline and summarized in descriptive tables for the analysis cohort:

- Age (years)
- Gender
- Height, weight, body mass index (BMI), heart rate, blood pressure
- Left ventricular ejection fraction (%) and LVEF method of measurement (baseline CRF)
- ECG: QRS duration, PR interval, RR interval, QTc interval (baseline CRF)

- NYHA classification
- Medical history
- Cardiovascular medications
- Left ventricular ejection fraction, left ventricular end systolic volume, left ventricular end diastolic volume (MUO MRI CRF)

BMI will be calculated as weight in kg/(height in m)^2. Age will be calculated by the following formula: year of enrollment – year of birth. The year of enrollment will be determined from the date of informed consent. Only "difficult" CRT patients are selected for this study in order to adequately address the potential benefit of MultiSpot Pacing in this patient population. The term "difficult" represent those patients with an increased likelihood of non-response to conventional cardiac resynchronization therapy (e.g. ischemic patients or non-LBBB left ventricular dyssynchrony patients).

The characteristics of the "difficult" CRT patient population will be summarized with regard to typical CRT response indicators in a table similar to the table below. The table cohort will be all enrolled patients and the analysis cohort.

Table 4: Subject Characteristics – CRT Response Indicators

Subject Characteristics	**Total Subjects For Analysis (N = Z)**	**Total Subjects (N = 40)**
No Left Bundle Branch Block	N (%)	N (%)
QRS duration (ms)		
Mean (SD)	x (x)	x (x)
Median	x	x
25th Percentile – 75th Percentile	x (x)	x (x)
Minimum – Maximum	x (x)	x (x)
QRS duration ≤ 150 ms	N (%)	N (%)
Amount of Scar (%)		
Mean (SD)	x (x)	x (x)
Median	x	x
25th Percentile – 75th Percentile	x – x	x – x
Minimum – Maximum	x – x	x – x
Number of Subjects with Measure Available	N (%)	N (%)
LBBB and QRS area above > 150 ms and myocardial scar	N (%)	N (%)
Amount of scar (%)		
Mean (SD)	x (x)	x (x)
Median	x	x
25th Percentile – 75th Percentile	x – x	x – x
Minimum – Maximum	x – x	x – x

Subject Characteristics	Total Subjects For Analysis (N = Z)	Total Subjects (N = 40)
Total (No LBBB or QRS ≤ 150 or (LBBB and QRS > 150 and myocardial scar))	N (%)	N (%)

7.7. Treatment Characteristics

For the EP study visit, three leads will be placed, namely one in the right atrium, one in the right ventricle and one in the left ventricle. A second left ventricular lead may be placed to reach the LV apex. The locations of these leads will be summarized.

For the EP study visit, the following variables will be summarized in descriptive tables:

- Procedure time (minutes) (from EP study CRF)
- Type of procedure after EP study visit
- RA, RV, LV transvenous lead I and lead II positions if applicable (from EP study CRF and/or fluoroscopy images)
- Types of LV transvenous lead I and II if applicable
- Atrial pacing rate (beats per minutes)
- Time between atrial pace and RV sense (AV timing)
- Time between atrial pace and end of P-wave
- Calculated optimal AV delay based on CardioSync™ formula
- VV delays in case of sequential pacing per electrode (apical, mid, basal electrode)

Cardiovascular medications are collected at baseline and will be summarized. Medications will be coded into medication categories. The number of medications in each category, and the number and percentage of subjects with medications in each category will be summarized.

7.8. Interim Analyses

No interim analysis is planned for this study.

7.9. Evaluation of Objectives

7.9.1. Primary Objective #1

Compare the hemodynamic response of a MultiSpot-SYN Left Ventricular pacing configuration (simultaneous LV pacing) to a single spot LV pacing configuration in patients undergoing a research study, an EP exploratory procedure or CRT implant using the contractility parameter positive LV dP/dt max.

7.9.1.1. Hypothesis

It is hypothesized that MultiSpot pacing simultaneously is superior to BiV pacing. The null and alternative hypotheses are:

$$H_0: \Delta_{\text{MultiSpot SYN}} - \Delta_{\text{BiV}} = 0\%$$
$$H_1: \Delta_{\text{MultiSpot SYN}} - \Delta_{\text{BiV}} \neq 0\%,$$

where Δ indicates percentage change from baseline for the respective pacing configuration. The hypothesis will be assessed for the following three comparisons: MultiSpot SYN to BiV basal (standard CRT), MultiSpot SYN to BiV mid, and MultiSpot SYN to BiV apical. In particular, the comparison of MultiSpot SYN to standard CRT is of interest.

7.9.1.2. Endpoint Definition

The contractile ability of LV is characterized by the positive LV dP/dt max. An increase in contractility is manifested as an increase in dP/dt max during isovolumic contraction. It is a measure of the initial velocity of myocardial contraction and is a derivative of the LV-pressure. LV pressure is measured invasively during the EP visit using a catheter inside the LV.
The endpoint is % change LV dP/dt max from baseline (AAI pacing) to correct for baseline differences and drifts. This percentage change is calculated as ([median dP/dt max during pacing On] – [median baseline dP/dt max during pacing Off])/[median dP/dt max during pacing Off]. Pacing Off denotes here AAI pacing (CRT pacing off). In general, eight non-ectopic beats will be considered during baseline and during pacing On to calculate the medians during baseline and the pacing On settings. If less than eight beats will be available, the maximum number of available beats will be used for calculation of the median. For each combination of pacing configuration and AV delay, there are four repetitions of pacing On/Off and thus eight percentage changes will be calculated per combination.

Other endpoints, e.g., blood pressures, might be considered instead of LV dP/dt max in an exploratory secondary analysis for this objective.

7.9.1.3. Analysis Methods

A. Statistical Methodology

The following steps will be applied for analysis.

1. Regression model per patient
2. Use the parameter estimates from regression model to obtain predicted maximum response and corresponding best AV delay per configuration
3. Use PROC GLM to obtain the standard error of the predicted maximum response
4. Perform weighted t-test for comparison between configurations

Step 1

For each patient, a regression analysis will be performed to model % change LV dP/dt max dependent on configuration and AV delay. The model will include effects for configuration, for AV delay up to a quadratic order, and interaction effects. AV delay will have values 0, -30, +30, -60, 60 ms to indicate the difference between the applied AV delay and the optimal AV delay based on the Cardio Sync formula. AV delay will be treated as a continuous variable. The following regression model will be applied for each subject:

$$\%\ \text{change} = \beta_1 * \text{Configuration}_1 + \beta_2 * \text{Configuration}_2 + \beta_3 * \text{Configuration}_3 + \beta_4 * \text{Configuration}_4 + \beta_5 * \text{Configuration}_5 + \beta_6 * \text{AVdelay} + \beta_7 * \text{AVdelay}^2 + \beta_8 * \text{Configuration}_1 * \text{AVdelay} + \beta_9 * \text{Configuration}_2 * \text{AVdelay} + \beta_{10} * \text{Configuration}_3 * \text{AVdelay} + \beta_{11} * \text{Configuration}_4 * \text{AVdelay} + \beta_{12} *$$

$\text{Configuration}_5 * \text{AVdelay} + \beta_{13} * \text{Configuration}_1 * \text{AVdelay}^2 + \beta_{14} * \text{Configuration}_2 * \text{AVdelay}^2 + \beta_{15} * \text{Configuration}_3 * \text{AVdelay}^2 + \beta_{16} * \text{Configuration}_4 * \text{AVdelay}^2 + \beta_{17} * \text{Configuration}_5 * \text{AVdelay}^2 + \varepsilon.$

Configuration_i is 1 if at time point t pacing configuration i is performed and 0 otherwise. The error is denoted by ε. For ease of interpretation, no intercept is included in the model such that the estimate $\hat{\beta}_i$ correspond to the estimated mean % change during configuration i. Alternatively, one could include an intercept which would then model a reference configuration.

[redacted]

Step 2

R code similar to the code below can be used to determine the AV delay (best AV delay) which leads to the maximum predicted response based on the fitted model for each patient.

[redacted]

Step 3

Within SAS, PROC GLM can be used to determine the standard error of the predicted change dP/dt max at best AV delay δ, i.e., the standard error of the predicted maximum change dP/dt max. We would like to take this standard error into account since subjects with less precise estimates of maximum LV dP/dt max should have less influence in the following comparison between configurations. [redacted]

[redacted]

[redacted]

Step 4

The table below shows the maximum predicted response for patient 10 and configuration BiV mid and MultiSpot from the iSpot study. The predicted maximum response is 33.3% for BiV mid at AV delay 9.9 with a standard error of 1.1.

Table 5: Results for patient 10

Pt	Configuration	Best AV delay	Mean	SE
10	BiV mid	9.9	33.3	1.1
10	Multispot	28	35.5	1.1

In the table below it can be seen that the standard errors are much larger for patient 11. Therefore, we would like to give this patient less influence in the analysis.

Table 6: Results for patient 11

Pt	Configuration	Best AV delay	Mean	SE
11	BiV mid	40	40.6	5.8
11	Multispot	-40	28.9	3.0

The table below shows the difference between MultiSpot and BiV mid for patient 10 and 11 in % change. The variance is calculated by the formula $Var(X-Y) = Var(X) + Var(Y) - 2 * Cov(X,Y) = STD(X)^2 + STD(Y)^2 - 2 * Cov(X,Y)$. The standard deviation of the mean response (predicted response) is the standard error. We neglect Cov(X,Y) which depends on the covariances between the regression estimators since results from the iSpot study show that the covariances between different estimators was small, i.e., smaller than 0.01. Therefore for patient 10, Var(MultiSpot – BiV mid) = Var(X-Y) ~ 1.1^2 + 1.1^2 = 2.42.

Table 7: Comparison between MultiSpot and BiV mid for patient 10 and 11

Pt	Configuration	Mean difference	Variance
10	Multispot – BiV mid	2.2	2.42

11	Multispot – BiV mid	-11.7	42.64

We will use inverse-variance weighting to weight each subject in the following testing, i.e., each subject is weighted with $w_i = \frac{1/v_i}{\sum_{i=1}^{N} 1/v_i}$. The variance for each subject i (i = 1,…,N) is here denoted by v_i.

Paired weighted two-sided t–tests will be used to evaluate whether there is a statistical significantly difference between MultiSpot-SYN and BiV pacing. Instead of paired t-tests, a Wilcoxon signed rank test might be performed if normality is violated. [redacted]

[redacted]

Variables config4 resp. config1 contain here the maximum % change LV dP/dt for configuration 4 resp. configuration 1. Dataset ttests_superior contains the p-value for the comparison between configuration 1 and 4 (superiority testing) while dataset conf_superior contains the confidence limits.

Results will be summarized in tables similar to the tables below:

Table 8: Percentage Change LV dP/dt max per configuration

Comparison	Number of Subjects	Difference in % change LV dP/dt max	95 % Confidence interval
BiV basal	N	x.xx	x.xx – x.xx
BiV mid	N	x.xx	x.xx – x.xx
BiV apical	N	x.xx	x.xx – x.xx
MultiSpot SYN	N	x.xx	x.xx – x.xx
MultiSpot SEQ	N	x.xx	x.xx – x.xx

Table 9: Results for Comparison MultiSpot SYN to BiV pacing

Comparison	Number of Subjects	Difference in % change LV dP/dt max	95 % Confidence interval	P-value
MultiSpot SYN – BiV basal	N	x.xx	x.xx – x.xx	x.xxxx
MultiSpot SYN – BiV mid	N	x.xx	x.xx – x.xx	x.xxxx
MultiSpot SYN – BiV apical	N	x.xx	x.xx – x.xx	x.xxxx

The difference between optimal and best AV delay and the obtained % changes at these AV delays will be summarized in a table similar to the table below. Since the analysis methods for primary objective #1, #2 and secondary objective #1 are similar, the table will summarize results from all three objectives.

Table 10: Difference between optimal AV delay and best AV delay

	BiV basal (N =X)	BiV mid (N =X)	BiV distal (N =X)	Multispot SYN (N =X)	MultiSpot SEQ (N =X)
Difference between optimal AV delay and best AV delay					
Mean ± Standard Deviation	X ± Y	X ± Y	X ± Y	X ± Y	X ± Y
Median	X	X	X	X	X
25th Percentile – 75th Percentile	X – Y	X – Y	X – Y	X – Y	X – Y
Minimum – Maximum	X - Y	X - Y	X – Y	X - Y	X - Y
Number of Subjects With Measure Available (N,%)	X (Y%)	X (Y%)	X (Y%)	X (Y%)	X (Y%)
Difference between % change LV dP/dt max at optimal AV delay and at best AV delay					
Mean ± Standard Deviation	X ± Y	X ± Y	X ± Y	X ± Y	X ± Y
Median	X	X	X	X	X
25th Percentile – 75th Percentile	X – Y	X – Y	X – Y	X – Y	X – Y
Minimum – Maximum	X - Y	X - Y	X – Y	X - Y	X - Y
Number of Subjects With Measure Available (N,%)	X (Y%)	X (Y%)	X (Y%)	X (Y%)	X (Y%)

B. Determination of Patients/Data for Analysis

The analysis will be performed on patients in the analysis cohort. Furthermore, it is necessary that patient have measurements during MultiSpot SYN pacing and during the respective BiV configuration used for comparison.

7.9.2. Primary Objective #2

Compare the hemodynamic response of a MultiSpot-SEQ Left Ventricular pacing configuration (sequential LV pacing) to a single spot LV pacing configuration in patients undergoing a research study, an EP exploratory procedure or CRT implant using the contractility parameter positive LV dP/dt max.

7.9.2.1. Hypothesis

It is hypothesized that MultiSpot pacing sequentially (from apex to mid and then to base) is superior to BiV pacing. The null and alternative hypotheses are:

$$H_0: \Delta_{\text{MultiSpot SEQ}} - \Delta_{\text{BiV}} = 0\%$$
$$H_1: \Delta_{\text{MultiSpot SEQ}} - \Delta_{\text{BiV}} \neq 0\%,$$

where Δ indicates percentage change from baseline for the respective pacing configuration.

Statistical analysis will use the methods described for the primary objective 1, with MultiSpot-SYN LV pacing replaced by MultiSpot-SEQ LV pacing configuration. The hypothesis will be assessed for the following three comparisons: MultiSpot SEQ to BiV basal (standard CRT), MultiSpot SEQ to BiV mid, and MultiSpot SEQ to BiV apical. In particular, the comparison of MultiSpot SEQ to standard CRT is of interest.

7.9.2.2. Endpoint Definition

The endpoint is the same as for the primary objective #1, i.e., % change LV dP/dt max from baseline (AAI pacing).

7.9.2.3. Analysis Methods

A. Statistical Methodology

Statistical analysis will use the methods described for the primary objective 1, with MultiSpot-SYN LV pacing replaced by MultiSpot-SEQ LV pacing configuration.

Results will be summarized in a table similar to the table below:

Table 11: Results for Comparison MultiSpot SEQ to BiV pacing

Comparison	Number of Subjects	Difference in % change LV dP/dt max	95 % Confidence interval	P-value
MultiSpot SEQ – BiV basal	N	x.xx	x.xx – x.xx	x.xxxx
MultiSpot SEQ – BiV mid	N	x.xx	x.xx – x.xx	x.xxxx
MultiSpot SEQ – BiV apical	N	x.xx	x.xx – x.xx	x.xxxx

B. Determination of Patients/Data for Analysis

The analysis will be performed on patients in the analysis cohort. Furthermore, it is necessary that patient have measurements during MultiSpot SEQ pacing and during the respective BiV configuration used for comparison.

7.9.3. Secondary Objective #1

Compare the positive LV dP/dt max from a MultiSpot-SEQ LV pacing configuration to a MultiSpot-SYN LV pacing configuration in patients undergoing a research study, an EP exploratory procedure or CRT-implant using the contractility parameter positive LV dP/dt max.

7.9.3.1. Hypothesis

It is hypothesized that MultiSpot pacing sequentially (from apex to mid and then to base) is non-inferior to MultiSpot pacing simultaneously.

The null and alternative hypotheses are thus:

H_0: $\Delta_{MultiSpot\ SEQ} - \Delta_{MultiSpot\ SYN} \leq -3\%$ (MultiSpot SEQ inferior)

H_1: $\Delta_{MultiSpot\ SEQ} - \Delta_{MultiSpot\ SYN} > -3\%$ (MultiSpot SEQ non-inferior)

7.9.3.2. Endpoint Definition

The endpoint is the same as for the primary objective #1, i.e., % change LV dP/dt max from baseline (AAI pacing).

7.9.3.3. Analysis Methods

A. Statistical Methodology

Statistical analysis will use the methods described for the primary objective 1, with single spot LV pacing configuration (standard BiV) replaced by MultiSpot-SEQ LV pacing.
Inferiority testing will be performed one-sided at a significance level of 0.025. Non-inferiority of MultiSpot SEQ to MultiSpot SYN will be declared if the lower limit of a two-sided 95% confidence interval for the mean difference between MultiSpot SEQ and SYN does not fall below -3%. Superiority testing will be performed two-sided at a significance level of 0.05.

Results for non-inferiority testing will be summarized in a table similar to the table below:

Table 12: Comparison between MultiSpot SEQ and MultiSpot SYN (non-inferiority testing)

Comparison	Number of Subjects	Difference in % change LV dP/dt max	95 % Confidence interval	P-value
MultiSpot SEQ– MultiSpot SYN	N	x.xx	x.xx – x.xx	x.xxxx

Results for superiority testing will be summarized in a table similar to the below if non-inferiority is significant:

Table 13: Comparison between MultiSpot SEQ and MultiSpot SYN (superiority testing)

Comparison	Number of Subjects	Difference in % change LV dP/dt max	95 % Confidence interval	P-value
MultiSpot SEQ– MultiSpot SYN	N	x.xx	x.xx – x.xx	x.xxxx

B. Determination of Patients/Data for Analysis

The analysis will be performed on patients in the analysis cohort. Furthermore, it is necessary that patient have measurements during MultiSpot SEQ and SYN pacing.

7.9.4. Secondary Objective #2

Correlate the (non)invasive measures (blood pressure, electrocardiographic mapping and RV/LV EGM timings) obtained during the different pacing configurations to the positive LV dP/dt max measures obtained.

The purpose of this objective is to evaluate the feasibility of other measures, in particular non-invasive measures, to assist with optimal lead placement and pacing sequence.

7.9.4.1. Hypothesis

There are no hypotheses specified.

7.9.4.2. Endpoint Definition

The following table summarizes measures collected for this objective and the tool which will be used during the EP study to acquire them. All these measures will be collected during the EP study and derived using algorithms developed by the scientists. In the table below it is further indicated whether these measurements are invasive or non-invasive. The final list of secondary endpoints will be specified at study end before the statistical analysis.

Table 14: Measures

Endpoint	Invasive/non-invasive	Tool
LV dP/dt max (mmHg/sec)	Invasive	LV catheter
Diastolic blood pressure (mmHg)	Invasive	Blood pressure transducer
Systolic blood pressure (mmHg)	Invasive	Blood pressure transducer
Diastolic blood pressure (mmHg)	Non-invasive	Finger volume clamp
Systolic blood pressure (mmHg)	Non-invasive	Finger volume clamp
QRS duration (msec)	Non-invasive	Surface ECGs
RV-LV timing (msec)	Invasive	Electrocardiogram
Q-LV interval (msec)	Invasive	Electrocardiogram and surface ECGs

LV dP/dt max and blood pressures are collected during the pacing protocol. The non-invasive blood pressures are collected optionally. RV-LV timing and Q-LV are collected during threshold testing and setup before the start of the pacing protocol.
The Q-LV interval is defined as the time from the onset of the QRS width of the surface ECG to the first large positive or negative peak of the LV electrogram (EGM) during a cardiac cycle. Percentage Q-LV (% Q-LV) will be calculated as the absolute Q-LV/QRS duration. Since there are three LV electrodes, the Q-LV interval can be determined for the apical, mid and basal LV electrode position.
The RV-LV timing gives the interval between intrinsic deflection of RV EGM and LV EGM. Since there are three LV electrodes, the RV-LV interval can be determined for the apical, mid and basal position. The following types of RV-LV timing (or LV-LV timing) might be collected:

- RV paced – LV sensed
- RV sensed – LV sensed
- LV paced – LV sensed
- LV paced – RV sensed

- LV sensed – LV sensed

The secondary endpoints will be used to calculate the pairwise correlation with the contractility endpoint (+LV dP/dt max) acquired during the different configurations. Correlation between LV dP/dt max and blood pressures will be based on % changes LV dP/dt max and % changes for the blood pressures. The % changes for the blood pressures are derived in the same way as for LV dP/dt max.
Correlation between LV dP/dt max and the QRS duration will be based on raw (untransformed) LV dP/dt max and raw QRS width. Correlation between LV dP/dt max and Q-LV timing will be based on % change LV dP/dt max and % Q-LV as well as raw LV dP/dt max and raw Q-LV timing.

If the number of measurements between a secondary endpoint and LV dP/dt max does not coincide (there are less measurements for the secondary endpoint), summary statistics for LV dP/dt max will be derived. In a subsequent step, the correlation between LV dP/dt max and the secondary endpoint will be derived on these summary statistics. For example for the iSPOT study, QRS duration was determined by the scientists with one measurement per combination of configuration and AV delay. For further analysis, raw LV dP/dt max was averaged over repetitions to obtain one value per combination of configuration and AV delay. In the next step, the correlation was determined between the averaged raw LV dP/dt max and QRS duration.

7.9.4.3. Analysis Methods

A. Statistical Methodology

Regression analysis will be used to determine pairwise Pearson's correlation between the secondary endpoints and LV dP/dt max.

The measures are collected longitudinally during the EP study such that there will be several measurements per subject. Therefore, we need to take the repeated measurements into account when calculating the correlation coefficient (Bland & Altman, 1995).

In order to handle the repeated measurements per subject, the following regression model will be applied (Bland & Altman, 1995) to determine the correlation between % change LV dP/dt max and % change endpoint x:

$$\%\text{ change endpoint x} = \beta * \%\text{ change LV } \frac{\text{dP}}{\text{dt}}\text{ max } + \sum \gamma_i * subject_i + \epsilon,$$

where subject_i is 1 if the measurements are from subject i and 0 otherwise. This model will fit parallel linear regression lines with one regression line for each subject and slope β. Similar regression models will be applied for the raw measurements.[redacted]

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The Pearson correlation can then be calculated as

$$r = \sqrt{\frac{74207.40510}{74207.40510 + 105036.5290}} \approx 0.6434$$

The sign of the correlation is the sign of the regression coefficient for PercChange_dPdtmax, i.e. +. The p-value of the Pearson correlation is the p-value of the regression coefficient. However, the p-value here should be interpreted keeping in mind the large sample size (N=6916). With a large sample size, a low strength of correlation, for example r = 0.3, can be highly significant. The confidence interval will be more informative to assess the strength of the association.

The Fisher z-transformation will be used to determine the confidence interval for the correlation coefficient. Using this approach, the (1-α) confidence interval for the correlation is given as $\left[\tanh(\tanh^{-1}(r) - z_{1-\alpha/2} * 1/\sqrt{N-3}), \tanh(\tanh^{-1}(r) + z_{1-\alpha/2} * 1/\sqrt{N-3})\right]$, where tanh is the hyperbolic tangent function and $\tanh^{-1}$ its inverse function, also called the artanh function. The (1-α/2) quantile of the normal distribution is denoted by $z_{1-\alpha/2}$. The sample size is given by N.

The results will be summarized in tables similar to the table below.

Table 15: Correlation between LV dP/dt max and other measures

Variable 1	Variable 2	Number of subjects for Analysis	Correlation	95% Confidence Interval
% change LV dP/dt	% change invasive	N	x.xx	[x.xx – x.xx]

max	SBP			

B. Determination of Patients/Data for Analysis

The analysis will be performed on patients in the analysis cohort.

7.9.5. Secondary Objective #3

Evaluate the (non)invasive measures ability to identify the pacing configuration with the highest positive LV dP/dt max.

7.9.5.1. Hypothesis

There are no hypotheses specified.

7.9.5.2. Endpoint Definition

All these measures will be collected longitudinally during the EP study and derived using algorithms developed by the scientists/engineers.

The following table summarizes measures collected for this objective and the tool which will be used during the EP study to acquire them. All these measures will be collected during the EP study and derived using algorithms developed by the scientists. In the table below it is further indicated whether these measurements are invasive or non-invasive. The final list of secondary endpoints will be specified at study end before the statistical analysis.

Table 16: Measures

Endpoint	Invasive/non-invasive	Tool
LV dP/dt max (mmHg/sec)	Invasive	LV catheter
Diastolic blood pressure (mmHg)	Invasive	Blood pressure transducer
Systolic blood pressure (mmHg)	Invasive	Blood pressure transducer
Diastolic blood pressure (mmHg)	Non-invasive	Finger volume clamp
Systolic blood pressure (mmHg)	Non-invasive	Finger volume clamp
QRS duration (msec)	Non-invasive	Surface ECGs

Q-LV timings and RV-LV timings can only be determined for BiV apical, BiV basal, and BiV mid configurations but not for the MultiSpot configurations since the timings are based on the time that the electrical signal takes from the Q-wave resp. RV EGM to the individual LV EGMs, i.e., LV1 EGM for electrode 1 (apical), LV2 EGM for electrode 2 (basal), and LV3 EGM for electrode 3 (LV3 EGM). As a consequence, these measures are not relevant for this objective. For LV dP/dt max and blood pressures, the analysis will be based on % changes from baseline.

7.9.5.3. Statistical Methodology

A. Statistical Methodology

A categorical variable of the best pacing configuration per patient will be calculated (the configuration that achieves the largest dP/dt value) and the agreement with each (non)invasive evaluation of best pacing configuration (also derived into a categorical variable) will be evaluated and tested with an unweighted Kappa statistic.

The following steps will be performed for analysis. These steps will be repeated for each endpoint.

1. Regression model per patient (see primary objective #1)
2. Use the parameter estimates from regression model to obtain predicted maximum response and corresponding best AV delay per configuration (see primary objective #1)
3. Determine the best configuration for each patient, i.e., the configuration with largest maximum response
4. Create a categorical variable which contains for each patient the best configuration

In the final step, we will evaluate and test the agreement between these ratings based on dP/dt max and the other endpoints using an unweighted Kappa statistic. The kappa statistics can be seen as a correlation between categorical variables. Our categorical variables give here the best configuration based on the different measurements. The kappa statistic adjusts for the agreement which might happen by chance. A kappa statistic of 1 indicates perfect agreement between the variables while a kappa statistic of 0 indicates that the agreement is due to chance. A kappa statistic lower than 0 indicates that the agreement is less than the agreement which might happen due to chance.

[redacted]

The results will be summarized into a table similar to the table given below. The total numbers x will be given, where the best configuration was chosen to be one configuration based on dP/dt max and another configuration or the same configuration based on the second measure. Furthermore, cell percentage, row percentage, column percentages will be indicated per xx.x %. The last cell will give the total number of subjects available for the analysis.

Table 17: Best configuration

	Best configuration based on dP/dt max					Total
	BiV proximal	BiV distal	BiV mid	MultiSpot SYN	MultiSpot SEQ	

	BiV proximal	x xx.x % xx.x % xx.x %	x xx.x % xx.x % xx.x % xx.x %	x xx.x % xx.x % xx.x % xx.x %	x xx.x % xx.x % xx.x % xx.x %	x xx.x % xx.x % xx.x %x	x xx.x%
	BiV distal	x xx.x % xx.x % xx.x %	x xx.x % xx.x % xx.x % xx.x %	x xx.x % xx.x % xx.x % xx.x %	x xx.x % xx.x % xx.x % xx.x %	x xx.x % xx.x % xx.x %x	x xx.x%
Based on non-invasive measure	BiV mid	x xx.x % xx.x % xx.x %	x xx.x % xx.x % xx.x % xx.x %	x xx.x % xx.x % xx.x % xx.x %	x xx.x % xx.x % xx.x % xx.x %	x xx.x % xx.x % xx.x %x	x xx.x%
	MultiSpot SYN	x xx.x % xx.x % xx.x %	x xx.x % xx.x % xx.x % xx.x %	x xx.x % xx.x % xx.x % xx.x %	x xx.x % xx.x % xx.x % xx.x %	x xx.x % xx.x % xx.x %x	x xx.x%
	MultiSpot SEQ	x xx.x % xx.x % xx.x %	x xx.x % xx.x % xx.x	x xx.x % xx.x % xx.x	x xx.x % xx.x % xx.x	x xx.x % xx.x % xx.x %x	x xx.x%

		% xx.x %	% xx.x %	% xx.x %		
Total	x xx.x %	x xx.x %	x xx.x %	x xx.x %	x xx.x %	N xx.x %

Table 18: Kappa statistic

Statistic	Value	Approximated standard error	95 % Confidence Limits	
Simple Kappa	0.3449	0.0724	0.2030	0.4868

Sample size = 40

Table 19: Test of H_0: Kappa = 0

Statistic	Value	Approximated standard error under H0	Z-statistic	P-value (One-sided Pr > Z)	P-value (Two-sided Pr > |Z|)
Simple Kappa	0.3449	0.0612	5.6366	<.0001	<.0001

Sample size = 40

B. Determination of Patients/Data for Analysis

The analysis will be performed on patients in the analysis cohort.

7.10. Safety Evaluation

Details about the safety reporting and adjudication for SYNSEQ can be found in the Safety Plan for the SYNSEQ study.

Adverse events and deaths will be summarized in tables with number of events, number and percentage of patients with one or more events, according to the characteristics given below.

Adverse Events

- Seriousness (investigator adjudication)
- Relatedness (AEAC adjudication)
    - Procedure

    - System
- Unanticipated Serious Adverse Device Effect (USADE) (Medtronic adjudication)

Deaths (per AEAC adjudication)

- relatedness (system and/or procedure)
- cardiac classification
    - cardiac death
    - sudden cardiac death
    - non-sudden cardiac death
    - non-cardiac death
    - unknown

Another table will be reported with for each MedDRA preferred term the number of events, number of patients with one or more events, and percentage of patients with event.

The AEAC classification will be used for reporting if available. If the AEAC adjudication is not available, the investigator classification will be used. USADE adjudication is only performed by the sponsor Medtronic, and therefore the sponsor adjudication will be used here. If there is a disagreement between investigator and AEAC, this disagreement will be reported in forms of AE listing. Adverse events and device deficiencies will be summarized for the 'All Enrolled' cohort.

7.11. Health Outcomes Analyses

No health outcomes analysis is planned for the SYNSEQ study.

7.12. Changes to Planned Analysis

This Statistical Analysis Plan does not deviate from the planned statistical analysis in the CIP. The analysis cohort has been described in the CIP as follows: "The Analysis Population is defined as patients, who are enrolled, have no inclusion or exclusion criteria violation regarding the most important criteria, i.e., inclusion criteria 1 and 2 and exclusion criterion 3, and for whom the EP procedure could be completed successfully." This definition has been clarified in the SAP to the following definition: "The Analysis Population is defined as patients who are enrolled, have no inclusion or exclusion criteria violation regarding the most important criteria, i.e., inclusion criteria 1 and 2 and exclusion criterion 3, and have less than 3 months between MRI and EP visit."

Any change to the data analysis methods described in the Clinical Investigational Plan will require an amendment only if it changes an objective of the Clinical Investigational Plan. Any other change to the data analysis methods described in the Clinical Investigational Plan and this Statistical Analysis Plan, and the justification for making the change, will be described in the clinical study report. Additional exploratory analyses of the data will be conducted as deemed appropriate.

8. [redacted]

[redacted]

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[redacted]

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9. References

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