Medtronic

Statistical Analysis Plan

Clinical Investigation Plan Title	Therapy coil Electrogram Collection Study (TEC Study)
Clinical Investigation Plan Version	V. 2.0 27 AUG 2014
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Table of Content

Version	Summary of Changes	Author(s)/Title
1.0	• First release	Gunderson Bruce

1. List of Abbreviations and Definitions of Terms

Abbreviation	Definition
AE	Adverse Event
ICD	Implantable Cardioverter Defibrillator
CRT-D	Cardiac Resynchronization Therapy Defibrillator
EGM	Electrogram
ECG	Electrocardiogram
RV	Right Ventricle
SVC	Superior Vena Cava

2. Introduction

The Therapy coil Electrogram Collection Study (TEC Study) is a Prospective non-randomized, multicentre, post market release study.

The purpose of this study is to collect electrograms from patients at risk of a suspected insulation failure to the high voltage portion of the defibrillator lead and evaluate the electrograms for unique noise characteristics.

The study is being conducted in Slovakia at two investigation sites. The first site is the National Institute of Cardiovascular Diseases, Department of Arrhythmias and Cardiac Pacing, Bratislava, Slovakia. The second site is the Middle Slovakia Institute of Cardiovascular Disease, SUSCCH a.s, Banska Bystrica, Slovakia. These sites were chosen because they have a unique, large pool of patients with Medtronic devices connected to St. Jude Riata leads.

All patients will have been previously implanted with an ICD or CRT-D and be attending a routine follow up visit. As part of the study patients will be asked to wear a 24 hour Holter. All treatment decisions will be at the discretion of the physician in accordance with local practice.

The Clinical Investigation Plan V. 2 27 AUG 2014 has been used to develop this Statistical Analysis Plan with the purpose to describe the Final Analysis foreseen for TEC Study.

3. Study Objectives

The primary objective is to report the number of patients with a unique noise characteristic (e.g. high frequency spike) on their Far-field EGM (RV coil to SVC coil or RV coil to Can) and a high voltage lead failure within 1 month.

The secondary objectives of this study are to:

- Compare the proportion of patients with a unique noise characteristic (e.g. high frequency spike) on their Far-field EGM (RV coil to SVC coil) and a high voltage lead failure within 1 month to those patients with a high frequency spike and no lead failure within 1 month.

- Identify additional characteristics in the Far-field EGM (e.g. RV coil to SVC coil) that may help identify patients at risk of a high voltage ICD lead failure.

The clinical endpoint is an abnormal EGM noise signature, one instance of a noise spike during the 24 hour recording will be sufficient to classify the noise signature as present.

4. Investigation Plan

This is a Prospective, non-randomized, multicentre, observational study, no randomization will be used in this study. Evaluation of the EGM signals will be done centrally at Medtronic and the scientist determining the clinical endpoint (i.e. an abnormal EGM noise signature) will be blinded from the lead status during evaluation of the EGMs Additionally the physician will be blinded from the scientist's evaluation of the Holter EGM during the study.Inclusion/Exclusion criteria are listed below:

Inclusion criteria

- Subject is willing to sign and date the study Informed Consent form
- Subject is at least 18 years of age (or older, if required by local law)
- Subject is willing and able to wear a Holter monitor for up to 24-hours.
- Subject has a Medtronic ICD or CRT-D device connected to a St Jude Medical Riata or Durata lead AND

One of the following events occurs:

1) Externalized conductor with normal pacing and sensing electrical characteristics; or

2) ICD or CRT-D change out with St Jude lead and normal pacing and sensing electrical characteristics; or

3) Abnormal device diagnostic for high voltage portion of lead including

- Abrupt high voltage impedance change (more than 75% increase or more than 25% decrease from baseline)
- Non-physiologic noise on a high voltage EGM
- Less than 50% of programmed shock energy delivered

Exclusion criteria

Subjects who meet any of the following exclusion criteria are not eligible to participate in the study:

- Subject has medical conditions that would limit study participation (per physician discretion)
- Subject is enrolled in one or more concurrent studies that would confound the study results of this study as determined by Medtronic

5. Determination of Sample Size

It is estimated that a population of 300 patients with the required combination of device and lead exist in Europe. Over a two year period, we expect approximately 50 patients to fulfill the inclusion criteria and provide analyzable Holter data. In the unlikely situation that Holter data from a patient is not analyzable due to signal quality they will be replaced by another patient.

With data from these 50 patients we estimate 10 patients will have a high voltage lead failure of which 5 will have the unique high frequency spike. In the 40 patients without a high voltage lead failure we estimate 1 may also have the unique high frequency spike.

Using a Fisher's exact test, assuming a two-sided alpha of 0.05 we will be able to detect differences with power greater than 80%.

Additionally with an estimated proportion of patients with the unique noise characteristic and a high voltage lead failure of 10%, 50 patients will provide a precision of +/- 7% with a confidence interval of 90%.

6. Statistical Methods

6.1. Study Subjects

6.1.1. Disposition of Subjects

Disposition of patient will be reported following the STROBE Statement Checklist(2). Number of individuals at each stage of study (number of total assessed for eligibility, number enrolled, number analyzed) will be reported (see the flowchart example). Reason for not participation at each stage will be reported where known.

Table. Number of Subject Enrollments by Site

Site	Date of First Enrollment	Eligible patient	Subjects Enrolled (N = X)	Subjects Analyzed (N = X)
NUSCH	XXDDDYYYY	N	X (Y%)	X (Y%)
NUSCH	XXDDDYYYY	N	X (Y%)	X (Y%)

6.1.2. Clinical Investigation Plan (CIP) Deviations

Reasons for deviation are:

- Patient informed consent procedure
- Patient eligibility criteria (for both consent and/or re-verified in the PACU)
- Study data collection and reporting

The following tables will describe study deviations:

Table. Types of Study Deviations by reason

Study Deviation Type	Number of Deviations (Number,% of Subjects)		
	Subjects in .... (N = N1)	Subjects in .... (N = N2)	Total Subjects (N = N)
Reason#1 Reason#1	NE (NS, Y%) NE (NS, Y%)	NE (NS, Y%) NE (NS, Y%)	NE (NS, Y%) NE (NS, Y%) ....
Total	NE (NS, Y%)	NE (NS, Y%)	NE (NS, Y%)

Listing. Reason for exclusion

Reason for exclusion	Reason for excluding from analysis
Patid#1	Text
Patid#2	
....	
Patid#N	

6.1.3. Analysis Sets

The following patient sets will be used for the analysis:

- The Full Analysis Set (FAS) includes all patients enrolled in the study that signed Informed Consent Form (ICF), fulfilled the inclusion and exclusion criteria, patients with a good quality Holter recording (minimum 12 hours of telemetry) and a documented assessment of the lead status by the physician will be used in the analysis a 24 hour Holter. The FAS will be used to evaluate clinical endpoints.

Population set	Baseline assessment	Primary and Secondary Endpoints
FAS	√	√

6.2. General Methodology

For FAS descriptive statistics will be used to summarize patient characteristics. This will include mean and standard deviation, minimum, maximum and median with the interquartile range [IQR]

for continuous variables, and counts and percentages for categorical variables. Summary statistics will be reported with maximum 2 decimals, as appropriate.

Minitab 17 (Minitab, Inc., State College, PA, USA) will be used to perform all statistical analyses. Statistical tests will be based on a two-sided significance level of 0.05. Additional exploratory analyses will be conducted as deemed appropriate.

Statistical test will be two-sided and p-value smaller than 0.05 will be considered statistically significant unless specified otherwise. P-value will be rounded to 3 decimal places. If a p-value is less than 0.001, it will be reported as <0.001. Unless otherwise specified, in case of multiplicity no adjustments will be made. Graphical representations of the data will be also examined.

Each Holter recording will be reviewed for the presence of an abnormal signal (e.g. noise) on the far-field (e.g. RVcoil to SVC) EGM. Only one instance of abnormal noise (e.g. spike) will be needed to classify the recording as abnormal.

The lead from each patient will be adjudicated as a lead failure or intact lead by the physician using routine current practice methods of assessing an ICD lead and recorded on the study exit CRF form. The proportion of Holter recordings with abnormal noise in the lead failure group will be compared with the control group with intact leads.

Fisher's exact test will be used to compare the proportions of the 2 independent groups.

6.3. Center Pooling

This study includes two centers. Data from both centers will be pooled.

6.4. Handling of Missing, Unused, and Spurious Data and Dropouts

Since the impact of missing data is expected to be small, no multiple imputation method for missing data is planned. The missing device data will not be imputed. Outliers and influential observations will be identified via graphical plots. Once identified outliers, or influential observations the study team will be informed and according to their decision the analysis for primary endpoint will be repeated excluding the outliers

6.5. Adjustments for Multiple Comparisons

No adjustments for multiple comparisons will be performed.

6.6. Demographic and Other Baseline Characteristics

Descriptive statistics will be used to summarize demographic and baseline characteristic variables for FAS. This will include mean, standard deviation, median, minimum, and maximum for continuous variables, and counts and percentages for categorical variables.

Demographic and Baseline variables will be collected through a password protected excel file database and described with Tables, Listings and Figures as appropriate.

6.7. Treatment Characteristics

Not applicable, no treatment in this study.

6.8. Interim Analyses

Interim analyses are not planned for this study.

6.9. Evaluation of Objectives

The clinical endpoint is an abnormal EGM noise signature. Abnormal noise is defined as a deviation from the standard R-wave, T-wave, and isoelectric line of a Far Field-EGM (e.g. spike). The Far Field-EGM is susceptible to low amplitude myopotentials which would be considered normal. An example of abnormal noise is a positive noise spike during the normally flat isoelectric line of the RVcoil to SVC EGM signal. This is one example and it is unknown whether all lead failures exhibit this same signature. The noise signature will be considered present if one instance is observed during the 24 hour recording.

The study hypothesis is that 10 out of the 50 patients will have a high voltage lead failure, of which 5 of these will also have an abnormal noise, manifesting as a high frequency spike.

The secondary objectives of this study are to:

- Compare the proportion of patients with a unique noise characteristic (e.g. high frequency spike) on their Far-field EGM (RV coil to SVC coil) and a high voltage lead failure within 1 month to those patients with a high frequency spike and no lead failure within 1 month.

  Secondary a chi-square test will be used to check differences between the two proportion. The chisquare test assumes that the expected value for each cell is five or higher. However, if this assumption will be not met in our data, the Fisher's exact test will be considered.

  • Identify additional characteristics in the Far-field EGM (e.g. RV coil to SVC coil) that may help identify patients at risk of a high voltage ICD lead failure.

6.10. Safety Evaluation

Since no adverse events are collected in the study, no Safety outcomes analyses were planned in the protocol.

6.11. Health Outcomes Analyses

No health outcomes analyses were planned in the protocol.

6.12. Changes to Planned Analysis

No major modifications are required from the analyses planned in the protocol

7. Validation Requirements

To ensure the quality of the results provided for the study in the form of tables, listings and figures the following processes are used:

- Statistical analysis will be done by qualified MDT personnel following best practices.

- Statistical results will be reviewed and confirmed by a second MDT statistician or designee.

According to Medtronic SOPs the validation will be implemented for statistical outputs

8. References

1. http://www.strobe-statement.org/index.php?id=available-checklist