Statistical Analysis Plan

Clinical Investigation Plan Title	Tachy Prediction Download (TPD)
Clinical Investigation Plan Version	1.0
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1. Version History

Version	Summary of Changes	Author(s)/Title
1.0 Draft	Not Applicable, New Document	Lou Sherfesee, Sr. Principal Statistician

2. List of Abbreviations and Definitions of Terms

Abbreviation	Definition
AE	Adverse Event
EGM	Electrogram
ICD	Implantable Cardioverter/Defibrillator
MRI	Magnetic Resonance Imaging
FVT	Fast Ventricular Tachycardia
TPD	Tachy Prediction Download
VT	Ventricular Tachycardia
VF	Ventricular Fibrillation

3. Introduction

Clinical studies demonstrate that ICDs can reduce mortality in selected patient populations by treatment of ventricular tachyarrhythmia by defibrillation. However, defibrillation shock therapy is applied after the development of VF (or fast VT) and may not prevent the morbidity of syncope during the event nor the pain and potential injury of the shock itself. Significant effort has been focused on reducing the need for defibrillation with ICDs by reducing inappropriate shocks and applying anti-tachycardia pacing (ATP) to prevent a slow ventricular tachycardia from developing into FVT or VF. Although these clinical studies were successful and shock rates were reduced, the need for defibrillation still exists. One strategy to reduce the need for shock therapy further is to prevent monomorphic ventricular arrhythmias (which can develop into VF) or idiopathic VF from developing. This might be accomplished by monitoring a marker in real time to predict the imminent onset of VT/VF in the seconds to minutes before it starts and inhibiting the arrhythmia by applying an intervention. Alternatively, if the arrhythmia cannot be successfully prevented from initiating, the patient might be warned that an arrhythmia is imminent to avoid injury from syncope or to provide time for medical intervention.

Based on the literature search, it seems all previous research has been population based. Because there are large variations in the underlying mechanism and trigger for VT/VF from patient to patient, none of the studies has shown high enough accuracy of prediction to use for imminent patient or caregiver interdiction. We should, therefore, consider studying individual patients who have serial arrhythmias to identify markers specific to a patient. Using that dataset, develop an algorithm to identify which markers of impending arrhythmias are most accurate predictors in an individual patient. It may be possible to identify marker changes that have useful prognostic value in individual patients, even though they fail to accurately correlate with initiation of an event on a population level.

The enrolled subject, either with an existing Evera MRI device or to be implanted with such a device, will then have investigational TPD RAMware downloaded to the device, with the device programmed per the study protocol, so that the device can record necessary data surrounding the occurrence of a ventricular arrhythmia for later research. After being followed 12 months, the subject will exit the study.

As the only objective of the study is to collect data on ventricular arrhythmias, no statistical analyses are planned beyond summary statistics for baseline demographic data and study deviations.

4. Study Objectives

The primary objective of this study is to collect data that can be used to predict the imminent onset of ventricular arrhythmias. These data will include pre-storage device EGMs, RR intervals, PVC density, activity and other physiologic variables before these ventricular arrhythmias, and matching control data.

5. Investigation Plan

The TPD Study is a prospective, non-randomized, non-interventional, multi-site data collection clinical study to collect ICD longitudinal data that may be used to develop a VT/VF prediction algorithm. The study subjects will include patients currently implanted, or who will be implanted with a market-approved Medtronic Evera MRI® ICD. Up to 300 subjects at up to 20 sites in the US and Hong Kong may participate in this study.

Once enrolled and (if necessary) having had an Evera ICD implanted, subjects will have investigational RAMware downloaded to their Evera MRI devices. Sparse long-term pre-VT/VF onset EGM, RR interval, activity, and PVC density data exist because it is hard to collect. Ideally, Holter recordings could provide this data without altering the function of the ICD under investigation. Unfortunately, the yield of spontaneous VT/VF events on Holter recording is minuscule due to the relatively short-term monitoring provided by Holter and the scarcity of VT/VF events in most patients. The best method for collecting periodic and longer pre-onset data is to modify an ICD's RAMware to allow it to collect the desired EGM, RR interval, and other data prior to VT/VF and heart failure events. This can be done without affecting device therapy. The data will later be used to determine if there are algorithmic indications that can predict imminent VT/VF.

It is expected that study subjects will remain in the study for 12 months, then be seen in-office for follow-up and study exit. Study data will be collected from enrollment until exit via CareLink® such that study involvement will not affect the normal follow-up practice or schedule.

6. Determination of Sample Size

Since the data pertaining to ventricular arrhythmias collected during this study is for research and development, there is no need for a study hypothesis or a formal sample size determination. It is expected that up to 300 subjects with Evera MRI ICD devices will be sufficient for at least 50 to experience at least one ventricular arrhythmia. This is expected to provide necessary data to meet the objective of the study.

7. Statistical Methods

7.1. Study Subjects

7.1.1. Disposition of Subjects

A STROBE diagram will be generated to describe the subject's enrollment and pattern of follow-up and exit or death. Once the subject receives the RAMware, the only required visit is the exit visit.

7.1.2. Clinical Investigation Plan (CIP) Deviations

Potential protocol deviations or violations include not programming the device per protocol, and not performing a device interrogation at exit. All study deviations will be listed in the final report and summarized by deviation type.

7.1.3. Analysis Sets

All enrolled subjects will be summarized. Should one or more subject not receive the investigational RAMware, a separate column in each demographics table will be included for only those subjects who received the RAMware.

7.2. Handling of Missing Data and Dropouts

Baseline demographic for all enrolled subjects will be summarized. Device data obtained prior to a subject's exit or death may be summarized.

7.3. Demographic and Other Baseline Characteristics

Descriptive statistics will be used to summarize baseline demographic characteristics. Counts and percentages will be utilized for qualitative variables, while mean, standard deviation, median, interquartile range, and range will be generated for quantitative variables such as age.

7.4. Interim Analyses

There are no interim analyses planned for this study.

7.5. Evaluation of Objectives

The purpose of the study is data collection of electrical data on ventricular arrhythmias for future research and development. Therefore, the TPD study is not powered to formally test a hypothesis. Descriptive statistics will be used to summarize baseline demographics for the final report.

7.6. Safety Evaluation

Only adverse events (AEs) potentially related to TPD RAMware or TPD Software Application, as well as data on all deaths, are being collected for this study. Adverse events will be summarized by MeDRA keyterm, as well as by relatedness to the RAMware and/or Software Application. Deaths will be summarized by dealth classification, as well as listed individually.

8. Validation Requirements

Level II validation will be performed for all statistical programs generating output for the final report.

9. References

Auricchio et al. 2011 and 2015; Wollmann et al. 2014; Köbe et al. 2013; Ruwald et al. 2014). The PainFree SST trial showed 97.5% of single chamber ICD patients were free of inappropriate shocks at 1 year (Auricchio et al. 2011). The MADIT-RIT trial showed that stepwise ICD programming resulted in a low incidence of ICD therapy (8% appropriate and 5% inappropriate therapy) during 1.4 years follow-up (Ruwald et al. 2014)