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Medtronic **Statistical Analysis Plan**	
Clinical Investigation Plan Title	Management of Device detected Atrial Tachyarrhythmia and Impact of Device treatment algorithms on Atrial Fibrillation in Indian population (MANDATE AF Study)
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1. Version History

Version	Date	Summary of Changes	Author(s)/Title
1.0	27-AUG-2021	• Initial version of the document.	Fabio Di Piazza /Sr Statistician Marco Scardapane/ Statistician

2. List of Abbreviations and Definitions of Terms

Abbreviation	Definition
ADE	Adverse Device Effect
AE	Adverse Event
AF	Atrial fibrillation
AT	Atrial Tachycardia
ATP	Anti-tachycardia pacing
CAD	Coronary Artery Disease
CIED	Cardiac Implantable Electronic Device
CIP	Clinical Investigation Plan
CRHF	Cardiac Rhythm and Heart Failure
CRF	Case Report Form
CRT-D	Cardiac Resynchronization Therapy Defibrillator
CRT-P	Cardiac Resynchronization Therapy Pacemaker
CV	Cardiovascular
DBL	DataBase Lock
DD	Device Deficiency
FAS	Full Analysis Set
HF	Heart Failure
HR	Hazard Ratio
ICD	Implantable Cardiac Defibrillator
ICF	Informed Consent Form
ICH	International Conference Harmonization
IPG	Implantable Pulse Generator
IQR	Inter-Quartile Range
ITT	Intention To Treat
LA	Left Atrial
PP	Per Protocol
SADE	Serious Adverse Device Effect
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SPR	Statistical Programming Requirements
TIA	Transient Ischemic Attack
USADE	Unanticipated Serious Adverse Device Effect
VHD	Valvular Heart Disease

3. Introduction

Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia. The prevalence of AF increases with age and, in the elderly population, cardiovascular (CV) risk factors and co-morbidities such as hypertension, diabetes, congestive heart failure, coronary artery disease, valvular heart disease (VHD), and stroke are common. It has also been shown that the prevalence and cost of AF is related to economic growth and an ageing population.

Data from a national atrial fibrillation registry (IHRS-AF) show that Indian AF patients are more than a decade younger than AF patients in the western world. This fact seems to be due to the higher prevalence of hypertension, diabetes, and coronary artery disease (CAD) in the young in India. Also, a subanalysis of the global RealiseAF survey confirms that hypertension is the most common underlying CV condition, followed by ventricular heart disease (VHD), CAD, diabetes, and dyslipidemia. Both the registries report a higher prevalence of persistent/permanent AF, compared to paroxysmal AF, unlike the western AF population.

Anti-tachycardia pacing (ATP) is a therapy delivering series of pacing stimuli that, if delivered at a specific rate, succeed in terminating tachycardias by interrupting the re-entry circuit.

ReactiveATP algorithm allows the device to restart delivering all the ATP therapies, after the entire therapies sequence has unsuccessfully ended, in case of change in arrhythmia rhythm and/or after a programmable time period.

The clinical benefit of Reactive ATP, in terms of reduced incidence of persistent and permanent AF, has been demonstrated in the International, randomized, controlled MINERVA trial. In particular a secondary analysis of that trial showed that ReactiveATP is more effective in case of slow and regular atrial arrhythmias, a condition that can be observed at the onset of the episode or over time.

The evidence of ATP programming is very limited and additional evaluations additional evaluations are required to understand which ATP programming in terms of efficacy is the best in interrupting the arrhythmia and improving battery longevity.

The MANDATE AF Study purpose is to show that a reduced ATP sequence programming is non-inferior to Minerva study ATP programming with respect to time to persistent AF among Indian patients with a Cardiovascular Implantable Electronic Device (CIED).

This Statistical Analysis Plan (SAP) describes methods used to assess the primary and secondary endpoints of this study. The SAP should be read in conjunction with the study protocol and electronic case report forms (eCRF). This version of the plan was developed based on CIP version 1.0 of the 26th February 2019. The SAP has been prepared in agreement with Medtronic internal

procedures and using the CONSORT Statement and International Conference Harmonization (ICH) guidelines E3, E6 and E9 as guidelines.

Due to COVID-19 pandemics that severely impacted the study enrollment, changes in CRHF product portfolio, very minimal Reactive ATP enabled devices available, and change in the local evidence strategy, the operating unit has decided to terminate the study earlier. The Database lock (DBL) is scheduled to occur on September 1st, 2021.

4. Study Objectives and Endpoints

4.1 Objectives

4.1.1 Primary Objective

The primary objective of this study is to show that a reduced ATP sequence programming is non-inferior to Minerva study ATP programming with respect to time to persistent AF among Indian patients with a CIED.

4.1.2 Secondary Objectives

The secondary objectives of the study are:

- to compare the two atrial ATP Programming arms in terms of clinical endpoints reported below, section 4.2.2;
- to evaluate the incidence of persistent AF in patients with sick sinus syndrome compared to the one found in the Minerva trial, and characterize the difference between the European and Indian populations;
- to evaluate the efficacy of atrial ATP therapies as a function of the device type (IPG, ICD, CRT-D, CRT-P), and population characteristics (baseline characteristics, implant indications);
- to describe the incidence of all collected endpoints in the study population.

4.2 Endpoints

4.2.1 Primary Endpoint

Time to persistent AF, defined as more than 7 consecutive days of AF, retrieved by using the device AT/AF diagnostics, or time to permanent AF. Time 0 for the time to event calculation is defined as the randomization date or the first day in sinus rhythm after enrollment.

4.2.2 Secondary Endpoints

1. To compare the two atrial ATP Programming arms in terms of clinical endpoints reported below:
   - all-cause death (at the end of 24 months), measured as time to event;
   - cardiovascular hospitalization (HF, AF or other), measured as time to first event and annual rate;
   - Annual rate for all-cause hospitalization;

- AT/AF burden metrics, measured in terms of time to first event (daily burden ≥1 day, ≥2 days, ≥30 days) or the ratio between time in AT/AF and the observation period;
- number of successful and unsuccessful treated AT/AF episodes out of detected episodes;
- number of delivered therapies per episode;
- number of ATP sequences;
- stroke, TIA or other thromboembolic events;
- LA diameter (where available);
- percentage of patients treated by anticoagulation therapy according management guideline;
- electrical or pharmacological cardioversions , measured as time to first event and annual rate;
- biventricular pacing percentage (in CRT-P /CRT-D patients).

2. Composite endpoint made of death, cardiovascular hospitalizations, stroke, TIA or other thromboembolic events;
3. To evaluate the incidence of persistent AF in patients with sick sinus syndrome compared to the one found in the Minerva trial, and characterize the difference between the European and Indian populations;
4. To evaluate the efficacy of atrial ATP therapies as a function of the device type (IPG, ICD, CRT-D, CRT-P), and population characteristics (baseline characteristics, implant indications).

5. Investigation Plan

MANDATE AF is a prospective, multi-center, randomized, single-blind study.

The study analyses patients implanted with a Medtronic cardiac implantable device with an atrial lead and equipped with atrial ATP therapies. The patients should have been implanted for no more than 18 months prior to enrollment.

The patients are randomized into two groups:

- a control arm including patients with the same atrial ATP therapies programming setting adopted in the Minerva trial;
- an interventional arm including patients with a conservative atrial ATP therapies programming setting that is intended to reduce number of ATP sequences by 50% compared with the control arm.

Study required adverse events will be collected prospectively for at least 24 months after enrollment. Physicians will be recommended to schedule in clinic follow-up visits every 6 months and remote follow-up visits every 3 months in between.

Every patient will be followed for at least 24 months, until the last patient enrolled exits the study.

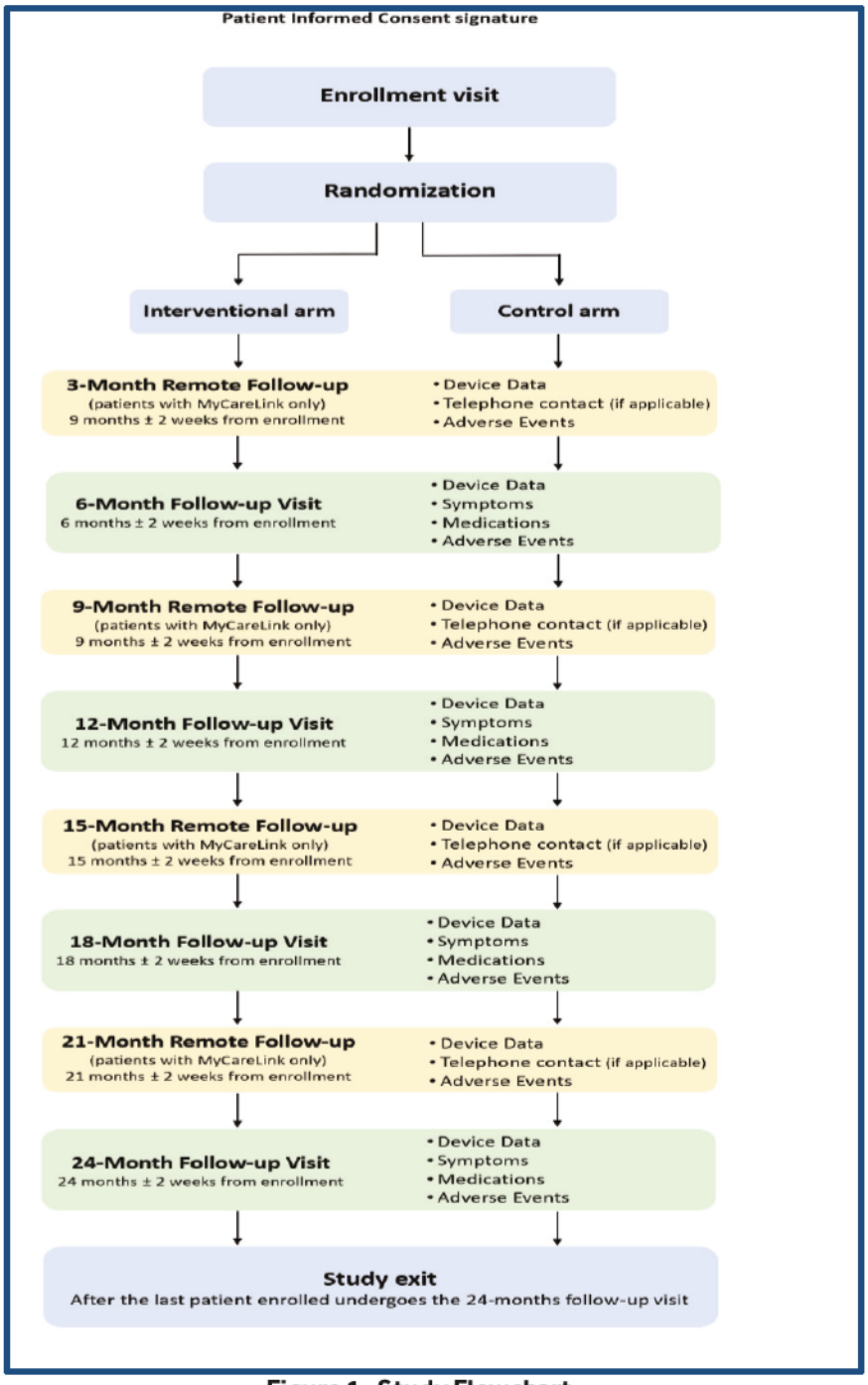

Figure 1- Study Flowchart

However, the study was terminated earlier in August 2021 due to problems in enrollment, changes in product portfolio, very minimal Reactive ATP enabled devices available, and change in the local evidence strategy with a sample size of approximately 75 patients (10% of estimated sample size) and with a final follow-up visit for ongoing subjects scheduled between June and July 2021.

6. Determination of Sample Size

The original study design aimed to recruit 758 (379 per arm) patients. The power calculations assumed a noninferiority margin of 7.5%. The survival was planned to be assessed at 24 month and the assumed survival probabilities were 85% for control arm and 77.5% or more for the experimental arm. The study had following assumptions:

- The accrual time is expected to be approximately 18 months for both arms.
- The total study exposure is expected to be at maximum 42 months for both arms.
- The follow-up time 24 months.
- Proportion of subjects lost to follow-up in the control and experimental groups 15%
- The sample size should be enough to produce an 80% chance (power) of a significant result at a one-sided 0.025 significance level.
- The non-inferiority margin that characterizes the largest absolute difference considered to be dismissible at 24 months is defined as 7.5%.
- History of AF is a stratification factor.

The calculations were performed by statistician using SAS software version 9.4 (SAS Institute Inc., Cary, NC, USA).

The study was terminated prematurely when 79 patients were screened and 75 (37 and 38 in the interventional and in the control arm, respectively) enrolled fulfilling the inclusion/exclusion criteria.

7. Statistical Methods

7.1 Study Subjects

7.1.1 Disposition of Subjects

The number of patients assessed for eligibility, enrolled, randomized, number of patients with follow-up visits completed and the number of patients with device data interrogation available will be summarized by table and by flow-chart.

The reason for study exit will be presented in table.

7.1.2 Clinical Investigation Plan (CIP) Deviations

Protocol deviations should be reviewed prior to study reporting by the study team. The counts and percentages protocol deviations will be presented in descriptive tables, overall and by follow-up visit.

7.1.3 Analysis Sets

The following analysis sets were defined in the CIP:

- The Per Protocol Analysis Set (PP) includes all patients actively enrolled in the study, who signed Informed Consent Form (ICF), fulfilled the inclusion/exclusion criteria and that have one day in Sinus Rhythm at the time of enrollment or after the enrollment.
- The Intention-to-Treat Set (ITT) includes all patients actively enrolled in the study, who signed ICF, and fulfilled the inclusion/exclusion criteria.

Since the study was terminated early with low number of patients enrolled, no significant differences in terms of sample size between the PP and ITT population sets are expected. Moreover, the device data interrogation compliance, due to the COVID-19 pandemic, was far from what expected in the investigation plan. For these reasons the Full Analysis Set (FAS) including all patients randomized into the study and fulfilling the inclusion/exclusion criteria will be used throughout the analysis.

The primary endpoint and the secondary endpoints will be analyzed in the FAS population with descriptive statistics without testing formal hypotheses. For the same reason no analyses on subsets of the FAS as outlined in the study protocol will be performed. In addition, individual subject listings could be generated, if needed.

The randomization arm will be used throughout the analysis.

Information about, patients assigned to the different treatment arm then the arm to which the patient was randomized (i.e. wrong device programming in terms rATP feature), will be reported in the protocol deviation table or listing if needed.

7.2 General Methodology

7.2.1 Statistical Methodology

All summary statistics will be presented by the actual randomization arm. FAS will be the main analysis set used for the analysis.

Descriptive statistics will be used to summarize patient demographics and baseline characteristics, medical history, procedure data, and other relevant study data. Mean and standard deviation, minimum, maximum, and median with the interquartile range (IQR) will be used for continuous

variables. Counts and percentages will be presented for categorical variables. Summary statistics will be reported with the same number of decimal places as original data collected.

Since the study was terminated early, also the primary and secondary endpoints will be analyzed with descriptive statistics without testing formal hypotheses.

For time-to-event analysis, if the number of observed events will be adequate, the Kaplan-Meier plots will be plotted by arm but only with a descriptive purpose. The survival probabilities at each follow-up visit will be calculated using Kaplan-Meier estimator together with 95% confidence intervals (using complementary log-log method) and will be presented in a table by arm for descriptive purpose.

Statistical analysis will be conducted in SAS version 9.4 or above (SAS Institute, Cary, NC).

Any deviations from the SAP will be described and justified in the Clinical Study Report

7.2.2 Derived Variables

Variables to evaluate the primary endpoint, as well as daily AF burden metrics, number of successful and unsuccessful treated AT/AF episodes out of detected episodes, number of delivered therapies per episode, and number of ATP sequences will be derived from the device datasets and will be described in detail in the SPR (ref).

The exposure time (months) for the time to first persistent AF will be computed from the date of randomization to the date of the last device save to disc for patients without persistent AF recurrence or to the date of first recurrence of persistent AF recurrence otherwise [(data end – data in)/30.4].

Variables to evaluate secondary endpoints as all-cause death, cardiovascular hospitalization (HF, AF or other), stroke, TIA or other thromboembolic events and annual rate for all-cause hospitalization will be derived from the adverse event dataset and will be described in detail in the SPR (ref).

The exposure time (months) for the secondary endpoints will be computed from the date of randomization to the date of the notice (follow-up visit or adverse event) for patients without events or to the date of the specific event otherwise [(data end – data in)/30.4].

7.3 Center Pooling

Since the study was terminated early, no assessment of poolability of data across centers will be performed.

7.4 Handling of Missing, Unused, and Spurious Data and Dropouts

Since the impact of missing data is expected to be small, and only descriptive statistics will be applied no multiple imputation method for missing data is planned. For subjects who are lost to follow-up, the time to event will be censored at the last available contact date.

7.5 Adjustments for Multiple Comparisons

No adjustments for multiple comparisons or multiple looks at data will be performed.

7.6 Demographic and Other Baseline Characteristics

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

Demographic and baseline variables will be collected through: Demographic information, medical history, and baseline ECG and ECHO. Medication started prior to the date of randomization will also be summarized.

7.7 Treatment Characteristics

Concomitant medications will be summarized descriptively by arm using counts and percentages.

Medications will be reported by time of occurrence (prior to the study enrollment of initiated during the study execution).

Reason for system modifications will also be presented by listing.

7.8 Interim Analyses

No interim analyses are planned for this study.

7.9 Evaluation of Objectives

Endpoints defined in the section 4.2 will be used to evaluate objectives.

A device data quality analysis will be performed before the derivation of the analysis variables. Endpoints based on device data could be biased by the not compliance of the device data interrogation process compared to the clinical investigation plan.

7.9.1 Primary Endpoint

The time to persistent AF, defined as more than 7 consecutive days of AF, retrieved by using the device AT/AF diagnostics, or time to permanent AF. Time 0 for the time to event calculation is defined as the enrollment date or the first day in sinus rhythm after enrollment. Kaplan-Meier plots will be presented for the time to persistent AF together with table with survival probabilities and 95% confidence intervals estimated using complementary log-log method, for each randomization arm, if the number of followed-up patients and observed events will be adequate. Descriptive

statistics will be presented for time to persistent AF. No formal hypothesis testing nor Hazard Ratio (HR) calculation is planned in this analysis.

7.9.2 Secondary Endpoints

The time-to-event outcomes defined in section 4.1.2 will be summarized using Kaplan-Meier plots, tables with survival probabilities and 95% confidence intervals estimated using complementary log-log method, for each randomization group, if the number of followed-up patients and observed events will be adequate. Descriptive statistics will also be presented for the time-to-event outcomes. No formal hypothesis testing nor HR calculation is planned. Details about all time-to-event variables will be listed.

Counts and percentages will be used for categorical variables, for each randomization arm. Continuous variables will be summarized by descriptive statistics as described in the section 7.2.1.

Annual rates will be calculated for appropriate endpoints together with their 95% confidence interval (95%CI), for each randomization group , if the number of followed-up patients and observed events will be adequate.

Since the study was terminated early with small number of patients enrolled (less than 10% of expected sample size), the evaluation of persistent AF in patients with sick sinus syndrome compared to the one found in the Minerva trial, and the characterization the difference between the European and Indian populations, and the evaluation of the efficacy of atrial ATP therapies as a function of the device type (IPG, ICD, CRT-D, CRT-P), and population characteristics (baseline characteristics, implant indications) would not be robust: thus, the analyses will not be performed.

7.10 Safety Evaluation

Adverse events (AEs), adverse device effects (ADEs) and device deficiencies (DDs)will be presented using the MedDRA coding and presented by tables and listings. The Adverse events will be presented using system organ class and/or preferred term. Counts and percentages will be used to summarize adverse events and device deficiencies. Tables will be repeated for serious adverse events (SAEs), serious adverse device effects (SADEs), unanticipated serious adverse device effects (USADEs) if applicable. Cardiovascular related AEs will be presented in a separate table.

Apart from that, time, severity, relation to procedure, action taken, and outcome will be presented descriptively in a separate table.

Deaths and reasons for death will be summarized descriptively using counts and percentages.

Detailed listings will be prepared for adverse events, deaths, and device deficiencies, if needed.

7.11 Health Outcomes Analyses

No specific health outcomes analyses are planned for this study.

7.12 Changes to Planned Analysis

The original analysis described in CIP assumed that the study would recruit 758 patients and formal hypotheses would be tested. Due to early termination of the study, the formal hypothesis testing will not be conducted in the analysis and only descriptive statistics and figures will be presented. A final decision on the study endpoints evaluation will be taken only when the complete set of clinical and device data will be collected and evaluate in terms of quality and reliability.

8. Validation Requirements

All collected data will be reviewed for completeness, correctness, and consistency. In case of issues, queries will be sent to the investigator to complete, correct or comment on the data. To ensure the quality of the results provided for the study in the form of tables, listings and figures, and the derived datasets the following processes are used:

- Statistical programming and analysis will be done by qualified programmer(s) and statistician(s) following applicable procedures and best practices;
- The derived datasets will be validated by a second programmer or statistician;
- The tables will be validated by a second programmer or statistician;
- Statistical results will be reviewed and confirmed by a second statistician.

The entire set of tables, listings, and figures (TLF) will be 100% checked for accuracy, completeness, and consistency prior to inclusion in the final clinical study report. According to Medtronic SOPs the level II validation (the peer reviewer reviews the code; where appropriate, performs manual calculations or simple programming checks to verify the output) will be implemented for both Datasets and TLFs.

9. Statistical Appendices

9.1 Tables, Listings and Figures

Detailed list and mock TLF shells used for this study can be found in SPR Mandate AF document v 1.0 27-AUG-2021 or later version.

Summary of Changes

Version	Effective Date	Summary of Changes	Change Author
1.0	27-AUG-2021	Initial Release	Fabio Di Piazza, Marco Scardapane