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Management of Device detected Atrial Tachyarrhythmia and Impact of Device treatment algorithms on Atrial Fibrillation in Indian population

"MANDATE AF study"

Medtronic **Clinical Investigation Plan**	
Clinical Investigation Plan/Study Title	Management of Device detected Atrial Tachyarrhythmia and Impact of Device treatment algorithms on Atrial Fibrillation in Indian population. (MANDATE AF STUDY)
Clinical Investigation Plan Identifier	MDT18039
Study Product Name	All rATP enabled Medtronic ICD's, Pacemakers and CRT-P/D devices
Sponsor/Local Sponsor	India Medtronic Pvt Ltd 1241, Solitaire Corporate Park Building Number 12, 4th Floor Andheri-Ghatkopar Link Road Andheri (East), Mumbai – 400093 Maharashtra, India Phone: (+91) 22 48810700 /1/2/3
Document Version	1.0, dated 26 Feb 2019
Lead Principal Investigator(s)	Not Applicable
Coordinating Investigator	Not Applicable
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1. Investigator Statement

Study product Name	All rATP enabled Medtronic ICD's, Pacemakers and CRT-P/D devices
Sponsor	India Medtronic Pvt Ltd
Clinical Investigation Plan Identifier	MDT18039
Version Number/Date	1.0, dated 26 Feb 2019
I have read the protocol, including all appendices, and I agree that it contains all necessary details for me and my staff to conduct this study as described. I will conduct this study as outlined herein and will make a reasonable effort to complete the study within the time designated. I agree to comply with the International Conference on Harmonization Guidelines on Good Clinical Practice, Declaration of Helsinki and the Indian GCP regulatory guidelines under which the study is being conducted e. I agree to ensure that the confidential information contained in this document will not be used for any purpose other than the evaluation and conduct of the clinical investigation without the prior written consent of Medtronic. I will provide all study personnel under my supervision copies of the protocol and access to all information provided by Medtronic. I will discuss this material with them to ensure that they are fully informed about the products and the study.	
Investigator's Signature:	
Investigator's Name:	
Institution:	
Date:	

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2. Glossary

Term	Definition
AE	Adverse Event
AF	Atrial Fibrillation
AT	Atrial Tachycardia
ATP	Antitachycardia Pacing
BMI	Body Mass Index
CAD	Coronary Artery Disease
CIED	Cardiac Implantable Electronic Device
CRT-P	Cardiac Resynchronization Therapy Pacemaker
CRT-D	Cardiac Resynchronization Therapy Defibrillator
CV	Cardiovascular
ECG	Electrocardiogram
ECHO	Echocardiogram
ICD	Implantable Cardiac Defibrillator
IPG	Implantable Pulse Generator
LAD	Left Atrial Diameter
NYHA	New York Heart Association
rATP	Reactive ATP therapy
RHD	Rheumatic Heart Disease
SCAF	Sub-clinical AF
TIA	Transient Ischemic Attack

Term	Definition
VHD	Ventricular Heart Disease
VKA	Vitamin K Antagonist

3. Synopsis

Title	Management of Device detected Atrial Tachyarrhythmia and Impact of Device treatment algorithms on Atrial Fibrillation in Indian population - "MANDATE AF study"
Clinical Study Type	Prospective, multi-center, randomized, single blind study
Product Name	Medtronic implantable cardiac devices such as: • dual chamber implantable pulse generators (IPG) • dual chamber implantable cardiac defibrillator devices (ICD) • cardiac resynchronization therapy pacemaker (CRT-P) • cardiac resynchronization therapy defibrillator (CRT-D) equipped with an atrial lead, atrial arrhythmias (AT/AF) diagnostic features and atrial Anti Tachy Pacing (ATP) therapies (rATP enabled). The below listed devices are rATP enabled and can be used on the study (but not limited to):
Sponsor	India Medtronic Pvt Ltd

Device Name	Device Type
Advisa DR, Astra DR	**PM**
Evera DR	**ICD**
Solara, Serena, Viva CRTP	**CRT-P**
Viva CRTD, Amplia	**CRT-D**

Local Sponsor	India Medtronic Pvt Ltd 1241, Solitaire Corporate Park Building Number 12, 4th Floor Andheri-Ghatkopar Link Road Andheri (East), Mumbai – 400093 Maharashtra, India Phone: (+91) 22 48810700 /1/2/3
Indication under investigation	The devices will be used within approved intended use per country/region.
Investigation Purpose	The MANDATE AF Study is a prospective randomized study aiming to show that a reduced Atrial anti-tachycardia pacing sequence programming, is as effective as Minerva trial programming.
Product Status	All the products used in the study are commercially available in India and will be used inside the intended use.
Primary Objective(s)	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 Cardiac Implantable Electronic Device (CIED).
Secondary Objective(s)	The secondary objectives of the study are: 1. To compare the two atrial ATP Programming arms in terms of clinical endpoints reported below: • all-cause death; • 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); average daily burden;

	• number of successful and unsuccessful treated AT/AF episodes out of detected episodes; • number of delivered therapies per episode, measured in terms of annual rate.; • 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 in terms of time to first event and annual rate; • biventricular pacing percentage (in CRT-P /CRT-D patients); 2. To evaluate the composite endpoint which includes 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).
Study Design	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 will be 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.

	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. The secondary objective is: 1) to compare the two atrial ATP Programming arms in terms of main clinical endpoints; 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; 3) 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); 4) to describe the incidence of all collected endpoints in the study population
Randomization	Patients will be randomized 1:1 to either interventional or control arm. The sequence of treatments will be randomly permuted in blocks of 2 or 4 patients per block. The blocked randomization will be centralized, and schedules will be created by the study statistician using statistical software. The randomization will be performed by the center via the EDC system (Oracle Clinical). To minimize the selection bias, the randomization procedure for this study will use the site (XX sites other important factors), as stratification factors, so that there will be a separate permuted block randomization list for each site. This guarantees treatment balance within sites.
Sample Size	The total number of patients enrolled in this study will be 758, 379 in the interventional arm, and 379 in the control arm. These numbers have been estimated considering the following hypotheses: • a 15% of incidence of the primary endpoint at 24 months among the control group; • Non-inferiority margin of 7.5% • 15% withdrawals;
Inclusion/Exclusion Criteria	Inclusion criteria

	1. Subject is implanted with a Medtronic cardiac implantable device with an atrial lead equipped with atrial ATP therapies (rATP) enabled no longer than 18 months and at the minimum 6 weeks has passed since the implant; 2. Age ≥ 55 years; 3. Subject provides informed consent; 4. Subject is willing and able to comply with the study procedures; 5. Subject has documented history of atrial fibrillation or atrial flutter, or one or more of the risk factors for developing AF as per AHA/HRS guidelines. [26]. ○ Age > 60 years; ○ Stroke/TIA; ○ Diabetes; ○ High Blood Pressure; ○ Coronary artery disease; ○ Cardiomyopathy; ○ Pericardial inflammation; ○ Prior heart attacks; ○ Congestive heart failure; ○ Structural heart disease (valve problems or congenital defects); ○ Prior open-heart surgery; ○ Untreated atrial flutter (another type of abnormal heart rhythm); ○ Thyroid disease; ○ Chronic lung disease; ○ Sleep apnea; ○ Excessive alcohol use; ○ Serious illness or infection. Exclusion criteria: Patients are not eligible to be enrolled in the study if any of the following criteria is met: 1. Subject has been implanted with a Medtronic cardiac implantable device with an atrial lead equipped with atrial ATP therapies (rATP) enabled for more than 18 months; 2. Subject is in permanent AF or persistent AF at the baseline visit: a. The definition of permanent AF will be based on the physicians' decision that nothing further can be done to cardiovert the patient or, in historical cases, we will refer to the Cardiac Compass reports: b. The definition of persistent AF at baseline will refer to the Cardiac Compass reports (>7 consecutive days in AF with the last day being the day of enrollment) 3. Participation in other studies which could potentially conflict with this study;

	4. Legal incapacity or evidence that a subject cannot understand the purpose and risks of the study or inability to comply fully with study procedures and follow up.
Study Procedures and Assessments	Patients newly implanted with a CIED or implanted within 18 months (index to enrollment date) with an atrial lead equipped with atrial ATP therapies can be considered for enrollment in the study. If all the inclusion/exclusion criteria have been and fulfilled, and the patient and the investigator have signed and dated the patient informed consent (PIC), the patient will be enrolled in the study. During the enrollment visit, which will be performed at least 6 weeks after implant or after leads stabilization (based on physician's discretion), baseline and implant data will be collected. Clinical data will be collected at the following time points: 1. At baseline visit; 2. At the follow up visits which should be performed, as per recommendation, in clinic /person at least every 6 months, and if on remote monitoring available then every 3 months in between. 3. at study closure visit (last patient last visit) , will be performed after the last enrolled patient completes 24 months on the study. The first patient enrolled will continue their follow up visits (per above follow-up schedule) till the last patient completes 24 months on the study.
Safety Assessments	The safety and clinical performance of the Medtronic market-released IPG, ICD, CRT-D and CRT-P systems have been demonstrated through previous pre-clinical testing and previous clinical studies. All products used in this study were market-released and none were experimental devices. Investigators are required to report all cardiovascular related AE, device related AE and all SAE regardless of relationship. Device deficiency will also be collected throughout the study.
Statistics	Sample size was calculated for two-sample comparison of survivor function using the log-rank test with the intent to prove that the conservative atrial ATP programming setting is not less effective than the standard programming in term of occurrence of persistent AT/AF. Based on the model assumptions and parameters, 758 (379 per group) patients are needed. Time to event analysis will be performed by means of the Kaplan Meier method. Difference in time-depending event between population subgroups will be evaluated using a Cox proportional hazard regression model.

4. Introduction

4.1. Background

4.1.1. Prevalence of Atrial fibrillation

Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia with a prevalence of 1–2% in the general population [1,2]. 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 [3–6].

The global prevalence and cost of AF are expected to surge owing to factors such as economic growth, an ageing population, and increased prevalence of risk factors for AF in both Western countries and rapidly developing countries such as Brazil, China, India, and Indonesia [7-10].

By 2050, the number of people with AF is projected to be 15 million in the United States [1,7], and a similar trend is projected for the European population too [8]. For India, the United Nations Populations Fund has projected a 326% increase in the number of people aged between 60 and 80 years by the year 2050 (from the year 2000). A 700% increase is projected in the number of people above the age of 80 years [11].

Though large-scale population-based studies on the prevalence of AF are not available in India, the recently published PANARM HF trial showed an AF incidence of 15% across a population of 2205 patients symptomatic for cardiac arrhythmias or HF, who were indicated for implantable device/radiofrequency ablation [12].

4.1.2. Characteristics of Indian AF patients

Data from a national atrial fibrillation registry (IHRS-AF) [13] show that Indian AF patients are more than a decade younger than AF patients in the western world [14]. 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 sub-analysis of the global RealiseAF survey confirms that hypertension is the most common underlying cardiovascular (CV) condition, followed by ventricular heart disease (VHD), CAD, diabetes and dyslipidemia [15].

Both the registries report a higher prevalence of persistent/permanent AF, compared to paroxysmal AF, unlike the western AF population. This seems to be related to the higher prevalence of rheumatic heart disease (RHD) among Indian AF population [13].

4.1.3. AF management in India

No relevant difference in AF management strategy arises between Indian and global population, even if there is a lack of availability of Class I C agents in India resulting in an excessive use of amiodarone either in the rate-control or in rhythm control strategy, despite guidelines recommendations [13-15].

Moreover, even if high-risk patients should be given vitamin K antagonist (VKA) and antiplatelets should be taken by low-risk ones, in the RealiseAF registry only 38% of high-risk patients received VKA, while 58% did not receive any anticoagulants [15].

Moreover, in the IHRS-AF registry, the overall use of anticoagulants was 70%, and this value increased to 83% if considering only RHD patients. Vast majority of the non-RHD patients had a high CHADS2 score (2 or more in 68.5%). There was a tendency to under anti-coagulate, as the average INR (International Normalized Ratio) of the entire cohort was 1.8 [13].

4.1.4. HF hospitalizations and death

A new publication from the ASSERT trial focuses on the progression of device-detected AF, also called 'sub-clinical AF' (SCAF), and the associated risk of heart failure hospitalization. Older age, greater body mass index (BMI), and longer initial SCAF duration have been identified as factors predicting SCAF progression, which is associated with a 5-fold increase in the risk of HF hospitalization [16]. Among patients with SCAF progression, the annual rate of HF hospitalization reported is 8.9% vs 2.5% for those without progression. The authors raise the question of whether strategies to reduce the progression of AF might be able to also reduce HF hospitalizations and potentially decrease mortality.

The IHRS-AF registry reports an annual mortality due to AF of 6.5%, which is like the one noted in the European AF registry [17], even if the European population analyzed is almost two decades older than the IHRS-AF registry one. The higher mortality among Indian population seems to be predominantly due to HF, myocardial infarction, sudden death and stroke. HF, together with rapid ventricular rate, has been detected as the main cause of annual hospitalization too [17].

4.1.5. Predictors of ATP efficacy

Atrial high-rate episodes detected by implanted devices are associated with a 2-fold increase in the risk of death and stroke [18], and, as said before, SCAF progression is associated with a 5-fold increase in the risk of HF hospitalization [16]. So, early termination of these kind of episodes is crucial in order to improve the clinical outcomes of AF patients.

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.

In a cohort of 316 consecutive patients implanted with a pacemaker equipped with atrial ATP (DDDRP) and included in a multicenter Italian registry, longer arrhythmia cycle lengths, shorter ATP delivery delay and NYHA Class I have been showed to be the main predictors of ATP efficacy [19].

Moreover, as atrial arrhythmias may occur with different morphologic characteristics and rates (atrial tachycardia, fibrillation or flutter) 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. [20] 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. [21] Indeed, the authors observed that long atrial tachyarrhythmia episodes undergo many rhythm transitions becoming amenable to ATP termination and that high efficacy Reactive ATP therapies are associated with a reduction in the risk of permanent or persistent AF [21] which are significantly associated with a higher risk of stroke or systemic embolism and death compared to paroxysmal AF [22-24].

Finally, a sub-analysis of the MINERVA trial, which analyses patients with paroxysmal or persistent AF, shows that ATP therapies are associated with a significantly reduction of AF early recurrence, compared with patients without ATP. [25] Furthermore, the percentage of early recurrence among ATP patients is significantly lower (20%) after episodes successfully terminated by ATP than episodes in which ATP therapies are not successful (39%) [25]. In addition, a more frequent reduction in left atrial diameter (LAD) has been noticed among ATP population. All these data suggest that ATP may reverse electrical and mechanical atrial remodeling, reducing the AF episodes recurrence.

Nowadays, small evidences on ATP programming optimization have been reported in literature.

The results from the PITAGORA trial showed that the ATP efficacy in interrupting atrial tachyarrhythmias is function of arrhythmia cycle length, type of ATP therapy delivered, and number of sequences delivered [26]. If considering the relationship between ATP therapy and arrhythmia cycle length, Ramp therapy showed a significant increase in ATP efficacy as per arrhythmias cycle length increase, while a flat relation for Burst+ therapy was found. In general, Ramp therapy was associated with a higher termination efficacy than Burst+ therapy in AT episodes with cycle length>240 ms. Furthermore, a higher efficacy of Ramp therapy was evident within the first six sequences, whereas subsequent ATP attempts showed comparable performances for both therapies. So, additional evaluations are required to understand which ATP programming in terms of efficacy is the best in interrupting the arrhythmia and improving battery longevity.

4.2. Purpose

The overall 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 CIED.

5. Objectives and/or Endpoints

5.1. Objectives

5.1.1. Primary Objective(s)

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.

5.1.2. 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 5.2.
- 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

5.2. Endpoints

The primary endpoint of the study is:

- 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 The secondary endpoints include:

- 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);
- 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 in terms of 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).

6. Study Design

This multi-center randomized 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.

Patients will be randomized into two groups:

1) an interventional arm including patients with a conservative atrial ATP therapies programming setting;
2) a control arm including patients with the same atrial ATP therapies programming setting adopted in the Minerva Trial.

At the time of randomization, if atrial ATP therapies are already enabled, the setting will be changed as per the assigned arm. The overall enrollment period will be 18 months from the first patient enrolled, and every patient will be followed for at least 24 months until the last enrolled patient exits the study. So, the total duration of the study will be maximum 42 months.

Physicians will be recommended to schedule in-person follow up visits with every patient every 6 months, and remote follow ups every 3 months if remote monitoring is available

A total of up to 758 patients will be enrolled on the study from up to 15 centers with 379 in the intervention arm and 379 in the control arm.

6.1. Duration

The study will be conducted for an estimated 42 months from enrollment of the first patient until the study has been formally terminated. The planned duration of enrollment is about 18 months.

The minimum expected time a patient will be on the MANDATE AF study is at least 24 months, consisting of the baseline visit, and follow-ups at 6 months (± 2 weeks), 12 months (± 2 weeks), 18 months (± 2 weeks) and 24 months (± 2 weeks) after the enrollment. The maximum time a patient may be part of the study is a up to 42 months depending on the enrollment time frame.

The expected time of participation for a clinical center is approximately 36 months.

6.2. Rationale

MINERVA trial showed the efficacy of atrial ATP therapies and ReactiveATP algorithm (rATP) in reducing the incidence of persistent AF. The MANDATE AF Study is designed as a multi-center prospective randomized trial to show that a reduced ATP sequence programming, designed to improve device battery longevity, is non-inferior to Minerva study ATP programming with respect to time to persistent AF.

7. Product Description

7.1. General

The study analyses patients implanted with a Medtronic cardiac implantable device with an atrial lead and equipped with AT/AF diagnostics and ATP therapies (rATP enabled).
The AT/AF diagnostics allow the device to detect atrial arrhythmias by considering:

- the mean A-A interval which should be < the AT/AF detection interval;
- the presence of more P waves during a V-V interval.

The below listed devices are rATP enabled and can be used on the study (but not limited to):

Device Name	Device Type
Advisa DR, Astra DR	**PM**
Evera DR	**ICD**
Solara, Serena, **Viva CRTP**	**CRT-P**
Viva CRTD, Amplia	**CRT-D**

Atrial arrhythmia detection can be programmed to one-zone (AT/AF) or two-zones (AT/AF and Fast AT/AF), depending upon if the device is setup to monitor for atrial tachyarrhythmias (MONITOR) or to detect and treat them with ATP therapy (ON) (Figure 1).

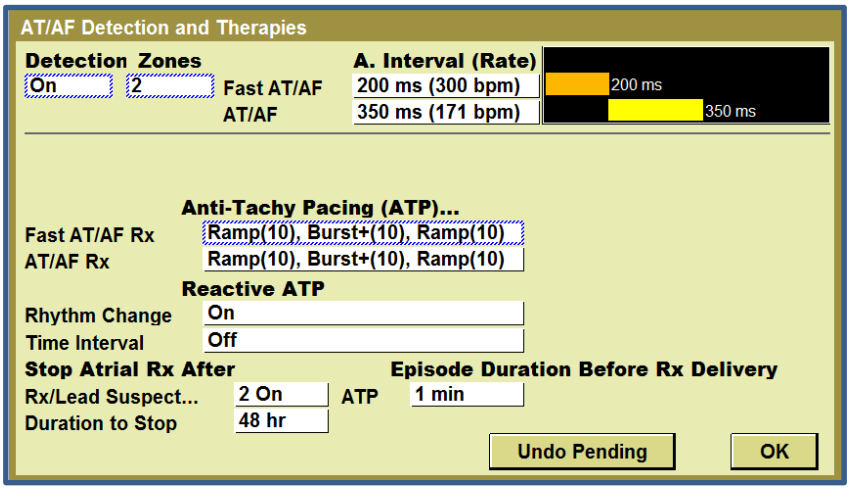

Figure 1- Atrial arrhythmias detection zones programming

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. There are three types of atrial ATP (Figure 2):

- Burst+: A programmable number of AOO stimuli are delivered as a "burst" train followed by two premature pulses;
- Ramp: A programmable number of AOO stimuli are delivered in a programmable number of sequences;
- 50 HZ: A manual in-office therapy delivering a burst of AOO stimuli delivered at 20 ms intervals.

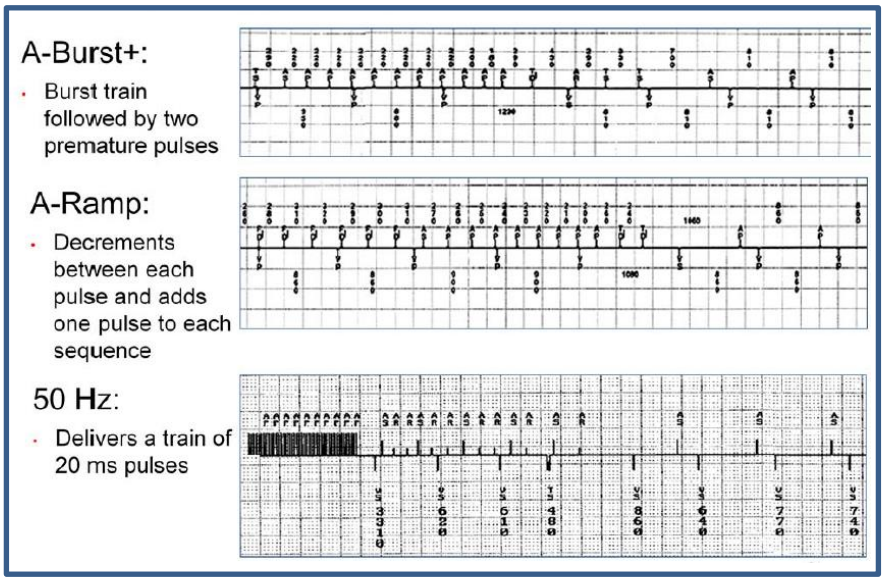

Figure 2- Atrial ATP functioning

Up to ten sequences of three different types of atrial ATP can be programmed to be delivered during a detected AT/AF episode (Figure 3).

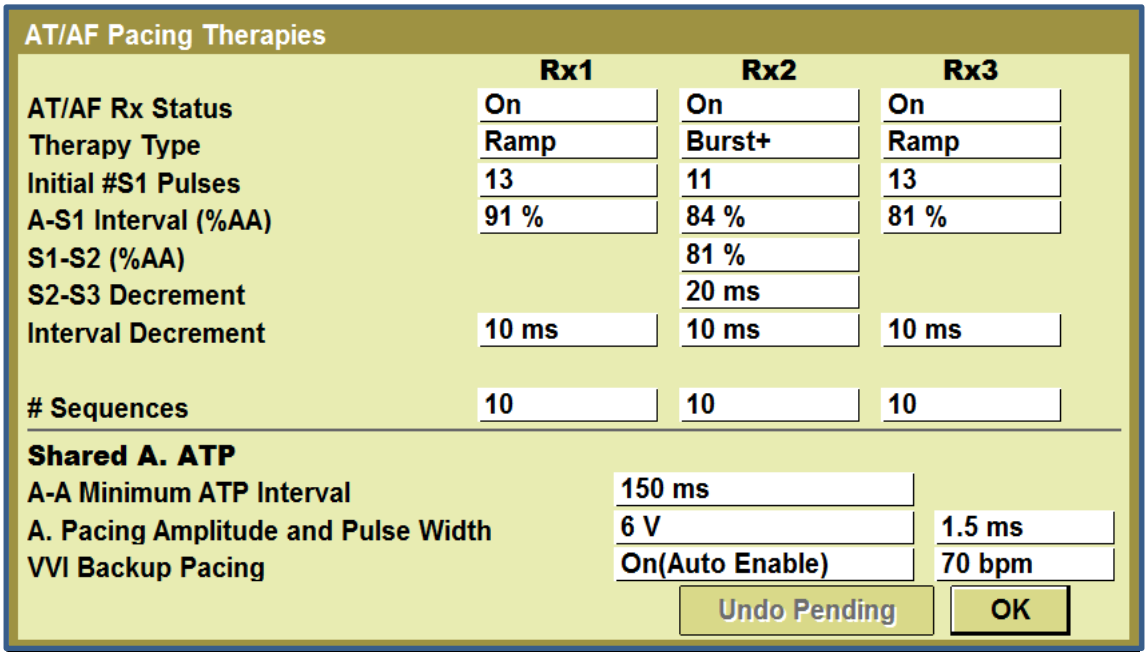

Figure 3- Atrial ATP programming

At the end of all the programmed sequences the device stops delivering the ATP, even if the arrhythmic episode has not been interrupted.
The rATP algorithm allows for multiple deliveries of programmed atrial ATP therapies if:

- rhythm changes occur;
- or a specified period of time has elapsed.

So rATP looks to restore sinus rhythm by continuously searching for new opportunities to initiate ATP therapy in AT/AF episodes, particularly those of longer duration that usually undergo many rhythm transitions becoming amenable to ATP termination [20-21].

7.2. Dosage Form and Route of Administration

This being a post market study, there are no devices under investigation as all devices are commercially available and are implanted prior to the start of the study and data will be collected based on the patients existing medical records per standard of care, the study however does not advice administration of any drug or particular dosage.

7.3. Manufacturer

The Manufacturer details for the respective devices used by subjects will be available in their respective device manuals or Instructions for Use (IFU)

7.4. Packaging

Since all the devices on the study are commercially available, there will be no additional packaging requirements specific to the study.

7.5. Intended Population

All subjects implanted with Medtronic Cardiac implantable devices equipped with an atrial lead, atrial arrhythmias (AT/AF) diagnostic features and atrial Anti Tachy Pacing (ATP) therapies (rATP enabled)can be evaluated for the study.

7.6. Equipment

No additional equipment will be used on the study for assessing the clinical investigation variables Maintenance and calibration of devices that will be used as part of the study (Non-Medtronic devices) will be done as applicable per the hospital SOP requirements.

7.7. Product Use

All devices used on the study are commercially available at the time of study start and the details of the product use will be available in the respective Instructions for Use (IFU).

7.8. Product Training Requirements

Since there is no specific device / product used on the study apart from the ones that are already implanted in subjects there is no requirement for a specific product training.

7.9. Product Receipt and Tracking

This being a post market study with no device distributed as part of the study and there will be no device tracking maintained for these products apart from the routine commercial device tracking .

7.10. Product Storage

As there is no product / device distribution on the study there will be no device storage or maintenance done as part of the study.

7.11. Product Return

Not applicable since there is no product / device distribution involved in the study.

7.12. Product Accountability

This being a post market study with no device distribution as part of the study there will be no device tracking maintained for these products apart from the routine commercial device tracking .

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8. Selection of Subjects

8.1. Study Population:

Patients implanted with a Medtronic pacemaker/defibrillator with an atrial lead, equipped with AT/AF diagnostics and atrial ATP therapies who meet the inclusion and exclusion criteria are intended to participate in this study. The patients should have been implanted for no more than 18 months prior to enrollment.

8.2. Subject Enrollment

The point of enrollment is defined as the time at which the inclusion and exclusion criteria have been checked and fulfilled and at which a subject and the investigator have signed and dated the PIC form. At that point, the patient can be enrolled on the study. A study patient ID number will be assigned, and the patient must be followed until study closure or study exit, whichever occurs first. The investigator will record on the medical file of the patient that he/she participates in the study. Up to 758 patients will be enrolled with about 379 patients randomized into each arm, this study does not set a minimum number per site as the enrollment will be competitive.

8.3. Inclusion Criteria

Patients are eligible to be enrolled in the study if the following criteria are met:

1) Subject is implanted with a Medtronic cardiac implantable device with an atrial lead equipped with atrial ATP therapies (rATP) enabled no longer than 18 months and at the minimum 6 weeks has passed since the implant;
2) Age $\geq$ 55 years, to be able to enroll patients with high risk of AF recurrence/onset;
3) Subject provides informed consent;
4) Subject is willing and able to comply with the study procedures;
5) Subject has documented history of atrial fibrillation or atrial flutter, or any one or more of the below listed risk factors for developing AF as per AHA/HRS guidelines [26].
    - Age > 60years;
    - Stroke/TIA
    - Diabetes;
    - High Blood Pressure;
    - Coronary artery disease;
    - Cardiomyopathy;
    - Pericardial inflammation;
    - Prior heart attacks;
    - Congestive heart failure;
    - Structural heart disease (valve problems or congenital defects);
    - Prior open-heart surgery
    - Untreated atrial flutter (another type of abnormal heart rhythm);
    - Thyroid disease;
    - Chronic lung disease;
    - Sleep apnea;
    - Excessive alcohol;
    - Serious illness or infection.

8.4. Exclusion Criteria

Patients are not eligible to be enrolled in the study if any of the following criteria is met:

1. Subject has been implanted with a Medtronic cardiac implantable device with an atrial lead equipped with atrial ATP therapies (rATP) enabled for more than 18 months;

2. Subject is in permanent AF or persistent AF at the baseline visit: a. The definition of permanent AF will be based on the physicians' decision that nothing further can be done to cardiovert the patient or, in historical cases, we will refer to the Cardiac Compass reports:

b. The definition of persistent AF at baseline will refer to the Cardiac Compass reports (>7 consecutive days in AF with the last day being the day of enrollment)

3. Participation in other studies which could potentially conflict with this study.

4. Legal incapacity or evidence that a subject cannot understand the purpose and risks of the study or inability to comply fully with study procedures and follow up.

9. Study Procedures

9.1. Schedule of Events

Following the informed consent signature and date by patient and investigator, each subject enrolled in this study will be follow the below visit plan (see study flow-chart in Figure 4):

1. At baseline visit;
2. At the follow up visits which should be performed, as per recommendation, in clinic /person at least every 6 months, and if on remote monitoring every 3 months in between;
3. At study closure visit (last patient last visit), will be performed after the last enrolled patient completes 24 months on the study. The first patient enrolled will continue their follow up visits (per above follow-up schedule) till the last patient completes 24 months on the study.

9.1.1. Baseline visit

Subjects may be enrolled into the study only after a minimum of 6 weeks from implant, or after leads stabilization (based on physician's discretion), to be sure about leads fixation.

During the baseline visit, the subject will be randomly assigned to one of the two study groups: intervention arm or control arm. If the atrial ATP therapies are already ON at the time of the randomization, the setting will be changed according to the assigned arm.

After enrolling the patient, the following data will be collected:

- **Demographics**, such as age and gender;
- **Medical History**, such as etiology, history of cardiovascular and arrhythmia events and surgical intervention as well as history of co-morbidities will be documented after enrolling a patient;
- Symptoms;
- **Device Data**, comprehensive of:
    - arrhythmic episodes stored in the device memory;
    - clinically significant changes in Cardiac Compass parameters (as per physician's opinion);
    - electrical parameters (leads impedance, sensing, threshold);
    - AT/AF therapies programming setting;

- ECG data: At the time of baseline (where available) from the patients' medical records (if done on the same day or ± 1 month from the date of the visit)
- **Echocardiographic (ECHO) data** obtained by performing an ECHO test (where available):
  - The test can be done on the same day of the baseline assessment, if recommended;
  - retrieving a previous ECHO exam not older than 1 month (±2 weeks) from the baseline assessment;
  - scheduling an ECHO test in 1 month (±2 weeks) from the baseline assessment;

  - Medications.

9.1.2. In-office /clinic follow-up visits

The first in-office follow-up visit is recommended to take place 6 months (± 2 weeks) after enrollment. During this assessment the following data will be collected:

- Symptoms;
- Device Data (collected via Save-To -Disk), comprehensive of:
- arrhythmic episodes stored in the device memory
- clinically significant changes in Cardiac Compass parameters (as per physician's opinion)
- electrical parameters (battery voltage, leads impedance, sensing, threshold)
- AT/AF therapies programming setting

- **ECG data**: will be collected (where available) from the patients' medical records (if done on the same day or ± 1 month from the date of the visit)
- **Echocardiographic (ECHO) data** obtained by performing an ECHO test (where available):
- The test can be done the same day of the follow-up visit
- retrieving a previous ECHO exam not older than 1 month (±2 weeks) from the follow-up visit
- scheduling an ECHO test in 1 month (±2 weeks) from the follow up

- Medication changes;
- Adverse Events (AEs).

It is recommended to schedule in-office follow-up visit for every patient enrolled every 6 months (± 2 weeks) for at least 24 months (± 2 weeks) after the enrollment, until the last enrolled patient exits the study

9.1.3. Remote follow-ups

The first transmission with MyCareLink (if applicable) is recommended to be performed 3 months (± 2 weeks) after enrollment. During this assessment the following data will be collected:

- Device Data(collected via Save -To-Disc), comprehensive of:
- arrhythmic episodes stored in the device memory;
- clinically significant changes in Cardiac Compass parameters (as per physician's opinion);
- electrical parameters (leads impedance, sensing, threshold);
- AT/AF therapies programming setting.
- AEs.

If any revision is required based on the device date a telephonic contact with the patient is done and following data will be collected:

- Symptoms,
- Actions performed or scheduled,
- Change in Medications

It is recommended to schedule MyCareLink transmissions (for patients provided with the monitor) after 3 (± 2weeks), 9(± 2weeks) 15 (± 2weeks) and 21 (± 2weeks) months after enrollment; in case the patients misses/refuses the in-office follow-up visits it is recommended to schedule MyCareLink transmissions every 3 (± 2weeks) months.

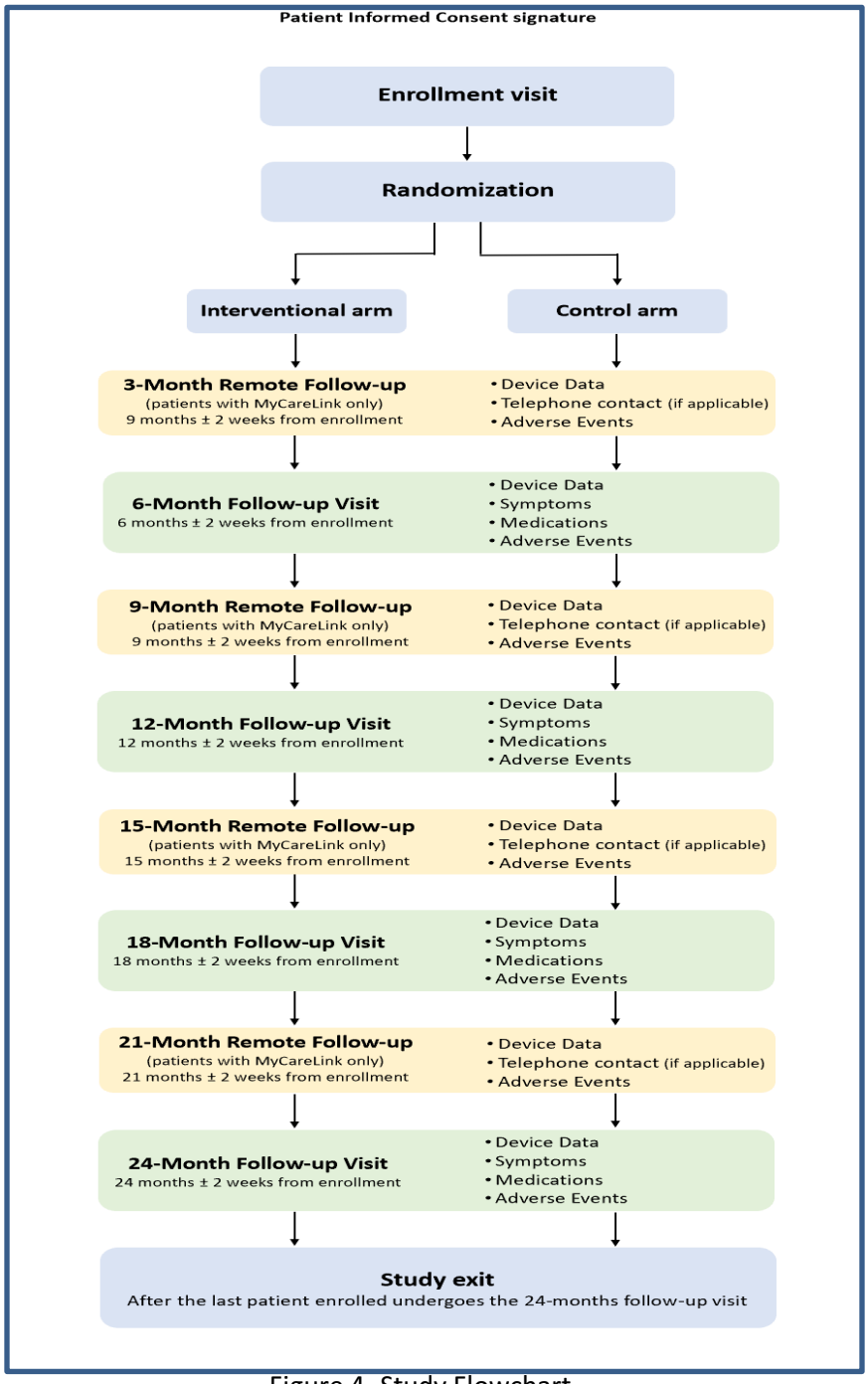

Figure 4- Study Flowchart

9.2. Subject Screening

All subjects will be prescreened based on their past medical records available within the hospital and will be considered eligible for the study once they meet all the Inclusion criteria.

9.3. Prior and Concomitant Medications

During the study, subjects will continue to take medication as advised by their physician per standard of care. The study does not advice or limit the patient from any medication. However any changes or dose alternations in medications made during the course of the study will be collected during the visits, including but not limited to : anticoagulation/antithrombotic therapy, anti-arrhythmic, rate control drugs (i.e. all drugs related to AF management or that can alter AF risk factors such as hypertension, HF, CAD, sleep apnea, valvular disease) like amiodarone or propranolol, diuretics, beta-blockers, ACE-inhibitors, vasodilators, electrolyte replacement, aldosterone antagonists, inotropes and Brain Natriuretic Peptide (BNP)

9.4. Subject Consent

The investigator or authorized designee must obtain written informed consent before any clinical study related activity takes.

Well in advance of the consent discussion, the subject should receive the Institutional Ethics committee (IEC) approved Patient Information and Informed Consent Form. During the consent discussion, the investigator or his/her authorized designee must fully inform the patient of all aspects of the clinical study that are relevant to the patient's decision to participate in the clinical study. If a patient is illiterate, an impartial witness must be present during the entire informed consent discussion and the written informed consent form as well as any other information shall be read aloud and explained to the patient. All items addressed in the Patient Information and the Informed Consent Form must be explained. The language used shall be native and non-technical as possible and must be understandable to the patient and the impartial witness, where applicable.

The patient must have ample time and opportunity to read and understand the Patient Information and the Informed Consent Form, to inquire about details of the clinical study, and to decide whether to participate in the clinical study. All questions about the clinical study should be answered to the satisfaction of the patient.

Neither the investigator, nor the investigation site staff shall coerce or unduly influence a patient to participate or to continue to participate in the clinical study. The informed consent process shall not waive or appear to waive the patient's rights.

When the patient decides to participate in the clinical study, the Informed Consent Form must be signed and personally dated by the patient and investigator or authorized designees. If applicable, the witness shall also sign and personally date the consent form to attest that the information in the Patient Information and Informed Consent Form was accurately explained and clearly understood by the subject, and that informed consent was freely given.

After all persons have signed and dated the Informed Consent Form, the investigator must provide the subject with a copy of the Patient Information and the signed and dated Informed Consent Form. The original Patient Information as well as signed and dated Informed Consent will be kept on-site as part of ISF.

Medtronic will inform the investigators whenever information becomes available that may be relevant to the subject's confirmed participation in the clinical study. The investigator or his/her authorized designees should inform the subject in a timely manner.

Medtronic will revise the written Patient Information and Informed Consent Form whenever new information becomes available that may be relevant to the subject's confirmed participation in the clinical study. The revised information will be sent to the investigator for approval by the IEC. After approval by the IEC, a copy of this information must be provided to the participating subjects, and the informed consent process as described above needs to be repeated.

9.5. Randomization and Treatment Assignment

The enrolled patients will be randomized by using the electronic data capture system.

Patients will be randomized 1:1 to either interventional or control arm. The sequence of treatments will be randomly permuted in blocks of 2 or 4 patients per block. The blocked randomization will be centralized, and schedules will be created by the study statistician using statistical software. The randomization will be performed by the center via the EDC system (Oracle Clinical). To minimize the selection bias, the randomization procedure for this study will use the site (15 sites) and history of AF (2 (Yes or No)), as stratification factors, so that there will be a separate permuted block randomization list for each site (30). This guarantees treatment balance within sites. In the event of any challenges in accessing Oracle Clinical for Randomization, please contact the Clinical Study Manager for next steps .

Patients included in the control arm will be programmed according to Minerva Trial programming setting (Figure 5 and 6):

- AT/AF Detection: programmed 2 Zone ON at 350 ms (171 bpm) for AT/AF, and 200 ms (300 bpm) for Fast AT/AF;
- AT/AF therapies enabled in AT/AF zone only:

- Ramp therapy composed by 10 sequences with 13 initial pulses at 91% of the rate of the arrhythmia, and each pacing pulse is decremented by 10 ms.
- Burst+ composed by 10 sequences of trains of 11 pulses at initial 84% of the rate of the arrhythmia with two premature beats at the end of the sequence at 81% of the rate of the arrhythmia with a decrement of 20 ms. The rate of each sequence is decremented by 10 ms from the previous one.
- Ramp therapy composed by 10 sequences with 13 initial pulses at 91% of the rate of the arrhythmia, and each pacing pulse is decremented by 10 ms.
    - Reactive ATP ON, triggered in case of shifts in arrhythmias' rate or regularity and after a time interval of 7 hours.

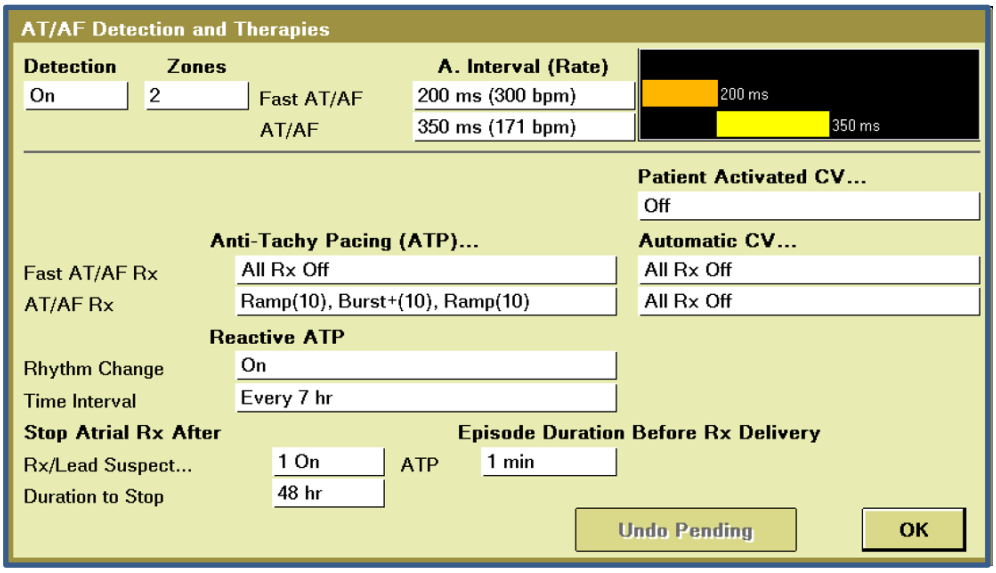

Figure 5- Control arm: detection and therapy zones; rATP programming setting

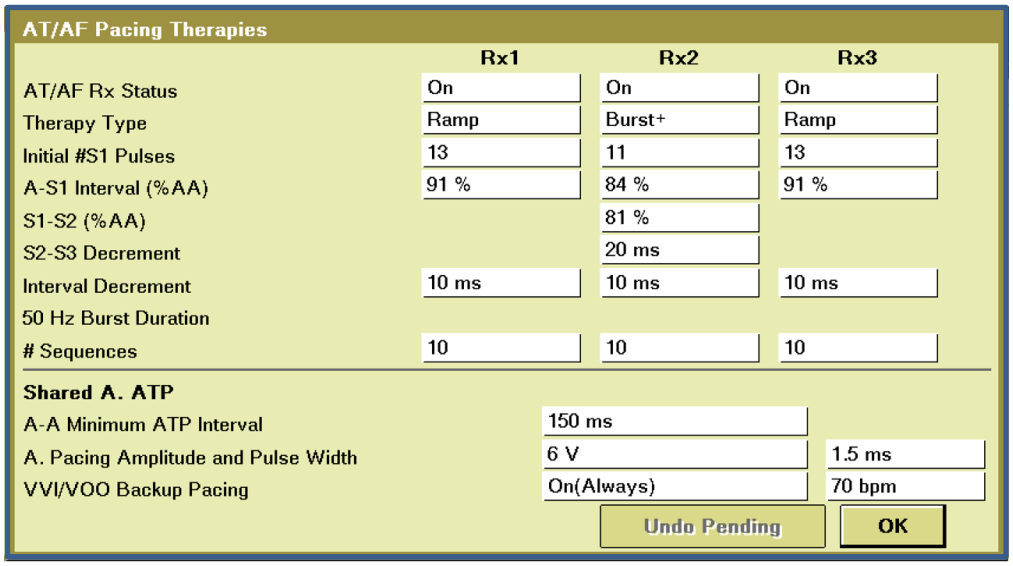

Figure 6- Control arm: ATP therapies programming setting

Patients included in the intervention arm will be programmed according to a reduced sequence programming setting (Figure 7 and 8):

- AT/AF Detection: programmed 2 Zone ON at 350 ms (171 bpm) for AT/AF, and 200 ms (300 bpm) for Fast AT/AF;
- AT/AF therapies enabled in AT/AF zone only:

- Ramp therapy composed by 6 sequences with 10 initial pulses at 91% of the rate of the arrhythmia, and each pacing pulse is decremented by 10 ms.
- Burst+ composed by 3 sequences of trains of 8 pulses at initial 91% of the rate of the arrhythmia with two premature beats at the end of the sequence at 81% of the rate of the arrhythmia with a decrement of 20 ms. The rate of each sequence is decremented by 10 ms from the previous one.
- Burst+ composed by 3 sequences of trains of 8 pulses at initial 91% of the rate of the arrhythmia with two premature beats at the end of the sequence at 75% of the rate of the arrhythmia with a decrement of 30 ms. The rate of each sequence is decremented by 10 ms from the previous one.
  - Reactive ATP ON, triggered in case of shifts in arrhythmias' rate or regularity and after a time interval of 12 hours.

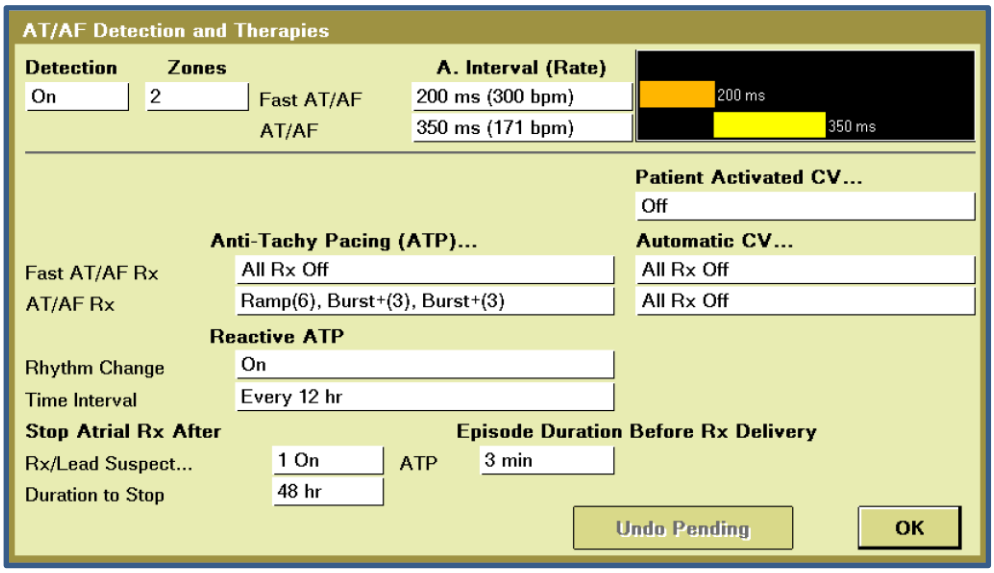

Figure 7- Intervention arm: detection and therapy zones; rATP programming setting

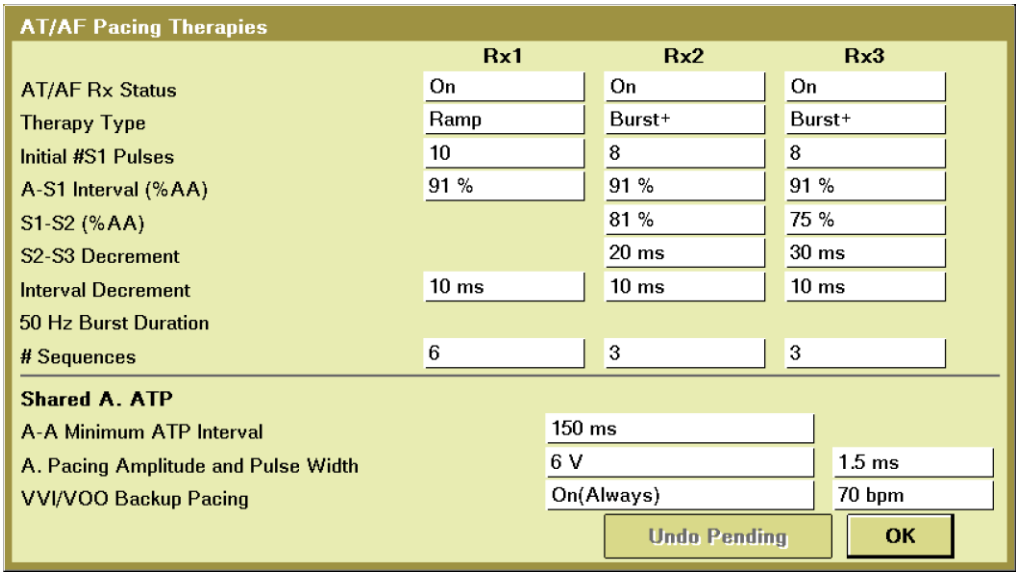

Figure 8- Control arm: ATP therapies programming setting

9.6. Assessment of Efficacy

Device data containing information about AT/AF episodes occurrence and duration will be collected every six months for all the enrolled patients, and every 3 months from patients who are on remote monitoring with a MyCareLink monitor. The list of arrhythmic episodes reported in the episode log and the cardiac Compass trends will be used to identify the following occurrences among the whole study population during the entire study period:

- AT/AF incidence and episodes duration;
- Incidence of persistent AF (defined as more than 7 continuous days of AF);
- Biventricular pacing percentage in CRTP/CRTD patients.

The definition of permanent AF will be based on the physicians' decision that nothing further can be done to cardiovert the patient.
All these data will be inserted in the study eCRFs, in addition to the save to disk collected during the in-office follow-up visits.
The primary endpoint will be measured in terms of time to persistent AF in the two study groups.

The secondary endpoints will be measured by using device and MyCareLink data, and hospital's clinical records reporting information regarding hospitalizations, deaths, cardioversions, AT/AF episodes incidence and daily burden, biventricular pacing percentage, occurrence of thromboembolic events and echocardiographic parameters.

9.7. Assessment of Safety

All cardiovascular related AE, device related AE and all SAE regardless of relationship will be assessed on the study. Sites are required to follow their respective Ethics committee requirements for safety reporting as needed (which includes any SAE/ SADE/ USADE) while the patient is still on the study. Refer to section 11.2 for Investigator reporting requirements.

9.8. Recording Data

The Table 1 below lists the data collection requirements at baseline as well as all subsequent study follow-up visits:

	Baseline visit	3rd month (± 2 weeks after baseline visit)	6th month (± 2 weeks after baseline visit)	9th month (± 2 weeks after baseline visit)	12th month (± 2 weeks after baseline visit)	15th month (± 2 weeks after baseline visit)	18th month (± 2 weeks after baseline visit)	21st month (± 2 weeks after baseline visit)	24th month (± 2 weeks after baseline visit)	Exit visit
		Remote follow-up	In-office follow-up	Remote follow-up	In-office follow-up	Remote follow-up	In-office follow-up	Remote follow-up	In-office follow-up	
Inclusion/exclusion Criteria	X									
Study PIC	X									
Randomization	X									
Medical and arrhythmia history	X									
ECG	X[1]		X[1]		X[1]		X[1]		X[1]	
ECHO	X[1]		X[1]		X[1]		X[1]		X[1]	
Medication	X	X[3]	X	X[3]	X	X[3]	X	X[3]	X	
Symptoms	X	X[3]	X	X[3]	X	X[3]	X	X[3]	X	
Device data	X	X	X	X	X	X	X	X	X	
SAE (include but not limited to hospitalizations and death)		X[4]	X[2]	X[4]	X[2]	X[4]	X[2]	X[4]	X[2]	
System modification			X[2]		X[2]		X[2]		X[2]	
AE (Cardiovascular related / Device related)		X[4]	X[2]	X[4]	X[2]	X[4]	X[2]	X[4]	X[2]	
Protocol Deviation	X[2]	X[2]	X[2]	X[2]	X[2]	X[2]	X[2]	X[2]	X[2]	
Device deficiency		X[2]	X[2]	X[2]	X[2]	X[2]	X[2]	X[2]	X[2]	
Exit form										X

Table1

(1) ECHO and ECG will be collected subject to the availability of the reports at each of the visits, if the test was done on the same day , or ±1 month from the visit .

(2) if occurring.

(3) if any updates to the existing device data/ programming requires a telephone contact with the patient.

(4) if a telephone contact reporting AE/SAE is done (while on remote monitoring)

In case of a device replacement, the new device should be programmed as per the randomization arm of the patient.
Remote Follow ups are done only if the patient is on remote monitoring, else all other subjects are recommended to come for their in clinic visits every 6 months. The maximum time a patient may stay on the study is about 42 months with a 6 monthly follow up period as listed in the table. The first patient on the study may continue on the study till the last patient completes 24 months .

9.9. Deviation Handling

A study deviation is an event where the investigator or site personnel did not conduct the clinical study according to the Clinical Investigational Plan or Clinical Investigation Agreement. The investigator is not allowed to deviate from the above-mentioned documents except with prior approval or under emergency circumstances to protect the rights, safety and wellbeing of the subject. All deviations shall be documented and explained, regardless the reason for the deviation.

Deviations will be collected on electronic Case Report Forms (eCRF). Investigators must report study deviations to Sponsor in a timely manner. Study deviations may include but are not limited to:

- missing follow-up visits;
- failure to obtain Informed consent Form prior to participation in the study;
- incorrect version of consent form provided to subject;
- not performed Protocol Required Data Collection/Testing;
- subject did not meet enrollment criteria;
- incorrectly performed testing;
- source data permanently missing.

Sponsor will review deviations as they are received. Corrective and preventative actions may be discussed with the site as needed.
The following will not be considered study deviations:

- incomplete data due to subject exit or withdrawal;
- no data collected from study components that are optional.

Medtronic will assess the significance of all deviations and evaluate the need to amend the CIP or to early terminate the investigation, in accordance with Medtronic standard operating procedures (SOPs).
Substantial and non-substantial amendments to the protocol will be notified to the IEC for notification and/or approval if required according to site requirements.

9.9.1. Reporting requirements for study deviations

The investigator shall adhere to IEC requirements and procedures for reporting study deviations.
All the Protocol Deviations will be documented in the appropriate eCRF, regardless of whether medically justifiable, pre-approved by Medtronic, an inadvertent occurrence, or taken to protect the subject in an emergency. The deviation must be recorded with an explanation for the deviation and corrective/ preventive action(s).
Medtronic is responsible for analyzing deviations, assessing their significance, and identifying any additional corrective and/or preventive actions (e.g. amend the CIP, additional training, terminate the study, etc.). Repetitive or serious investigator compliance issues may represent a need to initiate a corrective action plan, and in some cases freeze enrolment or ultimately terminate the investigator's participation in the study.

9.10. Subject Withdrawal or Discontinuation

Participation in this clinical trial is voluntary and any subject may withdraw from the study at any time without explanation given. This will not affect his right for future medical care.

If a subject withdraws from the study, the investigator must be informed immediately and the date, circumstances and any reason provided will be documented on the CRF. No data obtained after withdrawal of consent will be recorded on eCRF and will not be evaluated as part of the clinical trial.

Subjects may also be withdrawn at the Investigator's discretion at any time if the patient's well-being is jeopardized by continuation of the study. Time, circumstances and reason/s for withdrawal will be documented on the eCRF. The following list gives examples of reasons for subjects' withdrawal:

- there is a major protocol violation considered to be relevant by the investigator and/or the sponsor (e.g. non-compliance, violation of randomization criteria);
- subject wishes to terminate study participation to investigator prior to study exit;
- investigator, at his or her own discretion, can withdraw a subject from the study at any time;
- death;
- subject is lost to follow-up.

The sponsor must be informed within 24 hours about any discontinuation of a subject including the reason. If at least one of the above-mentioned withdrawals is met, the investigator will inform the sponsor within 24 hours in writing.

If a subject is withdrawn from the study, the reason for withdrawal shall be recorded via the completion of 'Study exit' eCRF and in the subject's hospital record.

Compliance to the follow-up schedule, is essential to enable an analysis of the results in a scientifically sound and meaningful way. If, for whatever reason, the subject follow-up cannot be scheduled within the

time window, it is still essential to document the subject data at a date as close as possible to the calculated follow-up date.

Investigator is urged to limit subject lost to follow-up as much as possible. If the subject does not come back at the scheduled visit four weeks after the planned visit, the investigator should contact the subject by phone in order to schedule the visit as soon as possible. Subjects will be considered lost-to-follow-ups after three documented unsuccessful attempts of contact. The relative information will be reported in the Study Termination Form.

10. Risks and Benefits

10.1. Potential Risks

The risks associated with participation in the clinical study are the same as for the other patients implanted with a CIED.

10.2. Potential Benefits

The potential clinical benefit for patients participating the study could be a decrease in persistent AF incidence, as showed in the Minerva Trial. The reduction in AT/AF incidence and episodes duration could also lead to an increase in biventricular pacing percentage (in patients with a CRT-P or CRT-D device) and a reduction in inappropriate shocks due to high rate ventricular conduction during AT/AF. Moreover, a reduced ATP sequence programming could improve device battery longevity, among patients included in this arm, apart from the pharmacological management of device detected AF.

10.3. Risk-Benefit Rationale

The conclusion of the risk assessment is that the benefits outweigh the risk for the patient; therefore, the investigation is justified. It is possible in any clinical study that harmful things can happen which is not known at this time.
The Investigator will continue monitoring, assessing and documenting any additional risk identified during the conduct of the study and the risk-to-benefit analysis updated accordingly.

To minimize or avoid bias the MANDATE study has been designed as a randomized, single-blind trial, where the patient

Each patient's assignment onto the respective arms on the study will be concealed in the study database (Oracle Clinical) and not revealed until all baseline data has been collected and the patient is considered eligible for randomization after having met the eligibility criteria. Investigators accessed patient

randomization through the study database and will further assign the patients who remained blind as for treatment arm onto the respective randomization arms.

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11. Adverse Events

11.1. Definitions/Classifications

The definition of Adverse events is described in the table below:

GENERAL	
Adverse Event (AE)	Any untoward medical occurrence, unintended disease or injury, or untoward clinical signs (including abnormal laboratory findings) in subjects, users or other persons, whether or not related to the investigational medical device. NOTE 1: This definition includes events related to the investigational medical device or the comparator. NOTE 2: This definition includes events related to the procedures involved. NOTE 3: For users or other persons, this definition is restricted to events related to investigational medical devices. (ISO 14155:2011, 3.2).
Adverse Device Effect (ADE)	Adverse event related to the use of an investigational medical device NOTE 1: This definition includes adverse events resulting from insufficient or inadequate instructions for use, deployment, implantation, installation, or operation, or any malfunction of the investigational medical device. NOTE 2: This definition includes any event resulting from an error use or from intentional misuse of the investigational medical device. (ISO 14155:2011, 3.1)
Device Deficiency (DD)	Inadequacy of a medical device with respect to its identity, quality, durability, reliability, safety or performance. NOTE: Device deficiencies include malfunctions, use errors and inadequate labeling (ISO 14155:2011, 3.15)
Unanticipated Serious Adverse Device Effect (USADE)	Serious adverse device effect which by its nature, incidence, severity or outcome has not been identified in the current version of the risk analysis report1

	NOTE: Anticipated serious adverse device effect (ASADE) is an effect which by its nature, incidence, severity or outcome has been identified in the risk analysis report. (ISO 14155:2011 3.42)
Serious Adverse Event (SAE)	Adverse event that a) led to death, b) led to serious deterioration in the health of the subject, that either resulted in : 1) a life-threatening illness or injury, or 2) a permanent impairment of a body structure or a body function, or 3) in-patient or prolonged hospitalization, or 4) medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function, c) led to foetal distress, foetal death or a congenital abnormality or birth defect NOTE: Planned hospitalization for a pre-existing condition, or a procedure required by the CIP, without serious deterioration in health, is not considered a serious adverse event. (ISO 14155:2011 3.37)
Serious Adverse Device Effect (SADE)	An ADE that has resulted in any of the consequences characteristic of a Serious Adverse Event. (ISO 14155:2011 3.36)
Cardiovascular Related AE	An AE relating to the heart and the blood vessels or the circulation. This includes but is not limited to syncope, stroke/TIA (Transient Ischemic Attack), myocardial infarction, heart failure, atrial or ventricular arrhythmia, and peripheral vascular disease.

11.2. Reporting of Adverse Events

11.2.1. Recording and reporting of Adverse Events

As this is a post market interventional study, we will collect all cardiovascular-related Adverse Event, device-related AE and all SAE.
The reporting requirements for the investigational study site is as below:

Events to Report	Reporting Requirement and Timeframe	Submit to
All SAE, SADE, USADE	Investigator shall report all SAEs, SADEs and USADEs to the Ethics Committee, monitor and Sponsor promptly of their occurrence. (Indian GCP section 3.3.4.3) For reported deaths the investigator shall supply any additional information (e.g., autopsy report and terminal medical reports.) (Indian GCP section 3.3.4.5) It is recommended for investigator to report all SAEs, SADEs and USADEs to the sponsor within 24 hours. It is recommended for investigator to report all SAEs, SADEs and USADEs to EC within 7 working days unless the stricter timeline is required by the EC.	Sponsor Monitor EC
New information that may adversely affect safety of the subjects or the conduct of the study	Investigator shall promptly report new information that may adversely affect safety of the subject or the conduct of the study. (Indian GCP section 3.3.4.4)	EC Sponsor Monitor

All cardiovascular related AEs and device related AEs should be reported immediately but no later than 3 calendar days after investigational site personnel's awareness of the event.
The investigator will report adverse events on the study database (EDC system) as soon as possible upon notification.

Sites are however required to follow their respective Ethics committee requirements for safety reporting as needed (which includes any SAE/ SADE/USADE) while the patient is still on the study, but only Device related AE, Cardiovascular related AE and all SAEs will be collected towards the study. Refer to the Adverse Event eCRF for the information to be reported for each Adverse Event.

In the event of a medical emergency if the investigator requires information from the sponsor, the investigator can contact the Clinical Study Team for details.

11.2.2. Recording and reporting of Device Deficiencies

Device Deficiency information will be collected throughout the study and reported to Medtronic. Device Deficiencies that did not lead to an Adverse Event should be reported on a Device Deficiency Form, one for each Device Deficiency. This Device Deficiency form must be filled in the EDC system (Oracle Clinical) directly with all the required information.
See the Device Deficiency eCRF for the information to be reported for each Device Deficiency that did not lead to an Adverse Event.

11.2.3. Product Complaint Reporting

Product Complaint: Any written, electronic or oral communication that alleges deficiencies related to the identity, quality, durability, reliability, safety, effectiveness or performance of a medical device that has been placed on the market.
It is the responsibility of the investigator to report all product complaint(s) associated with a medical device distributed by Medtronic, regardless whether they are related to intended use, misuse or abuse of the product. Reporting must be done immediately and via the regular channels for market - released products. Medtronic Complaint Handling Unit will ensure prompt review, and appropriate reporting. The reporting of product complaints is not part of this clinical study and should be done in addition to the Clinical Adverse Event reporting requirements.

11.2.4. Emergency contact details in case of serious AEs

In case of a Serious Adverse Event the investigators can contact the study safety specialist, and if the investigator requires information from the sponsor in the event of an emergency, the investigator can contact the Medtronic Clinical Study Manager. All Contact information are provided in the Study Contact List and will be filed in the Investigator Site File and updated over the course of the study.

12. Data Review Committees

This study will not be using a Data Review Committee.

13. Statistical Design and Methods

13.1. Determination of sample size

The sample size was estimated using data from previous studies and from Steering Committee Experience with the intent to prove that the Reactive ATP is not less effective than the standard programming in term of occurrence of persistent AT/AF.

The incidence of persistent AT/AF occurrence lasting more than 7 continuous days at 18 and 24 months (95% IC) was 11% (8%-15%) and 15% (12%-20%) in the experimental group of the MINERVA trial (ref.1), respectively. Furthermore, analogous results were obtained in the PATTERNS study, a retrospective observational study on similar patients in India where the incidence of AT lasting more than 7 days at 18 months was 12% (ref.2).

In a population of patients implanted with Medtronic cardiac implantable device with an atrial lead equipped with atrial ATP therapies (rATP) enabled the AT/AF occurrence at 24 months (95% IC) is expected to be slightly higher due to the unknown effect of the rATP in IPG, ICD, CRT-D, CRT-P devices.

Considering that the incidence of AT/AF occurrence in the control arm of the MINERVA trial was 26% (23%-31%), it is defined that a margin of 7.5% as non-inferiority margin is clinically reasonable in the experimental arm of the MANDATE study. It will be claimed that the experimental arm is not appreciably worse compared to control arm. Based on this information, the non-inferiority tests for the difference of two survival models were applied.

The assumptions for the sample size are: The survival is to be assessed at 24 months, it is expected to be 85% in the control arm, and 77.5% or more in the experimental arm, respectively. A difference in the actuarial incidence of 7.5% or less is considered clinically unimportant for this comparison. It is considered the maximum acceptable increase in the incidence compared to the control arm.

- 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%. Since smaller values of the incidence are better, the hypotheses are based on lower-tailed test:

$$H0: pE < pC - \delta NI$$

$$H1: pE \geq pC - \delta NI,$$

where pE is the probability of the primary endpoint for the experimental treatment; pC is the probability of the primary endpoint for the control treatment; $\delta NI > 0$ is the clinically meaningful difference.

Based on this statistical test and assuming a one-sided type I error rate of 0.025 and a type II error rate of 0.20 or equivalently, power of 0.80 for the final analysis, it will be claimed that Experimental arm is not inferior to Control if the difference between the two hazards is less than the margin.

Thus, the non-inferiority hypothesis will require a sample size of 758 (379 per arm) subjects. Sample size calculation have been performed with SAS software v.9.4 (SAS Institute Inc., Cary, NC, USA).

13.2. Statistical methods

13.2.1. Disposition of Subjects

Disposition of subjects will be reported following the CONSORT Flow Diagram. Reason for not participation at each stage will be reported where known.

13.2.2. Analysis sets

The following population sets will be considered:

- 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.

13.2.3. General methodology

For both PP and ITT populations descriptive statistics will be used to summarize patient characteristics. Variables on a continuous scale will be described as mean, standard deviation, median, 25th and 75th percentiles, minimum and maximum. Variables on a categorical scale will be presented as counts and percent. Summary statistics will be reported with maximum 2 decimals, as appropriate.

13.2.4. Center pooling

Center impact on primary outcome could be investigated. A description on primary outcome by site will be provided, as appropriate. Additional exploratory analysis on baseline characteristics could be performed to check potential difference on primary outcome among sites.

13.2.5. 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. For subjects who are lost to follow-up, the time to event will be censored at the last available contact date.

In case of missing data, the imputation of missing data will be performed using the most appropriate method depending on the pattern of missing in the data and the type of the imputed variable. After the imputation of the missing values the analysis will be rerun.

13.2.6. Adjustments for multiple comparisons

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

13.2.7. Demographics and other baseline characteristics

Descriptive statistics will be used to summarize demographic and baseline characteristics and medical history variables for both PP and ITT. 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 the study CRF and described with Tables, Listings and Figures as appropriate.

Device implant data, collected through the study CRF or stored in the device memory and transmitted by MyCareLink, will be described with Tables, Listings and Figures as appropriate by using descriptive statistics (including mean, standard deviation, median, minimum, and maximum for continuous variables, and counts and percentages for categorical variables).

For PP analysis set, demographics and other baseline characteristics will be also described separately for the interventional and the non-interventional arm. Continuous variables will be compared using the T-test or the Mann-Whitney test, as appropriate. Normality of distribution will be tested, calculating skewness and kurtosis values. Comparisons of categorical variables will be performed by Chi-square's test.

13.2.8. Interim analysis

No interim analyses are planned. Data will be analyzed once the last enrolled patient will complete the 24 months follow-up.

13.2.9. Evaluation of objectives

Time to event analysis will be performed by means of the Kaplan Meier method. Time to event must be calculated as time from enrollment date or the first day in sinus rhythm after enrollment, to the date of event for patients with complications, and time from enrollment date to the last patient information date otherwise (the date of last transmission, date of last follow-up, exit or death date). Difference in time-depending event between population subgroups will be evaluated using a Cox proportional hazard regression model. The proportionality of the risk will be tested with the Shoenfeld method. Confounding factors will be identified among baseline characteristics and device data eventually collected before inclusion . All outcomes will be evaluated considering confounding factors by means multivariate models or stratification as appropriate. Rates were computed for 100-person years and were compared by means of the Poisson model using the scale deviation parameter to adjust for over-dispersion. Incidence rate ratios (IRRs) with their 95% confidence intervals (CIs) were computed to measure events reductions in the interventional arm. IRRs were also adjusted to account for the effect of potential confounders.

13.2.10. Safety

Adverse events in the ITT will be presented in summary tables and supporting data listings.

13.2.11. Health outcomes analyses

No specific health outcomes' analyses were planned in the protocol, except for those considered in the secondary objectives.

13.2.12. Changes to planned analysis

Any deviation(s) from the original statistical plan will be described and justified in the final report.

14. Ethics

14.1. Statement(s) of Compliance

- The study will be conducted in accordance with the protocol and ethical principles that have their origin in the Declaration of Helsinki (2003),the International Conference on Harmonization Guidelines on Good Clinical Practice , India GCP.
- The study will not begin until an IRB/EC approval as required are received.
- Any special requirements imposed by an IRB/EC will be followed for the respective sites.
- Since this is a post market study with follow up visits per the standard of care no additional compensation will be provided to subjects for the respective follow-up visits .
- Medtronic maintains appropriate clinical trial liability insurance coverage as required under applicable laws and regulations and will comply with applicable local law and custom concerning specific insurance coverage. If required a Clinical Trial insurance statement/certificate will be provided to the Medical Institution and Ethics Committee.
- The Name(s), title(s), address(es), and contact numbers of the investigator(s) who are responsible for conducting the study, along with their consent letter(s) (Investigator Statement),will be listed and kept separate from the CIP and will be updated by the sponsor.
- The Name(s), address(es) and contact numbers of the institution(s) particulars of the head(s) of the institution(s), will be kept separate from the CIP. The sponsor will maintain an updated list.
- If any action is taken by a IEC/IRB with respect to the investigation, that information should be forwarded to the sponsor.
- Warranty information is provided in the product packaging for the commercially released devices.

15. Study Administration

15.1. Monitoring

Monitoring visits will be conducted in accordance with Medtronic SOPs and the Monitoring Plan.

Frequency of monitoring visits may be based on subject enrollment, duration of the study and study compliance.

During the monitoring visit, it will be verified whether signed and dated Informed consent Forms have been obtained from each subject before any clinical-study-related procedures are undertaken.

Regulatory documents (e.g. EC approval letters and Clinical Trial Agreements) will be reviewed at each study center. Subject data will be monitored against source documentation (e.g. clinic and hospital charts). Center study progress, investigator's adherence to the CIP and maintenance of records and reports will also be checked.

The principal investigator(s), his/her delegate(s) and the study coordinator(s) shall be accessible to Medtronic field personnel, study monitors and the Clinical Study Manager. This accessibility is of particular importance for reviewing data in the eCRF. Direct access to patient medical files for source data verification will need to be granted and prepared prior to any monitoring visits. Subject compliance to the study and visits will be monitored periodically and all efforts to contact the patient telephonically and ensure availability for the visit will be done by the site team.

15.2. Data Management

The investigator must ensure accuracy, completeness and timeliness of the data reported in the eCRFs and in all other required reports. Data reported on the eCRFs which are derived from source documents and worksheets must be consistent with the source documents and worksheets as well. All discrepancies need to be justified in a documented rationale, signed and dated by the (principal) investigator and filed in the patient medical file.

Only authorized persons can complete eCRFs. eCRFs shall be signed by investigators (physicians only) as specified on the Delegated Tasks List included in the Investigator Site File.

The Electronic Data Capture (EDC) system maintains an audit trail on entries, changes or corrections in eCRFs. If a person is only authorized to complete eCRFs or make changes to an already signed eCRF, the investigator shall re-sign this eCRF.

A copy of the electronic Case Report Forms will be provided under a separate cover.

It is recommended that eCRF will be updated as soon as possible from the date the visit is completed .A delayed completion of the eCRF will not be considered a Protocol Deviation.

Data management will be done according to Medtronic SOPs and the Data Management Plan for this study. These documents will be made available on request.

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 the data.

15.3. Direct Access to Source Data/Documents

In addition to regular monitoring visits, Medtronic may conduct audits at participating investigation sites. The purpose of an audit is to verify the adequate performance of the clinical study related activities. Independent of the employees involved in the clinical study. Regulatory authorities may also perform inspections at participating investigation sites. Any regulatory authority inspection announcements shall be forwarded immediately to Clinical Study Team.

The investigator and/or institution shall permit Medtronic and regulatory bodies direct access to source data and documents, taking into account any restrictions due to local law, to perform clinical study-related monitoring, audits, IEC review (if applicable), and regulatory inspections.

15.4. Confidentiality

All records and other information about subjects participating in this study will be treated as confidential.

Subject confidentiality will be maintained throughout the clinical study in a way that ensures the information can always be tracked back to the source data. For this purpose, a unique subject identification code (e.g. site number, subject number and subject initials) will be assigned and used to allow identification of all data reported for each subject.

Study data may be made available to third parties, e.g. in the case of an audit performed by regulatory authorities, provided the data are treated confidentially and that the subject's privacy is guaranteed. The identity of a subject will never be disclosed in the event that study data are published. Sites will maintain subject privacy according to local and national regulations and institutional requirements.

15.5. Liability

The India Medtronic Pvt Ltd is wholly owned subsidiary of Medtronic Inc., which as the parent company of such entity maintains appropriate clinical study liability insurance coverage as required under applicable laws and regulations and will comply with applicable law and custom concerning specific insurance coverage. If required, a Clinical Trial Insurance statement/certificate will be provided to the IEC.

15.6. CIP Amendments

In case the investigator proposes any appropriate modification(s) of the CIP or investigational device or investigational device use, Medtronic will review this and decides whether the modification(s) will be implemented.

Medtronic will submit any significant amendment to the Clinical Investigation Plan, including a justification for this amendment, to the appropriate regulatory authorities and to the investigators to obtain approval from their IEC, if applicable. Administrative amendments to the CIP will be submitted to the IEC and appropriate regulatory authorities for notification, if applicable.

15.7. Record Retention

At a minimum, the following records must be kept by the investigator:

- CIP and, if applicable, any amendments;
- instructions For Use;
- Medtronic and IEC approved Informed consent form (ICF);
- fully signed clinical investigation agreement and confidentiality agreement (if not included in the clinical investigation agreement);
- insurance certificates;
- completed Delegated Task List and Curriculum Vitae of all investigation site team members;
- training documentation of all site study members;
- relevant communications;
- subject identification;
- enrollment log;
- signed, dated and fully executed Informed consent Forms;
- fully executed eCRFs and corrections;
- interim and Final report;
- EC notification, correspondence and approval;
- EC membership list;
- statistical analyses;
- all essential correspondence concerning the clinical study between Medtronic and the clinical site;
- any other records as required by local requirements.

15.8. Publication and Use of Information

A detailed description of the Publication Policy will be described in the Publication Plan.

The Medtronic study team will collaborate to publish the results of the study in an appropriate/highest impact local (Indian) and global publications.

Publications and presentations referring to the MANDATE Study will be coordinated by Medtronic to allow the use of all available data. The following publication policy will have to be adhered to by all participating Investigational Centers:

Authorship on any publication(s) resulting from this study will be assigned according to substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data, drafting the article or revising it critically for important intellectual content and final approval of the version to be published. This is in accordance with the Vancouver principles (The Uniform Requirements for Manuscripts Submitted to Biomedical Journals: Writing and Editing for Biomedical Publication, ICMJE, October 2008), as agreed upon by the editors of all major medical journals.

The number of authors will be dependent on the regulations of the concerning journal. Names of all participating investigators will appear in the Acknowledgment of the paper.

Based on the principle that Medtronic owns the data of the MANDATE study, a single Investigational Center may access and use the data provided by itself for scientific publications following prior approval by Medtronic.

Medtronic as the owner of the data can use the data and/or any results derived from the data or publications based on that data for marketing purposes, further research and development of devices or educational use.

The study sponsor will collect data in such way that no subject can be identified and monitor study records.

Participating subjects will not be identified by name in any published reports about the study.
The study will be recorded on www.clinicaltrials.gov and www.CTRI.in before the first enrollment.

15.9. Suspension or Early Termination

Medtronic or Regulatory Authority may decide to suspend or prematurely terminate the study (e.g. if information becomes available that the risk to study subject is higher than initially indicated or because interim analysis indicates that the results significantly differ from the study objectives or statistical endpoints). If the study is terminated prematurely or suspended, Medtronic shall promptly inform the clinical investigators of the termination or suspension and the reason(s) for this. The investigator shall then promptly inform the reviewing IEC and the study subjects. The clinical research agreement will be amended or terminated.

15.9.1. Early investigation site suspension or termination

Medtronic, IEC or Regulatory Authority may decide to suspend or prematurely terminate an investigation site (e.g. in case of expiring approval of the reviewing IEC, non-compliance to the CIP or lack of enrollment). If an investigation site is suspended or prematurely terminated, Medtronic shall promptly inform the investigator(s) of the termination or suspension and the reason(s) for this. The investigator shall then promptly inform the reviewing IEC, if required, the study subjects and their general practitioner. When the risks are found to outweigh the potential benefits or when there is conclusive proof of definite outcomes, investigators must assess whether to continue, modify or immediately stop the clinical study in the respective investigation site and immediately inform the sponsor and reviewing IEC, if applicable.

15.9.2. Subject follow-up in case of termination

In case of early investigation site suspension or termination, all subjects will continue to be followed according to the standard hospital procedure for patients implanted with a CIED.

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17. Appendices

NA

18. Version History

Version	Summary of Changes	Author(s)/Title
1.0	• 'Not Applicable, New Document'	Sindhu John Clinical Study Manager


Medtronic