Medtronic

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| **Document Title** | Stroke AF Statistical Analysis Plan |
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# Statistical Analysis Plan

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| **Clinical Investigation Plan Title** | Stroke AF |
| **Clinical Investigation Plan Version** | Version 2 (27/JAN/2016) |
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# 1. Version History

| Version | Summary of Changes | Author(s)/Title |
|---|---|---|
| **1.0** | Not Applicable, New Document | Francesca Lemme, Sr. Statistician<br>Brett Peterson, Sr. Statistician |
| **2.0** | • Added description of events required to demonstrate the primary objective of the study in section 6.1<br>• Clarified that mentioned attrition and crossover rates are for each treatment group in section 6.2 | Francesca Lemme, Sr. Statistician<br>Carola Alfaro Vives, Pr. Statistician |

# 2. List of Abbreviations and Definitions of Terms

| Abbreviation | Definition |
|---|---|
| AE | Adverse Event |
| AF | Atrial Fibrillation |
| AT | Atrial Tachycardia |
| CABG | Coronary Artery Bypass Grafting |
| CEC | Clinical Events Committee |
| CIP | Clinical Investigation Plan |
| CRF | Case Report Form (synonymous with eCRF) |
| CRT | Cardiac Resynchronization Therapy |
| CT | Computerized Tomography |
| ECG | Electrocardiogram |
| eCRF | electronic Case Report Forms (synonymous with CRF) |
| ICD | Implantable Cardioverter Defibrillator |
| ICM | Insertable Cardiac Monitor |
| IS | Ischemic Stroke |
| ITT | Intention To Treat |
| LA | Left Atrial |
| LAA | Left Atrial Appendage |
| LVEF | Left Ventricular Ejection Fraction |
| MRI | Magnetic Resonance Imaging |
| NIH | National Institutes of Health |
| OAC | Oral anticoagulation |
| PP | Per Protocol |

| | |
|---|---|
| RDC | Remote Data Capture |
| SAP | Statistical Analysis Plan |
| SOC | System Organ Class |
| TIA | Transient Ischemic Attack |

# 3. Introduction

The purpose of the Stroke AF study is to compare the incidence of atrial fibrillation (AF) through 12 months by continuous cardiac rhythm monitoring with the Reveal LINQ™ Insertable Cardiac Monitor (ICM) (continuous monitoring arm) vs standard of care (SoC) medical treatment (control arm) in subjects with a recent ischemic stroke of presumed known origin. AF will be defined as an AF event lasting more than 30 seconds and adjudicated by the endpoint adjudication committee.

The study is conducted at approximately 40 sites located in the United States (U.S.) and approximately 496 subjects are being enrolled in the study. A total of 23 first documented AF events within 12 months of randomization are required for the study to test the primary objective. In addition, a guidance was sent to sites stating that a maximum of 3 subjects with lacunar stroke (i.e. small vessel disease) may be enrolled at each site. This restriction is not in the CIP.

The enrollment period started in April 2016 and will take approximately 20 months. Subjects will be followed for 3 years, until end of device life or until official study closure, whichever occurs first. Therefore, the expected study duration from first enrollment to official study closure (final report) is approximately 4.5 years. The duration of individual subject participation will vary based on timing of site activation and their enrollment; however, participation of an individual subject will be for 3 years, until end of device life or until study closure, whichever occurs first.

This Statistical Analysis Plan (SAP) has been designed to document, before data is analyzed, the rationale for the study design, and the planned analyses that will be included in a 12-month follow-up study report related to the primary objective (primary report), and a final report related to the secondary objective. This SAP does not limit the analysis in reports, and additional analysis of the study data beyond this plan is expected.

The Stroke AF CIP Version 2, dated 27/JAN/2016 was used to create this SAP.

# *4. Study Objectives*

The Stroke AF study will compare the incidence rate of AF through 12 months between continuous monitoring and standard of care in subjects with a recent ischemic stroke of presumed known origin. Subjects will be randomized 1:1 to the continuous monitoring arm or control arm.

### *4.1. Primary objective*

To compare the incidence rate of AF through 12 months between the continuous monitoring arm vs control arm in subjects with a recent ischemic stroke of presumed known origin.

### *4.2. Secondary objective*

To compare the incidence rates of AF through the duration of study follow-up between study arms.

### *4.3. Primary and final reports*

The objectives for the primary report can be analyzed after all enrolled subjects have 1) had their 12-month visit, 2) missed the 12-month visit and the 12-month visit window has closed, or 3) exited prior to the 12-month visit window closing. A data snapshot will be used to analyze data for the primary report since follow-up will continue. Once follow-up is complete and the study data collection and cleaning is finalized, a second data snapshot will be used to analyze data for the final report.

Table 1 shows which objectives will be analyzed for the primary and final reports. All objectives will be included in the final report using the final data snapshot.

**Table 1: Objectives analyzed for the primary and final reports**

| Objective | Primary Report | Final Report |
|---|---|---|
| Primary Objective | X | X |
| Secondary Objective | | X |

## *5. Investigation Plan*

### 5.1 Study Design and background information

The Stroke AF study is a prospective, multi-site, randomized, controlled, non-blinded, post-market study, comparing the incidence rate of Atrial Fibrillation (AF) through 12 months between continuous cardiac monitoring and standard of care in subjects with a recent ischemic stroke (IS) of presumed known origin. No interim analyses are planned.

Most patients with IS are treated with anti-platelet (AP) therapy. However, patients with IS who have been diagnosed with AF are normally treated with long-term oral anticoagulation (OAC) as OAC is dramatically more effective at preventing recurrent IS than AP therapy in patients with AF. Therefore, detection of AF after IS crucial, as it results in an important change in the administration of antithrombotic therapy from AP to OAC, thereby reducing the risk of recurrent stroke. The CRYSTAL AF study demonstrated that continuous monitoring via the Reveal LINQ ICM is superior to standard of care for detecting AF after cryptogenic stroke. However, it remains unclear what the long-term rate of AF is in the IS patient population with a presumed known origin. The results of the Stroke AF clinical study will then provide evidence that could impact the treatment and long-term prognosis for patients classified as having an IS of presumed known origin by demonstrating the value of long term monitoring for AF in this patient population.

### 5.2 Eligibility

The inclusion and exclusion criteria to be enrolled into the study are as follows:

**Inclusion criteria**

- Subject has had an ischemic stroke believed to be due to small vessel disease, large vessel cervical or intracranial atherosclerosis within the past 10 days
- Subject is willing and able to undergo study requirements and expected to be geographically stable during study follow-up
- Subject is 60 years of age or older, or age 50 to 59 years plus a documented medical history of at least one of the following additional risk factors for stroke:
    - Congestive heart failure
    - Hypertension (Systolic Blood Pressure >140)
    - Diabetes Mellitus
    - Prior Stroke (>90 days ago, other than study qualifying index event)
    - Vascular disease (e.g. coronary artery disease, heart attack, peripheral artery disease and complex aortic plaque)

**Exclusion criteria**

- Subject has had a cryptogenic stroke
- Subject has had a cardioembolic stroke
- Subject has untreated hyperthyroidism
- Subject has had a recent myocardial infarction <1 month of stroke
- Subject has had a recent cardiac surgery (e.g. coronary artery bypass surgery (CABG)) <1 month of stroke
- Subject has a mechanical heart valve
- Subject has valvular disease requiring immediate surgical intervention
- Subject has documented prior history of atrial fibrillation or atrial flutter
- Subject has permanent indication for oral anticoagulation
- Subject has permanent contraindication to oral anticoagulation such that detection of AF would not change medical management, based on enrolling investigators judgment
- Subject is enrolled in a concurrent study that may confound the results of this study. Co-enrollment in any concurrent clinical study (including registries) requires approval of the study manager or designee.
- Subject's life expectancy is less than 1 year
- Subject is pregnant
- Subject has or is indicated for implant with a pacemaker, ICD, CRT, or an implantable hemodynamic monitor
- Subject with a medical condition that precludes the patient from participation in the opinion of the investigator

### 5.3. Treatment and Study Procedures

#### 5.3.1. Treatment

Subjects are randomized 1:1 to the continuous monitoring arm or the control arm. Subjects randomized to the continuous monitoring arm will have a Reveal LINQ ICM inserted within 10 days of the qualifying stroke and undergo continuous remote monitoring. Subjects randomized to the control arm will be followed per site specific standard of care.

#### 5.3.2. Study Procedures

Data will be collected via electronic Case Report Forms (eCRF), Reveal LINQ ICM device interrogation files and Medtronic CareLink transmissions. A web-based application tool, Remote Data Capture (RDC), will be used for data entry of the eCRF. Clinical data will be collected at baseline, 1, 6 and 12 months post-randomization, and then at recurring 6 months intervals until study exit. Additionally, subjects randomized to the continuous monitoring arm will have data collected at REVEAL LINQ ICM insertion, 3 and 9 months.

## *6. Determination of Sample Size*

### 6.1. Primary Objective

A total of 23 first events across the two treatment groups are required to demonstrate the primary objective of the study. Assuming 2% attrition from enrollment to randomization, approximately 486 subjects will be randomized. Subjects will be followed for 3 years, until end of device life or until official study closure, whichever occurs first. However, the primary objective of the study, upon which this sample size calculation is based, will be analyzed considering data up to the 12 months follow-up visit for all subjects in the study at the time of the analysis. This sample size calculation then assumes a follow-up time equal to 1 year and an accrual time equal to zero (data from all subjects is analyzed from randomization to the $12^{th}$ month follow-up visit, regardless of how long they've been in the study at the time of the analysis). Withdrawn subjects will not be replaced.

The assumptions used for the calculations were:

- Two-sided log-rank test
- Alpha = 0.05
- 85% power
- Annual Attrition rate = 10% (in each treatment group)
- Annual Crossover rate = 5% (in each treatment group)
- Follow-up Time = 1 year
- Event-free one-year survival rate of 92% in the continuous monitoring arm
- Event-free one-year survival rate of 98% in the control arm (hazard ratio of 4.13)

The procedure "Logrank tests (Lakatos) using proportion surviving" in PASS 2008 was used to calculate the number of events required to test this objective.

### 6.2. Secondary Objective

A number of 486 subjects randomized to achieve the primary objective and the assumptions below will also ensure 100% power to test the **secondary objective** of the study.

The assumptions used for the calculations were:

- Two-sided log-rank test
- Alpha = 0.05
- Annual Attrition rate = 10% (in each treatment group)
- Annual Crossover rate = 5% (in each treatment group)
- Accrual Time = 2 years
- Follow-up Time = 3 years
- Event-free survival rate of 80% in the continuous monitoring arm
- Event-free survival rate of 97% in the control arm (hazard ratio of 7.33)

The procedure "Logrank tests (Lakatos) using proportion surviving" in PASS 2008 was used to calculate the power to test this objective.

# *7. Statistical Methods*

## *7.1 Study Subjects*

### *7.1.1. Disposition of Subjects*

A subject is enrolled in the study when he/she signs and dates the Patient Informed Consent. The subject is then eligible for randomization assignment after study enrollment and verification of eligibility criteria. Enrollment, randomization and insertion of the Reveal LINQ ICM must occur within 10 days of the qualifying stroke event. Once a subject is assigned to a study arm, he is considered eligible. A flow chart similar to Figure 1 will be created to describe patient disposition.

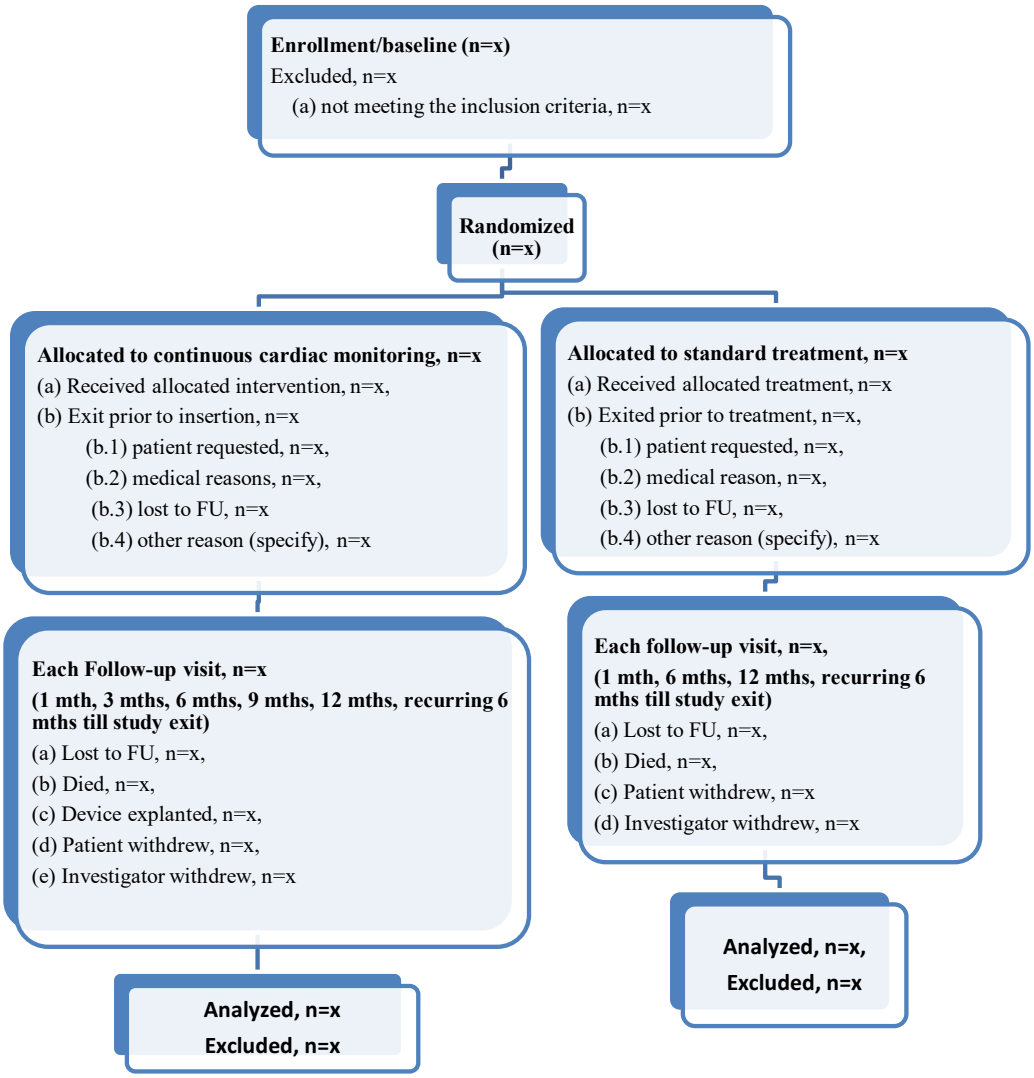
Study exits will be summarized according to exit reason. Violation of inclusion and exclusion criteria at baseline will be summarized for all enrolled patients.

The following tables will be considered to summarize patient disposition:

1. Number (%) of patients per center and randomization group
2. Number (%) of patients by visit and randomization group
3. Follow-up time per randomization group

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

**Figure 1: Patient Disposition Flow Chart**




### *7.1.2. Clinical Investigation Plan (CIP) Deviations*

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

### *7.1.3. Analysis Sets*

The following analysis sets will be used in this study:

**Enrollment Cohort:** All subjects who signed the informed consent and meet inclusion/exclusion criteria.

**Intent to Treat (ITT) Cohort:** Enrolled subjects who are randomized, according to the treatment arm to which they were randomized.

**Per Protocol (PP) Cohort:** All subjects who fulfill the protocol as follows:

- In ITT cohort (i.e., meets inclusion/exclusion criteria, gave informed consent, and was randomized)
- Exclude subjects that cross-over to the other arm
- Exclude subjects that are not programmed as follows at any point during the study (from CIP):
    - Reason for Monitoring = Cryptogenic Stroke
    - AF Detection Sensitivity = Balanced Sensitivity
    - Ectopy Rejection = Aggressive
    - AT/AF Recording Threshold = All Episodes
    - Type of AT/AF Detection = AF Only

The ITT Cohort will be used to analyze the primary and secondary objectives. The use of the PP Cohort will be specified in each evaluation objective.

Table 2 below shows the use of each analysis set:

**Table 2: Use of analysis cohorts**

| Analysis Item | Analysis Cohort |
|---|---|
| All baseline summaries (i.e.: demographic, medical history) | ITT |
| Primary Objective | ITT, PP |
| Secondary Objective | ITT, PP |
| Adverse Event summary | ITT |
| Device Deficiency summary | ITT |
| Deviation summary | ITT |

Summaries for subjects enrolled but not in the ITT set can be presented if necessary.

## *7.2. General Methodology*

Data summaries for categorical data will be summarized as count, e.g., number of patients, and/or number of events, and a percentage relative to the total number of patients/events. Continuous variables will be represented by mean, standard deviation, median and quartiles.

Time to event methods will be used for the primary and secondary objectives. P-values for hypothesis testing will be evaluated based on two-sided testing using a significance level of 0.05. Confidence intervals will be reported as two-sided 95% confidence intervals.

## 7.3. Center Pooling

The study is expected to be conducted in approximately 40 centers in the USA. The data from all centers will be pooled. There will be no minimum limit that each investigator must enroll. The maximum number of enrolled subjects per center is 50 subjects. In addition, a guidance was sent to sites stating that a maximum of 3 subjects with lacunar stroke (i.e. small vessel disease) may be enrolled at each site. This restriction is not in the CIP. Adjustment for center effect will not be included in statistical modeling.

## 7.4. Handling of Missing Data and Dropouts

The primary and secondary objectives use time to event methods, thus there will only be missing data for subjects with no follow-up time. Otherwise, each subject will have data to contribute to the analysis.

## 7.5. Adjustments for Multiple Comparisons

No adjustments for multiple comparisons will be made.

## 7.6. Demographic and Other Baseline Characteristics

Baseline variables such as demographics, physical examination, cardiac disease classification, testing results, qualifying stroke event, medications, modified rank scale, and NIH stroke scale information may be reported. Continuous variables will be reported as mean, standard deviation, median, minimum, maximum, and quartiles and categorical variables will be reported as number and percentage of subjects.

The summary tables will include a column for ITT treatment arm subjects, ITT control arm subjects, and all ITT subjects.

A summary table for subjects enrolled but not in the ITT cohort may be presented if necessary.

## 7.7. Treatment Characteristics

Treatment characteristic variables from the Insertion Procedure and System Modification CRFs will be reported. Continuous variables will be reported as mean, standard deviation, median, minimum, maximum, and quartiles. Categorical variables will be reported as number and percentage of subjects.

The summary tables will include a column for ITT treatment arm subjects who underwent the Reveal implant procedure.

## 7.8. Subgroup Analyses

Stroke Subgroups

Subgroup analysis for subjects with small vessel disease stroke and large vessel cervical or intracranial atherosclerosis stroke will be presented.

The source data for defining the subgroups come from the question "TOAST Classification of Subtypes of Acute Ischemic Stroke" on the BASELINE CRF.

- If the CRF value is "Large-artery atherosclerosis", then the subject is in the "large vessel cervical or intracranial atherosclerosis" subgroup
- If the CRF value is "Small-vessel occlusion (lacune)", then the subject is in the "small vessel disease stroke" subgroup

Kaplan-Meier curves will be generated for each randomization arm in each subgroup.

A Cox proportional hazards model will be used to test the interaction using the Wald test between treatment and subgroup.

AF Subgroups

Subgroup analysis for subjects with AF and without AF will be presented. AF events adjudicated by the CEC will be used to identify subgroups.

- If a subject has at least one AF event as adjudicated by the CEC during the follow-up period, then the subject is in the "AF" subgroup
- If a subject does not have any AF events as adjudicated by the CEC during the follow-up period, then the subject is in the "No AF" subgroup

The number of events and the number of subjects in each subgroup will be reported overall and within each randomization arm. OAC medications may also be considered in the temporal pattern. A logistic regression model will be used to test the interaction between treatment and subgroup.

Recurrent Stroke Subgroups

Subgroup analysis for subjects with recurrent stroke and without recurrent stroke will be presented. Stroke events adjudicated by the CEC will be used to identify subgroups.

- If a subject has at least one stroke event as adjudicated by the CEC during the follow-up period, then the subject is in the "Stroke" subgroup
- If a subject does not have any stroke events as adjudicated by the CEC during the follow-up period, then the subject is in the "No Stroke" subgroup

The number of events and the number of subjects in each subgroup will be reported overall and within each randomization arm. A logistic regression model will be used to test the interaction between treatment and subgroup.

## *7.9. Evaluation of Objectives*

### Primary Objective

The primary objective is to compare the incidence rate of AF through 12 months between the continuous monitoring arm vs control arm in subjects with a recent ischemic stroke of presumed known origin.

*i. Hypothesis*

$H_0$: $h(t) = h_T(t)$ for $t \leq 12$ months

$H_A$: $h_C(t) \neq h_T(t)$ for $t \leq 12$ months

where $h_T(t)$ and $h_C(t)$ are the hazard functions of first detected and adjudicated AF at time t for subjects with and without the Reveal LINQ diagnostics for AF, respectively. Hazard functions and survival functions are transformations of each other.

*ii. Endpoint Definition*

AF will be defined as an AF event lasting more than 30 seconds. The first AF episode detected and adjudicated by the endpoint adjudication committee will be used for this analysis.

*iii. Performance Requirements*

The null hypothesis will be rejected if the two-sided log-rank test p-value is less than 0.05.

*iv. Analysis Methods*

Arrhythmic episodes recorded by the subject's inserted/implanted device or from external monitoring will be adjudicated by the adjudication committee to determine if they meet the primary endpoint definition. Only first detected and adjudicated AF episodes within 12-months (365 days) will be included for analysis. Each subject's time to first detected and adjudicated AF will be defined as the time from randomization date to the date of first documented AF (i.e. the date of event per Reveal LINQ ICM, ECG, etc.) to meet the primary endpoint definition, and Kaplan-Meier curves will be generated for each randomization arm. Subjects who have not experienced an AF endpoint through 12 months will be censored at:

(1) their point of last contact, usable Reveal LINQ ICM interrogation or CareLink transmission if they occur before or at 12 months, whichever is later

or

(2) 12 months if their point of last contact, usable Reveal LINQ ICM interrogation or CareLink transmission go beyond 12 months.

A two-sided log-rank test will be performed to compare the rates between arms. The 12-month survival estimate with its 95% confidence interval will be reported for each arm. The hazard ratio estimate for the treatment effect with its 95% confidence interval will be reported.

The types of monitoring (i.e., wired monitor, wireless monitor, etc.) used to identify AF events in the control arm may be reported to further characterize the events.

*v. Determination of Patients/Data for Analysis*

The ITT cohort will be used to analyzed this objective. The PP cohort may be used to analyze this objective as a supplementary analysis.

*vi. Subgroup Analyses*

Subgroup analysis for subjects with small vessel disease stroke and large vessel cervical or intracranial atherosclerosis stroke will be presented. See section 7.9 for details.

## Secondary Objective

To compare the incidence rates of AF through the duration of study follow-up between study arms

*i. Hypothesis*

$H_0$: $h_C(t) = h_T(t)$ for $t > 0$ months

$H_A$: $h_C(t) \neq h_T(t)$ for $t > 0$ months

where $h_T(t)$ and $h_C(t)$ are the hazard functions of first detected and adjudicated AF at time t for subjects with and without the Reveal LINQ diagnostics for AF, respectively. Hazard functions and survival functions are transformations of each other.

*ii. Endpoint Definition*

AF will be defined as an AF event lasting more than 30 seconds. The first AF episode detected and adjudicated by the endpoint adjudication committee will be used for this analysis. This is the same definition used for the primary objective.

*iii. Performance Requirements*

This secondary objective will be tested in a hierarchical fashion. This means that if the primary objective is met, then this secondary objective will be tested. The null hypothesis will be rejected if the two-sided log-rank test p-value is less than 0.05.

*iv. Analysis Methods*

Arrhythmic episodes recorded by the subject's inserted/implanted device or from external monitoring will be adjudicated by the adjudication committee to determine if they meet the secondary endpoint definition. Only first detected and adjudicated AF episodes during all follow-up will be included for analysis. Each subject's time to first detected and adjudicated AF will be defined as the time from randomization date to the date of first documented AF (i.e. the date of event per Reveal LINQ ICM, ECG, etc.) to meet the secondary objective endpoint definition.

Each subject's time to first detected and adjudicated AF will be defined as the time from randomization date to the date of first documented AF (i.e. the date of event per Reveal LINQ ICM, ECG, etc.) as in the secondary endpoint definition above, and Kaplan-Meier curves will be generated for each randomization arm. Subjects who have not experienced an AF endpoint through the duration of the study follow-up will be censored at their point of last contact, usable Reveal LINQ ICM interrogation or CareLink transmission, whichever is later.

A two-sided log-rank test will be performed to compare the rates between arms. Survival estimates with 95% confidence intervals will be reported for each arm. The hazard ratio estimate for the treatment effect with its 95% confidence interval will be reported.

The types of monitoring (i.e., wired monitor, wireless monitor, etc.) used to identify AF events in the control arm may be reported to further characterize the events.

*v. Determination of Patients/Data for Analysis*

The ITT cohort will be used to analyze this objective. The PP cohort may be used to analyze this objective as a supplementary analysis.

*vi. Subgroup Analyses*

Subgroup analysis for subjects with small vessel disease stroke and large vessel cervical or intracranial atherosclerosis stroke will be presented. See section 7.9 for details.

## *7.10. Safety Evaluation*

Relatedness of adverse events using the CEC adjudication will be summarized using counts and percentages. Seriousness of adverse events using the Medtronic classification will be summarized using counts and percentages. Details of individual adverse events will be listed.

### *7.11. Health Outcomes Analyses*

Health outcomes will be compared between study arms using the EQ-5D questionnaire and symptoms collected in the symptoms assessments.

### *7.12. Changes to Planned Analysis*

Any changes to the data analysis methods described in the CIP and this Statistical Analysis Plan, and the justification for making the change, will be described in the clinical study report. Additional exploratory analyses of the data will be conducted as deemed appropriate.

## 8. Validation Requirements

Minimum validation requirements for the programs written to execute the analyses in this SAP:

- Primary objective: Level I (independent program)
- Secondary objective: Level II (peer review)
- AE tables and listings: Level II (peer review)
- Deviation table and listing: Level II (peer review)
- Patient disposition flowchart numbers: Level II (peer review)
- Other programs needed for final report analyses not specified: Level II (peer review)

Programs previously validated at Level I or Level II further modified with minor changes may be validated at Level III.

It is expected that Standard Operating Procedures will be followed for other programs that effect the programs written to execute the analyses in this SAP, such as data retrieval programs, dataset mapping programs, analysis dataset programs, etc.