Reveal LINQ Registry

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Statistical Analysis Plan

Clinical Investigation Plan Title	Reveal LINQ Registry
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1. Version History

Version	Summary of Changes	Author(s)/Title
1.0	Not Applicable, New Document	[redacted] / Sr. Statistician

2. List of Abbreviations and Definitions of Terms

Abbreviation	Definition
AE	Adverse Event
AF	Atrial Fibrillation
CIP	Clinical Investigation Plan
EMEA	Europe, Middle East & Africa
EKG	Electrocardiogram
HF	Heart Failure
ICM	Insertable Cardiac Monitor
SAP	Statistical Analysis Plan

3. Introduction

Medtronic, Inc. is sponsoring the Reveal LINQ Registry, a prospective, non-randomized, observational, multi-center, post-market, global clinical study.

The purpose of the Reveal LINQ Registry is to generate reliable long-term “real world” data of product performance, economic valuation, site-of-service procedural information, and will assist with identification of the Reveal LINQ Insertable Cardiac Monitor (ICM) in the care pathway. The primary endpoint will characterize clinical actions initiated by Reveal LINQ arrhythmia detection and estimate procedure-related acute infection rate.

The registry data is intended to benefit and support interests of patients, hospitals, clinicians, regulatory bodies, payers, and industry. Observational data collection in large populations over time provides an effective means of assessing product performance, patient safety and other clinical outcomes.

This post market registry is not required by any regulatory body. However, data collected in this registry may be submitted to a regulatory body for specific purposes when appropriate.

The study is expected to be conducted at approximately 100 study sites globally. Participating geographies are expected to include, but are not limited to: the United States, Europe Middle East and Africa (EMEA), and Japan. Subjects will be followed for 3 years or until study closure.

All subjects will be followed in-office in accordance with standard care practices of their respective care provider. In the version of the protocol associated with this document, follow-up data collection is required at minimum every 6 months post-insertion (previously 12 month follow-up intervals were required) and real time reporting is required for arrhythmia events and actions taken as a result of the Reveal LINQ ICM. This data may be collected via in-office subject clinic visit, remote monitor transmissions review, or chart review. Subjects are followed until subject death or exit, the implanted device becomes inactive or explanted, the subject has been followed for 3 years, or study closure.

The purpose of the Statistical Analysis Plan (SAP) is to describe the minimal requirements for statistical methods that will be used to analyze study objectives stated in the CIP.

4. Study Objectives

Primary Objectives:

- Characterize clinical actions initiated by Reveal LINQ arrhythmia detection
- Estimate procedure-related acute infection rate

Ancillary Objectives:

[redacted]

5. Investigation Plan

The Reveal LINQ Registry will characterize clinical actions and procedure related data in subjects implanted with Medtronic Reveal LINQ ICM.

The study is observational in nature.

Patients will be screened to ensure they meet all of the inclusion and none of the exclusion criteria prior to study enrollment. Ethics Committee approval of the Reveal LINQ Registry Clinical Investigation Plan and Informed Consent Form or Data Release Form must be obtained prior to enrolling patients in the study.

Subjects are considered enrolled in the study upon signing the Informed Consent Form or Data Release Form. In the version of the protocol associated with this document, enrollment of the subject must occur before insertion of the Reveal LINQ ICM. In previous versions of the protocol, subjects were allowed to enroll post-consent.

Inclusion criteria

- Subject or legally authorized representative provides written authorization and/or consent per institution and geographical requirements
- Subject is intended to have a Reveal LINQ ICM inserted in the next 30 days

- Subject consent prior to Reveal LINQ ICM insertion

Exclusion criteria

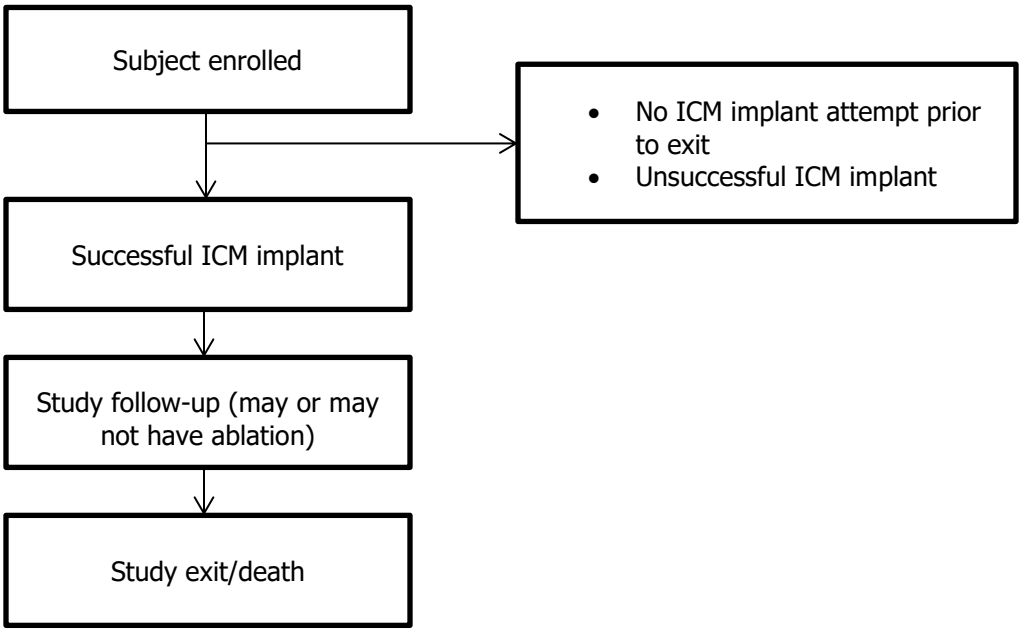
- Subject who is, or is expected to be inaccessible for follow-up
- Subject with exclusion criteria required by local law
- Subject is enrolled in a concurrent study that may confound the results of this study. Co-enrollment in any concurrent clinical study (including registries) requires approval of the study manager or designee.

6. Statistical Methods

6.1. Study Subjects

6.1.1. Disposition of Subjects

Subject flow will be summarized using STROBE guidelines as follows:



6.1.2. Clinical Investigation Plan (CIP) Deviations

Deviations from the CIP will be summarized by type.

6.1.3. Analysis Sets

A set of analysis datasets will be created based on forms (enrolled, procedure, follow-up (including deaths & exits), atrial fibrillation (AF) ablation, events, deviations). A flagging variable will indicate whether or not subject was enrolled prior to LINQ product insertion procedure.

Only subjects enrolled prior to LINQ insertion will be used in safety analyses of procedure-related adverse events and will comprise the Safety Analysis Set. For all other analyses, any study subjects may be used, comprising the Full Analysis Set.

6.2. General Methodology

Medtronic employees or designees will perform all statistical analyses. Additional exploratory analyses of the data may be conducted as deemed appropriate. Data analysis may be carried out throughout the study without having all enrolled subjects completing study required follow-ups.

6.3. Center Pooling

Centers/investigators will be pooled for analysis of study objectives.

6.4. Handling of Missing Data and Dropouts

Missing data imputation methods will not be used for the study objectives unless specified otherwise within the analysis methods.

As reflected in specific analysis methods below, any analyses related to infections could be biased by the fact that in prior versions of the protocol, subjects were allowed to be enrolled up to 30 days post insertion. Subjects who had an early infection (especially if it lead to an early explant) may have been less likely to have enrolled post-procedure. Thus, subjects enrolled after day of insertion will not be included in analyses of procedure-related adverse events.

6.5. Adjustments for Multiple Comparisons

No adjustments are planned for multiple comparisons.

6.6. Demographic and Other Baseline Characteristics

Baseline characteristics and relevant medical history will be collected on eCRFs for all enrolled subjects. Baseline characteristics will be summarized for all enrolled subjects. Baseline variables to be summarized may include, but are not limited to: age, sex, race, height, weight, LVEF, NYHA, medical history (symptoms), cardiovascular surgical/intervention history, general cardiovascular history, spontaneous arrhythmia history, diagnostic/monitoring history and baseline medications,

For continuous variables, mean, standard deviation, median, and range will be reported. For categorical variables, frequency and percentage will be reported.

6.7. Treatment Characteristics

ICM procedure characteristics and exposure to study product will be collected on eCRF for all attempted insertions. Procedure characteristics to be summarized may include, but are not limited to: referring physician type, procedure clinician type, procedure location type, reason for ICM insertion, procedure time, anesthesia usage, insertion tools, monitor suturing, wound closure method, infection control methods, monitor position/orientation.

For continuous variables, mean, standard deviation, median, and range will be reported. For categorical variables, frequency and percentage will be reported.

6.8. Interim Analyses

Abstracts, posters and presentations are expected based on this dataset throughout the study. No type I error correction or alpha spending will be performed for analyses conducted in support of publications occurring while the study is ongoing.

6.9. Evaluation of Objectives

Primary Objective #1

Characterize clinical actions initiated by Reveal LINQ arrhythmia detection.

i. Analysis Methods

This objective is descriptive in nature. New onset of arrhythmias diagnosed as results of ICM data review, and the subsequent clinical actions taken are reported through CRFs.

Study sites will review device recorded arrhythmia episodes via remote transmission or at a regularly scheduled clinic visit. Clinical treatments may be prescribed upon diagnosis.

Summary statistics will be obtained for frequencies of diagnosis and treatment. Frequencies of each action taken, such as medication changes, surgical intervention, new cardiac device implant, etc. will be obtained.

Endpoint definition: First incidence of onset of new arrhythmias for each type diagnosed as result of ICM data review during the study, regardless of whether or not the patient had arrhythmias also reported in their medical history. The subsequent clinical actions taken are reported through Follow-up CRFs.

Follow-up CRF question 9) "Were any new diagnoses made as a result of review of ICM data during this visit" where arrhythmia type is selected, considering only the *first* diagnosis of each type for the subject and linking to Treatment log "Treatment Type" with Treatment Trigger checked as being "Monitor Data" and where treatment date is on or after first diagnosis of event.

Example output shell:

Arrhythmia type	**Number of patients (%)**
Atrial Fibrillation	N (%)
Bradycardia	N (%)
Tachycardia	N (%)
Overall total	**N (%)**

Treatment Type **Arrhythmia type**	AF Ablation	Electrical cardio-version	Pharma-cological cardio-version	Percutaneous Coronary Intervention	CABG	Medication	IPG implant	ICD implant	CRT-P implant	CRT-D implant	Other cardiac treatment

Atrial Fibrillation	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
Bradycardia	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
Tachycardia	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
Overall total	**N (%)**	**N (%)**	**N (%)**	**N (%)**	**N (%)**	**N (%)**	**N (%)**	**N (%)**	**N (%)**	**N (%)**	**N (%)**

Additional analysis

An additional sensitivity analysis will be performed to account for the follow-up time of subjects in study and characterize the incidence of first arrhythmias and actions taken by arrhythmia type. This sensitivity analysis will be done to account for potential differences in reporting for those subjects enrolled after insertion who may not have fully reported actions taken between insertion and consent.

ii. Determination of Subjects/Data for Analysis

Any enrolled subjects who are diagnosed with an arrhythmia detected by Reveal LINQ will be included in analysis.

iii. Sample Size

There is no statistical hypothesis formulated for this analysis therefore there is no sample size for this objective.

Primary Objective #2

Estimate procedure-related acute infection rate (up to 30 days post insertion procedure).

i. Analysis Methods

The post insertion procedure visit can be either in office visit or CareLink visit. Infection events will be reported by study sites upon awareness. The acute infection rate will be calculated by dividing the number of subjects with infection events within 30 days post insertion procedure by the number of subjects in the risk set (the analysis cohort). Two-sided 95% confidence interval will be calculated using the Exact Binomial method. Additionally, rate for infection SAE may be calculated (see CIP v2 Appendix for SAE definition).

Also, since infection rates may be quite small, a sensitivity analysis will be performed using the Wilson Interval.

Endpoint definition: The numerator will be number of subjects with Infection (Question 4 “Classify the event/primary diagnosis” on Event CRF is marked as “Infection”) where days to event onset is less than or equal to 30 day post-insertion. Denominator as per Determination of Subjects/Data for Analysis below.

Infection is considered serious if any of the questions under the “Seriousness: Did the adverse event meet any of the following criteria” header on the event CRF are answered as “Yes”

Example SAS code:

```
PROC FREQ data=events;
        TABLE InfectionAcute / alpha=0.05 binomial (exact);
RUN;

PROC FREQ data=events;
        TABLE InfectionAcute / alpha=0.05 binomial (Wilson);
RUN;
```

ii. Determination of Subjects/Data for Analysis

A subject will be included in the analysis cohort for this objective as long as the subject was enrolled in the study prior to implant and one of the following criteria is met:

a) A subject who undergoes a Reveal LINQ insertion procedure and completes a minimum of one visit at a time point ≥ 30 days post insertion procedure will be included for the analysis.

b) A subject will be included in the analysis if an infection event is reported regardless if the subject has completed 30 day follow-up.

c) A subject with a Reveal LINQ device explanted after a successful implant procedure that occurred prior to 30 days post insertion procedure will be included in the analysis cohort.

d) A subject who undergoes a Reveal LINQ implant procedure without having a Reveal LINQ device chronically implanted will be included in the analysis with a confirmation of patient status at ≥ 30 days post implant.

Ancillary Objectives

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6.10. Safety Evaluation

Adverse events will be summarized by relatedness (procedure & component (ICM, insertion tool, incision tool, other)), seriousness, and event primary diagnosis.

6.11. Health Outcomes Analyses

No health outcomes analyses are planned as part of this study.

6.12. Changes to Planned Analysis

Changes and clarifications to planned analysis from CIP are as noted.

Primary objective 1:

- Clarified only consider *first* incidence of onset of new arrhythmia during the study *regardless of* whether or not subject has *history* of incidence.

- Added a sensitivity analysis that considers follow-up time. This is to account for possibility of missed reporting of actions taken for subjects who enrolled after insertion.

Primary objective 2:

- Clarified "Determination of Subjects" so that subject *must have enrolled in the study prior to implant* and met one of the four (A-D) criteria. CIP only requires consent for subjects in bullet A, and does not require that consent be given *prior* to insertion.
- Added a sensitivity analysis using Wilson interval, since infection rates may be quite small.

Ancillary objective 1

[redacted]

Ancillary objective 2

[redacted]

Ancillary objective 4

[redacted]

- [redacted]

6.13. Handling of non-CRF data

This study will collect the results of diagnostic imaging (for e.g. EKG, CT scan) conducted for subjects from the sites when available. These images are not part of the CRF data collection. Images will be sent to the study via Clinical Transfer and stored in a designated shared drive. CareLink will store device data that is uploaded from the device. For statistical analysis of study objectives, these data will not be used. However, these files may be reviewed for data completeness and data quality.

7. Validation Requirements

All analysis of primary objectives will have level I validation.

All analysis of ancillary objectives will require level II (or better) validation.

8. References

N/A