Medtronic

Statistical Analysis Plan

Clinical Investigation Plan Title	Reveal LINQ™ for Chronic Obstructive Pulmonary Disease (COPD)
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Confidentiality Statement

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1. Version History

Version	Summary of Changes	Author(s)/Title
1.0	• Not Applicable, New Document	[redacted] Principal Statistician CRHF Clinical Research Statistics

2. List of Abbreviations and Definitions of Terms

Abbreviation	Definition
AE	Adverse event
BCSS	Breathlessness, Cough, and Sputum Scale
BNP	Brain natriuretic peptide
CIP	Clinical Investigation Plan
COPD	Chronic Obstructive Pulmonary Disease
CV	Cardiovascular
EAC	Event Adjudication Committee
eCRF	Electronic case report form
HF	Heart failure
ICM	Insertable cardiac monitor
IDE	Investigational Device Exemption
LINQ HF RAMware	Investigational software downloaded to the LINQ™ device in study subjects
MedDRA	Medical Dictionary for Regulatory Activities
PRN	'pro re nata' – as needed
RR	Respiration rate
SAE	Serious adverse event
UADE	Unanticipated Adverse Device Effect

3. Introduction

Medtronic, Inc. is sponsoring the Reveal LINQ™ for COPD study. This study will be referred to by LINQ™ for COPD in this document. This is a Non-Significant Risk Investigational Device Exemption (IDE), prospective, non-randomized, multi-center, observational, pre-market clinical study.

The purpose of the study is to collect and characterize Reveal LINQ™ derived data from patients with COPD by assessing the relationship between changes in LINQ™ derived data with COPD exacerbation events. The study will also collect information regarding COPD related clinical events during the same period.

The study is utilizing the Reveal LINQ™ device with an investigational LINQ-HF RAMware download. The Reveal LINQ™ device is designed to automatically record the occurrence of ventricular tachyarrhythmias, bradyarrhythmias, pause, atrial tachyarrhythmias, and atrial fibrillation. The patient is

also able to activate the insertable cardiac monitor (ICM) to record their cardiac rhythm while experiencing or immediately after a symptomatic event. In addition, the LINQ™-HF RAMware enables the hardware to record and store impedance, temperature, activity, respiration rate (RR) interval, R-wave amplitude, posture change count (based on z-axis accelerometer values) and x, y, and z-axis accelerometer measurements periodically.

Following consent, subjects will undergo a baseline assessment followed by the LINQ™ ICM device insertion procedure. Following insertion, subjects will complete a daily diary entry, which includes answering the Breathlessness, Cough, and Sputum Scale (BCSS) Questionnaire and recording any pro re nata (PRN) medications. Additionally, subjects will complete telephone follow-up visits every three months post device insertion (visits may also be conducted in-person if desired). The 6-month follow-up visit however, will need to be conducted in office. Study subjects will be followed until the last enrolled subject reaches their 12-month visit or until official study closure defined as when Medtronic and/or regulatory requirements have been satisfied per the Clinical Investigation Plan and/or by a decision by Medtronic or regulatory authority, whichever occurs first.

This Statistical Analysis Plan has been designed to document, for internal use, the LINQ™ for COPD study design and the planned analyses to be included in a final report.

4. Study Objectives

The study objective has been defined to characterize the Reveal LINQ™ derived data in patients with COPD related to COPD events.

The study objective will be characterized, and a final study report will be completed after the last enrolled subject is followed for 12-months or study closure, whichever occurs first.

4.1 Primary Objective

The primary objective is to characterize Reveal LINQ™ derived data from patients with COPD by assessing the relationship between changes in LINQ™ derived data with subsequent COPD events.

COPD event is defined as an adverse event where the underlying COPD condition exacerbates beyond normal day-to-day variations, where an increase in dyspnea, cough, and/or sputum production presents with acute onset and necessitates supplementing regular COPD medications with antibiotics for respiratory pathogens and/or steroids.

5. Investigation Plan

The LINQ™ for COPD is a prospective, non-randomized, multi-center, observational, pre-market clinical study. The study may enroll up to 100 COPD subjects at up to 10 sites in the US, with no more than 20 subjects enrolled per site. Study subjects will be followed until the last enrolled subject reaches their 12-month visit or until official study closure defined as when Medtronic and/or regulatory requirements have been satisfied per the Clinical Investigation Plan and/or by a decision by Medtronic or regulatory authority, whichever occurs first. Accordingly, the expected total study duration is approximately 25 months, representing approximately 12 months of patient enrollment and 12 months of subject follow-up with 1 month between enrollment and insertion. All Reveal LINQ™ system and procedure-related adverse events will be collected and reported per the study protocol. In addition, all SAEs, all Respiratory related AEs (regardless of seriousness) and all Cardiovascular related AEs (regardless of seriousness) will be collected and reported per study protocol.

Following consent, subjects will undergo a baseline assessment followed by the LINQ™ ICM device insertion procedure. Following insertion, subjects will complete a daily diary entry, which includes answering the BCSS Questionnaire and recording any PRN medications. Additionally, subjects will complete telephone follow-up visits every three months post device insertion (visits may also be conducted in-person if desired). The 6-month follow-up visit however, will need to be conducted in office. All enrolled subjects will be followed until study closure. A study flowchart is shown in Figure 1.

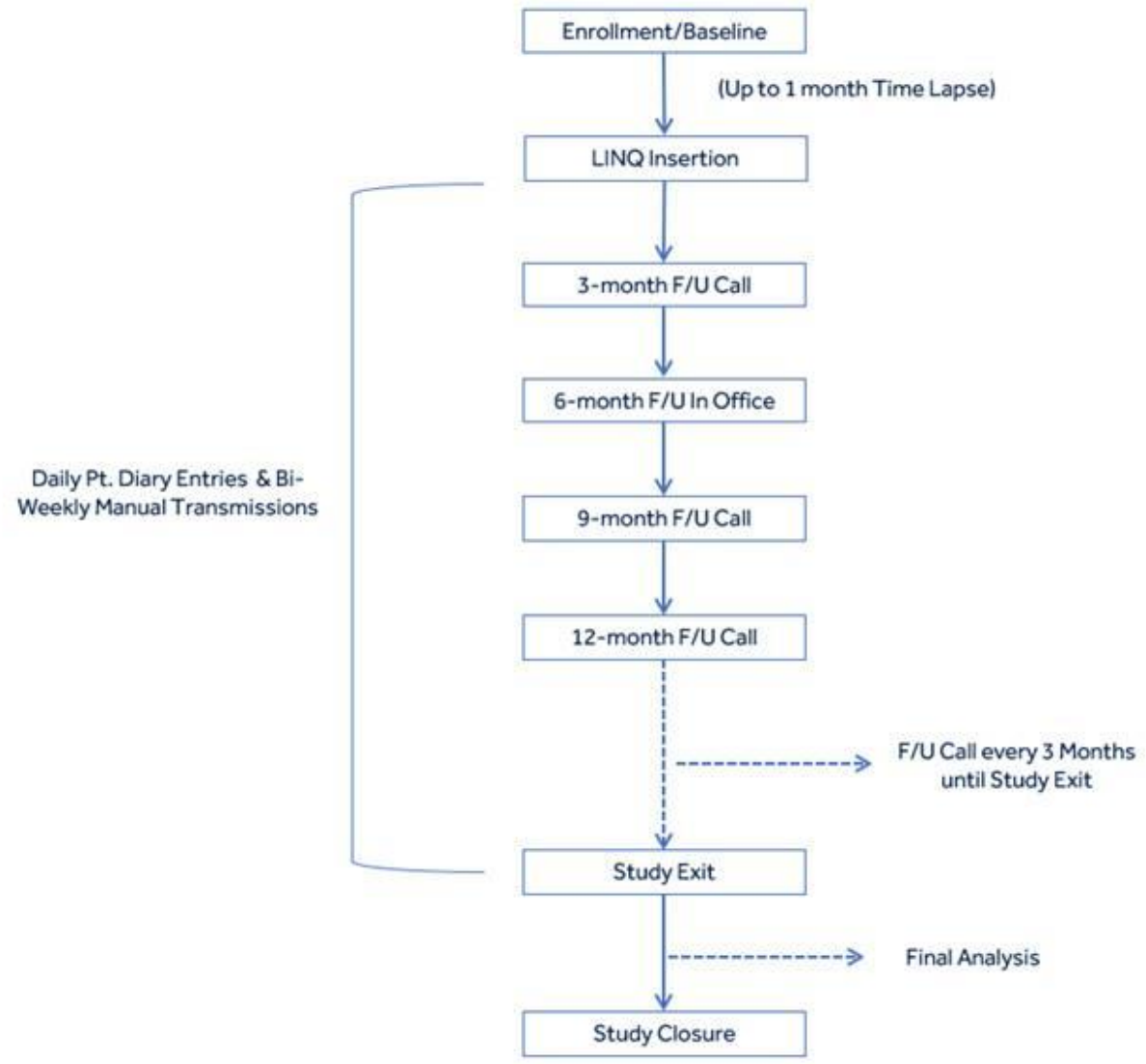

Figure 1: Study Flowchart

The subject population for the LINQ™ for COPD study is COPD patients who are known to have frequent exacerbations (at least two in the past year). Inclusion and Exclusion criteria are listed below.

5.1 Inclusion Criteria

- Patient is ≥ 45 years old
- Patient (or patient's legally authorized representative) is willing and able to provide written informed consent
- Patient is willing and able to comply with the protocol, including follow-up visits, electronic diary submissions and CareLink transmissions
- FEV_1 (post bronchodilator) ≤ 70% of predicted

- Current or former smoker with lifetime cigarette consumption of ≥ 10 pack-years
- Two COPD exacerbations within the previous 12 months defined as taking antibiotics and/or prednisone for respiratory symptoms, hospitalization or emergency department visit for respiratory illness.
- The patient's medical records must be accessible by the enrolling site over the follow-up period

5.2 Exclusion Criteria

- Less than 30 days from treatment from a COPD exacerbation as defined as taking antibiotics and/or prednisone for respiratory symptoms, hospitalization or emergency department visit for respiratory illness.
- Less than 30 days from treatment from a HF event as defined as any cardiovascular-related (including hypervolemia) Health Care Utilizations (HCUs) for any one of the following events.
    - Admission with primary diagnosis of HF
    - Intravenous HF therapy (e.g. IV diuretics/vasodilators) or ultrafiltration at any one of the following settings:
        - Admission with secondary/tertiary diagnosis of HF
        - Emergency Department
        - Ambulance
        - Observation Unit
        - Urgent Care
        - HF/Cardiology Clinic
- Active respiratory infection being treated by health care professional.
- Class IV heart failure
- Clinical diagnosis of unstable angina, asthma, bronchiectasis, or cystic fibrosis
- Any concomitant condition that might endanger the patient through participation in the study or interfere with study procedures, as assessed by the investigator
- Patient is pregnant (all females of child-bearing potential must have a negative pregnancy test within 1 week of enrollment)
- Patient is enrolled in another study that could confound the results of this study, without documented pre-approval from a Medtronic study manager
- Patient has an existing or planned implantation of Medtronic IPG, ICD, CRT-D or CRT-P device in the near future
- Patient has an existing and active insertable cardiac monitor, regardless of manufacturer
- Concurrent disease with life expectancy less than 1 year

6. Determination of Sample Size

There are no sample size requirements as this is an observational study with no hypothesis for the study objective. A sample size of up to 100 enrolled subjects was selected assuming sufficient data can be collected from this cohort to explore the relationship between changes in LINQ™ derived data with COPD events.

According to a review by Seemungal et al., the annual rates of COPD exacerbations were estimated to be as low as 0.5 to a high of 3.5 exacerbations per patient from several studies, and hospitalization rates ranged from as low as 0.09 to 2.4 per patient per year.[1] This study requires that a subject should have 2 COPD exacerbations within the previous 12 months as one of the inclusion criteria. Assuming the COPD exacerbation rate remains as 2 COPD exacerbations per patient year after subjects are enrolled, a group of 60 enrolled subjects being followed up for 12 months after successful insertion of Reveal LINQ™ device and download of LINQ™ HF investigational RAMware would expect to have 120 COPD exacerbations. Assuming 50% of the COPD exacerbations would meet the study definition of "COPD event", a total of 60 COPD events would be expected.

A COPD event is defined as an adverse event where the underlying COPD condition exacerbates beyond normal day-to-day variations, where an increase in dyspnea, cough, and/or sputum production presents with acute onset and necessitates supplementing regular COPD medications with antibiotics for respiratory pathogens and/or steroids.

7. Statistical Methods

7.1 Study Subjects

7.1.1 Disposition of Subjects

This is a single-arm study. A subject will be considered enrolled in the study once they sign and date the Informed Consent. Following consent, subjects will undergo a baseline assessment followed by the Reveal LINQ™ ICM device insertion procedure. After the device is inserted, the LINQ™ HF investigational RAMware will be downloaded to the device via the 2090 programmer. Following insertion, subjects will also complete a daily diary entry, which includes answering the BCSS Questionnaire and recording any PRN medications. Subjects will complete their bi-weekly manual device transmissions and follow-up visits every three months post device insertion. Subjects will be followed until the last enrolled subject reaches their 12-month visit or until study closure, whichever occurs first. A STROBE diagram will show each of these stages of follow-up with categories for completed visits, missed visits, deaths and exits.

7.1.2 Clinical Investigation Plan (CIP) Deviations

Study deviations will result in corresponding Study Deviation eCRFs being completed. These deviations will be summarized with descriptive statistics including, for each type of deviation, number of occurrences in the study, and the number of subjects experiencing each type of deviation.

7.1.3 Analysis Sets

Enrolled subjects who have Reveal LINQ™ device successfully inserted, the LINQ™ HF investigational RAMware successfully downloaded to the device and have completed a first successful CareLink transmission will be included in the analysis of the primary objective.

7.2 General Methodology

Data analysis will be performed by a Medtronic statistician or designee, and after all subject exit the study. All analyses will be performed on an "As Treated" basis. Any change to the data analysis methods

described in the protocol will require an amendment only if it changes a principal feature of the protocol. Any other change to the data analysis methods described in the protocol, and the justification for making the change, will be described in the clinical study report.

7.3 Center Pooling

Due to the feasibility nature of this study and reduced sample size, statistical comparisons of sites' performance will not be performed.

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

Missing data will not be imputed. An adjudicated COPD event will be considered in the analysis to assess changes in LINQ™ derived data if it has device data before and after the event onset date.

7.5 Adjustments for Multiple Comparisons

No adjustment for multiple comparisons will be made since this is a single-arm study.

7.6 Demographic and Other Baseline Characteristics

Baseline data such as demographics, medical history, physical exam (heart rate, blood pressure, weight, spirometry assessment, etc.), and blood measurements (Creatinine, BNP, NT-pro BNP, White Blood Cells and Eosinophils) will be summarized using descriptive statistics.

For categorical data such as gender, counts and percentages will be employed, while for continuous variables such as age, means, standard deviation, quartiles, minimum, and maximum will be provided. These statistics will be provided both for all enrolled subjects and for the subset of subjects who will be analyzed for the primary objective described in section 7.1.3.

7.7 Treatment Characteristics

Descriptive statistics will be used to summarize all procedure information collected, including

- Procedure location
- Location of inserted device (e.g. parallel to sternum over 4th intercostal space)
- Number of repositioning/modifications during the insertion procedure
- Whether device was sutured
- Closure method used (e.g. staple(s), suture(s))
- Whether topical skin adhesive/Dermabond (Registered) was applied per its labelling if used
- Whether LINQ HF Investigational RAMware was successfully downloaded

Additionally, the percentage of subjects on CV and pulmonary medications will be assessed as of each follow-up visit.

7.8 Interim Analyses

No interim analyses are planned for this study. Therefore, there are no criteria for early termination based on statistical evidence.

7.9 Evaluation of Objectives

The primary objective is to characterize Reveal LINQ™ derived data from patients with COPD by assessing the relationship between changes in LINQ™ derived data with subsequent COPD events.

7.9.1 Hypothesis

There is no statistical hypothesis for this objective.

7.9.2 Endpoint Definition

The COPD events as adjudicated by the Event Adjudication Committee (EAC) will be used in the analysis. In the case where a subject has multiple COPD events per EAC adjudication during the study, all the COPD events of the subject will be included in the analysis.

A COPD event is defined as an adverse event where the underlying COPD condition exacerbates beyond normal day-to-day variations, where an increase in dyspnea, cough, and/or sputum production presents with acute onset and necessitates supplementing regular COPD medications with antibiotics for respiratory pathogens and/or steroids.

7.9.3 Analysis Methods

Data from multiple study components will be collected in this study, of which the Reveal LINQ™ HF derived data is of the most interest. This includes subcutaneous electrocardiogram, impedance, temperature, accelerometer and patient activity measurements.

Descriptive statistics such as mean and standard deviation for continuous variables and count and proportion for categorical variables will be used to summarize the derived data from Reveal LINQ™ HF. The relationship between changes in LINQ™ derived data and COPD events per EAC adjudication will be evaluated. Specifically, for each subject that has experienced at least one COPD event per EAC adjudication, the average daily measurements of LINQ™ derived data before and after a COPD event will be plotted to identify patterns and signals related to the occurrence of the COPD event.

In addition, exploratory survival analyses for time to first COPD event through 12-months of follow-up such as a Kaplan-Meier curve and Cox proportional hazards regression models with independent variables such as demographics and comorbidities will be included.

Each subject's time to first detected and adjudicated COPD event will be defined as the time from insertion date to the onset date of first COPD event. Subjects who have not experienced a COPD event 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 (374 days) if their point of last contact, usable Reveal LINQ ICM interrogation or CareLink transmission go beyond 12 months.

Survival estimates and hazard rate with 95% confidence intervals will be reported.

7.9.4 Determination of Subjects/Data for Analysis

Enrolled subjects who have Reveal LINQ™ device successfully inserted and have the LINQ™ HF investigational RAMware successfully downloaded to the device and who have completed a first successful CareLink transmission.

7.10 Safety Evaluation

All adverse events that are Reveal LINQ™ system-related or procedure-related are reported with onset occurring between a subject's consent and exit will be summarized. An overall summary table will be generated that shows the number of events and number and percentage of subjects that experience adverse events for each category of seriousness, complication/observation status, whether the event is an Unanticipated Adverse Device Effect (UADE), and each level of relatedness to the procedure and/or Reveal LINQ™ system.

Adverse events will each be assigned a Medical Dictionary for Regulatory Activities (MedDRA) term and will be summarized by MedDRA preferred term. The statistics will include the number of adverse events assigned that term, the corresponding number and percentage of subjects who experienced such an adverse event. Separate tables will be done in this way for all adverse events, for just the procedure-related adverse events, and the Reveal LINQ™ system-related adverse events.

A listing table of all adverse events will also be generated. Each row will contain the subject ID, the MedDRA preferred term, the onset date and days post-insertion, whether the event was a complication or observation, whether the event was serious, the relatedness to the procedure or system (if any), a summary of actions taken in response to the event, and the outcome of the event (whether it was resolved, and the date of resolution).

7.11 Changes to Planned Analysis

There are no changes to the CIP planned analysis. However, this document describes more analyses.

8. Validation Requirements

Due to the descriptive nature of the analyses, level II validation will be performed on programs related to the primary objective, as well as adverse events. Level II validation may occur for programs summarizing baseline demographics, study deviations, follow-up compliance, and study exits.

9. References

1. Seemungal et. Al. Exacerbation rate, health status and mortality in COPD – a review of potential interventions, International Journal of COPD, 2009.