Medtronic

Clinical Study Document Approval Form

Study Name/Identifier	Reveal LINQ Heart Failure (HF)
Document Name	Clinical Investigation Plan Version 2.0
Document Reference Number	N/A

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Medtronic

Reveal LINQ™ Heart Failure (HF)

Clinical Investigation Plan

Version 2.0

26 Oct 2016

Regional Sponsors and Contacts
United States (Sponsor) Medtronic, Inc. 8200 Coral Sea Street NE Mounds View, MN U.S.A. 55112 1-800-328-2518

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1 ADMINISTRATIVE INFORMATION

1.1 List of Abbreviations

AE: Adverse Event
ADHF: Acute decompensated heart failure
AF: Atrial Fibrillation
AHF: Acute Heart Failure
CEC: Clinical Events Committee
CIP: Clinical Investigational Plan
CRF: Case Report Form
CRT: Cardiac Resynchronization Therapy
CTA: Clinical Trial Agreement
eCRF: electronic Case Report Form
ECG: Electrocardiogram
EF: Ejection Fraction
FDA: Food and Drug Administration
GCP: Good Clinical Practice
HCU: Healthcare Utilization
HF: Heart Failure
ICD: Implantable Cardioverter-Defibrillator
ICM: Insertable Cardiac Monitor
IPG: Implantable Pulse Generator
IRB: Institutional Review Board
MDT: Medtronic
PIC: Patient Informed Consent
RAMware: Software downloaded onto LINQ™ device
RDC: Remote data capture
RPIS: Report of Prior Investigations
SAE: Serious Adverse Event
SCD: Sudden Cardiac Death

1.2 Sponsor Contact Information

Medtronic contact information is provided below. This information is subject to change during the course of the clinical study. Periodic updates to study contact information will be sent to the centers as needed. A complete listing of the monitors will be maintained in a separate cover.

Table 1: Study Sponsor Contact Information

Study sponsors and contacts	
Worldwide clinical study leader Kara Southall, Pr. Clinical Research Specialist 8200 Coral Sea Street NE Mounds View, MN U.S.A. 55112 Phone: 612-963-2640 Email: kara.l.southall@medtronic.com	*Worldwide monitoring leader* Taryn Randall, Clinical Monitoring Manager 8200 Coral Sea Street NE Mounds View, MN U.S.A. 55112 Phone: 763-250-0785 Email: taryn.randall@medtronic.com

1.3 CROs and Core Labs

CRO and core lab information is provided below. This information is subject to change during the course of the clinical study. Periodic updates to CRO and core labs information will be sent to the centers as needed.

Table 2: CRO and Core Lab Information

Contact Information	Duties performed
Cognizant Technology Solutions 500 Frank W. Burr Blvd. Teaneck, NJ 07666 Direct Phone: (201) 801-0233 Direct Fax: (201) 801-0243	• Development of study electronic case report forms, edit checks, and study management reports. • Review of electronic case report forms, management of discrepancies, and coding of medications and deviations.

1.4 Steering Committee

Steering Committee contact information is provided below.

Table 3: Steering Committee Contact Information

Name	Contact Information
Sanjeev Gulati, MD	Sanger Heart & Vascular Institute/ Carolinas HealthCare System Charlotte, NC [redacted]
Michael Zile, MD	Medical University of South Carolina Charleston, SC [redacted]
Mandeep Mehra, MD	Brigham and Women's Hospital Boston, MA [redacted]
Gregg Fonarow, MD	University of California Los Angeles Los Angeles, CA [redacted]

2 SYNOPSIS

TITLE

Reveal LINQ™ Heart Failure (HF) Clinical Study

PURPOSE

The LINQ™ HF study is a Non-Significant Risk Investigational Device Exemption (IDE) study. The study is utilizing the Reveal LINQ™ device with an investigational LINQ™ HF RAMware download. [redacted]

The purpose of the LINQ™ HF study is to characterize Reveal LINQ™ derived data from patients with heart failure by assessing the relationship between changes in LINQ™ derived data and other physiologic parameters with subsequent acute decompensated heart failure (ADHF) events. The study will also collect information regarding HF related clinical events during the same period.

DESIGN

The study is a prospective, non-randomized, multi-center, observational, pre-market clinical study. The study is expected to be conducted at up to 30 centers in the United States. Up to 300 subjects will be enrolled to achieve approximately 40 heart failure events (no more than two per subject will contribute to the cumulative total). Study subjects will be followed for up to 3 years post-insertion 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. The expected study duration is approximately 4 years representing 1.5 years of enrollments and 2.5 years of follow-up.

MEDICAL DEVICE

Table 4: System Component Information

Model Number	Component	Manufacturer	Investigational or Market-released
LNQ11	Reveal LINQ™ Insertable Cardiac Monitor	Medtronic	Market-Released*
LNQ11	Incision Tool	Medtronic	Market-Released
LNQ11	Insertion Tool	Medtronic	Market-Released
SW026	2090 Programmer	Medtronic	Market-Released*
Not Applicable	Reveal LINQ™ RAMware titled: LINQ HF Research System, Rev 1.0, and subsequent versions as they are released**	Medtronic	Investigational
PA96000	Patient Assistant	Medtronic	Market-Released
24950	MyCareLink® Home Monitor	Medtronic	Market-Released
DR220	Holter	NorthEast Monitoring, Inc.	Market-Released

*The LINQ™ device and the 2090 programmer are market-released, but once the investigational LINQ™ HF RAMware is downloaded into the devices, they are considered investigational.

**Subjects will receive the most current approved version of the investigational RAMware at the time of their device insertion. In the case that a new RAMware version is released during the course of the study, subjects previously receiving an older version of the RAMware will receive an upgrade to the new version.

OBJECTIVE

Primary Objective: The primary objective is to characterize Reveal LINQ™ derived data from patients with heart failure by assessing the relationship between changes in LINQ™ derived data and other physiologic parameters with subsequent ADHF events.

SUBJECT POPULATION

The subject population for the LINQ™ HF study is patients with heart failure with a NYHA Class III. Inclusion and Exclusion criteria are listed below.

INCLUSION CRITERIA

- Patient is 18 years of age or older
- 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 and Carelink transmissions
- Patient is NYHA Class III, per most recent assessment or at any time within 30 days prior to enrollment
- Patient had a HF event (HF event defined as meeting any one of the following three criteria):
    1. Admission with primary diagnosis of HF within the last **6 months**, OR
    2. Intravenous HF therapy (e.g. IV diuretics/vasodilators) or ultrafiltration at any one of the following settings within the last **6 months**:

- Admission with secondary/tertiary diagnosis of HF
- Emergency Department
- Ambulance
- Observation Unit
- Urgent Care
- HF/Cardiology Clinic
- Patient's Home, OR

3. Patient had the following BNP/NTpro-BNP within the last **3 months**:
   - If EF ≥ 50%, then BNP> 200 pg/m**l** or NTpro-BNP > 400 pg/m**l** OR
   - If EF is <50%, then BNP> 400 pg/m**l** or NTpro-BNP > 800 pg/m**l**

EXCLUSION CRITERIA

- 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 severe valvular heart disease as defined by hemodynamically significant valve stenosis and/or prosthetic heart valve
- Patient has existing IPG, ICD, CRT-D or CRT-P device
- Patient has severe renal impairment (eGFR <25mL/min)

CLINICAL PROCEDURES

A patient will be considered enrolled in the study once they sign and date the patient informed consent (PIC). The subjects will be followed via 1, 6 and 12 month in-office visits as well as monthly device transmission/healthcare utilization (HCU) calls. Study subjects will be followed for up to 3 years post-insertion 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. Table 4 below describes the required data collection and study procedures at the subject's visits.

Table 5: Data Collection and Study Procedure Requirements at Subject Visits

STUDY PROCEDURE	Baseline	LINQ Insertion	1 Mo Visit	6 Mo and 12 Mo Office Visit	Device Transmission/ HCU Monthly Call	Study Exit
Patient Informed Consent	X					
Inclusion/Exclusion Assessment	X					
Medical History	X					
Demographics	X					
Physical Exam	X		X	X		
Medication Assessment	X		X	X		X
Laboratory results	X			X		
Symptoms and Temperature (via ear is recommended)			X	X		
Final system configuration		X				
Insertion procedure information		X				
LINQ™ HF RAMware download onto LINQ™ device		X				
[redacted]		X				
Device Data		X	X	X	X	X
NYHA functional classification assessment			X	X		
6 minute hall walk test			X	X		
Holter (DR220) with 6 Minute Hall Walk Test (Recommended)				X*		
[redacted]			X	X		
LINQ™ HF RAMware removal from LINQ™ device						X
Adverse Event	As Occurs					
Healthcare Utilization						
Device Deficiency						
System Modification						
Study Deviations						
Death						

*DR220 Holter is recommended at the 6 Month Visits.

3 INTRODUCTION

3.1 Study Purpose

Medtronic, Inc. is sponsoring the Reveal LINQ™ Heart Failure (HF) study, a prospective, non-randomized, multi-center, observational, pre-market clinical study. The purpose of this clinical study is to characterize Reveal LINQ™ derived data from patients with heart failure by assessing the relationship between changes in LINQ™ derived data and other physiologic parameters with subsequent acute decompensated heart failure events (ADHF).

The study is utilizing the Reveal LINQ™ device with an investigational LINQ™ HF RAMware. [redacted] Additionally, the device will collect the standard information collected in the market released LINQ™ device such as atrial fibrillation burden, average ventricular rate during AF, night and day heart rate and heart rate variability. The study will also collect information regarding HF related clinical events during the same period.

3.2 Study Description

The study is expected to be conducted at up to 30 centers located in the United States. Up to 300 subjects will be enrolled to achieve approximately 40 heart failure events (no more than two per subject will contribute to the cumulative total). Approximately 300 LINQ™ devices will be used in the study.

To ensure a widespread distribution of data and minimize center bias in study results, the maximum number of subjects enrolled at a single center is 60 subjects.

Study subjects will be followed for up to 3 years post-insertion 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 4 years, representing approximately 1.5 years of patient enrollment and 2.5 years of subject follow-up.

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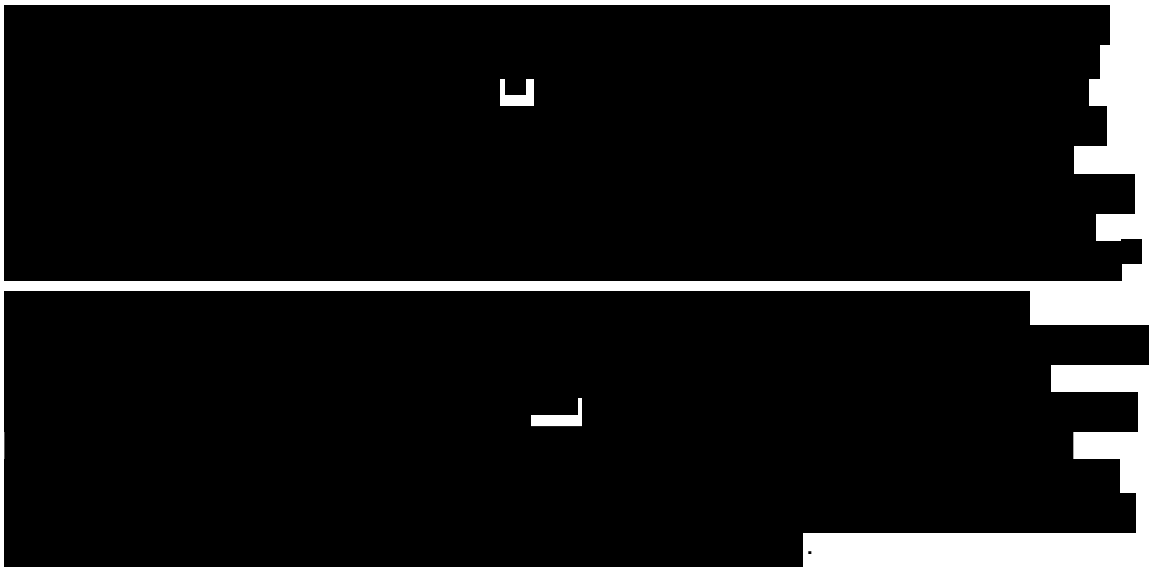
4 BACKGROUND AND JUSTIFICATION

Acute decompensated heart failure (ADHF) is the leading cause of hospitalizations in patients aged 65 and older. In 2004, ADHF accounted for over one million hospitalizations and >6.5 million inpatient days. Heart Failure (HF) is the most common diagnosis associated with 30-day readmission to hospitals in the US. Twenty percent of Medicare beneficiaries are re-hospitalized within 30 days of HF discharge, and 37% of those repeat hospitalizations are again due to HF. It is estimated that about 90% of these hospitalizations are unplanned and potentially preventable. Recurrent hospitalizations account for over 75% of the $46 billion in annual US HF expenditures.[1]

Reducing healthcare utilization associated with HF patient management (i.e. short-term readmission and chronic disease management) is a critically important unmet need for patients, caregivers, and hospitals due to its high morbidity and cost. Repeated hospitalizations in subjects with HF are highly associated with poor subject outcomes. Studies report that hospitalization for HF, in itself, is one of the most important predictors for re-hospitalization and mortality. [2,3,4]

The ability to predict which patients will subsequently be hospitalized for HF provided the traditional evaluation measures such as physical signs and symptoms is limited and poorly associated with hemodynamics. These methods are administered intermittently and may not identify patients early enough to prevent ADHF. [5] To reduce short-term readmission and improve chronic disease management, the integration of multiple HF diagnostics is required and has been shown to identify patients at a higher risk of HF hospitalization.[5,6,7,8] Prior studies have shown implantable device-measured diagnostics like intra-thoracic impedance, [9] AF burden, heart rate metrics,[10] respiration,[11] and patient activity metrics[12] can be used individually or in a combined fashion to identify when patients are at risk for HF events. We hypothesize that these measurements made in the subcutaneous thoracic space may be sensitive enough to detect physiological changes associated with ADHF.



For further literature review, pre-clinical testing and previous clinical experience refer to the Report of Prior Investigations Summary (RPIS).

5 SYSTEM DESCRIPTION AND INTENDED USE

The study will be conducted using the components described in the table below. All components of the Reveal LINQ™ system are manufactured by Medtronic, Inc. Instructions for use of the devices used in this study are provided in their respective manuals or Report of Prior Investigations Summary (RPIS).

The Reveal LINQ™ is a programmable device that continuously monitors a patient's ECG and other physiological parameters. The device records cardiac information in response to automatically detected arrhythmias and patient activation. The LINQ™ device is indicated for the following:

- Patients with clinical syndromes or situations at increased risk of cardiac arrhythmias
- Patients who experience transient symptoms such as dizziness, palpitation, syncope and chest pain that may suggest a cardiac arrhythmia

Table 6: System Component Information

Model Number	Component	Manufacturer	Investigational or Market-released
LNQ11	Reveal LINQ™ Insertable Cardiac Monitor	Medtronic	Market-Released*
LNQ11	Incision Tool	Medtronic	Market-Released
LNQ11	Insertion Tool	Medtronic	Market-Released
SW026	2090 Programmer	Medtronic	Market-Released*
Not Applicable	Reveal LINQ™ RAMware titled: LINQ™ HF Research System, Rev 1.0, and subsequent versions as they are released**	Medtronic	Investigational
PA96000	Patient Assistant	Medtronic	Market-Released
24950	MyCareLink® Home Monitor	Medtronic	Market-Released
DR220	Holter	NorthEast Monitoring, Inc.	Market-Released

*The LINQ™ device and the 2090 programmer are market-released, but once the investigational LINQ™ HF RAMware is downloaded into the devices, they are considered investigational.

** Subjects will receive the most current approved version of the investigational RAMware at the time of their device insertion. In the case that a new RAMware version is released during the course of the study, subjects previously receiving an older version of the RAMware will receive an upgrade to the new version.

5.1 Reveal LINQ™ Insertable Cardiac Monitor (ICM)

The Reveal LINQ™ is a leadless device that is recommended to be inserted in the region of the thorax. A specific recommended location is provided within the product manual. Two electrodes on the body of the device continuously monitor the patient's subcutaneous ECG. The device can store up to 30 min of ECG recordings from the patient-activated episodes and up to 27 min of ECG recordings from the automatically detected arrhythmias. Documentation of episode occurrence will be retained.

Figure 1: Reveal LINQ™ ICM

5.2 Incision Tool

The Incision Tool is designed to create an incision of repeatable width and depth with a single motion. It is composed of a blade, designed to make a repeatable incision, and handle, designed to ergonomically fit the clinician's hand. The Reveal LINQ™ Incision Tool is intended to make the incision simple and repeatable.

Figure 2: Incision Tool

5.3 Insertion Tool

The Insertion Tool delivers the device through the incision and into the subcutaneous tissue. The tool is designed to ensure the device is delivered into a tight pocket to maximize electrode contact with the surrounding tissue in a highly repeatable manner, and is composed of two parts: a handle and a plunger. The Handle is composed of a "channel" section, used to hold the device and guide it during insertion, and a "Tunneler," used to bluntly dissect an implant path for the device to travel down while being inserted. The plunger part is used to push the device out of the handle, through the incision, and along the insertion path created by the Tunneler to the final insertion location.

The Reveal LINQ™ device will be loaded in the Insertion Tool and sterile packaged with the Incision Tool.

The Reveal LINQ™ Insertion Tool is used to create an implant path in the body, and deliver the Reveal LINQ™ into the desired location.

Figure 3: Insertion Tool

5.4 2090 Programmer

The Medtronic CareLink® Programmer is used to program the Reveal LINQ™ ICM to detect arrhythmias with various pre-specified characteristics. In addition, the programmer allows the physician to view, save, and print the ECG records currently held within the Reveal LINQ™ ICM.

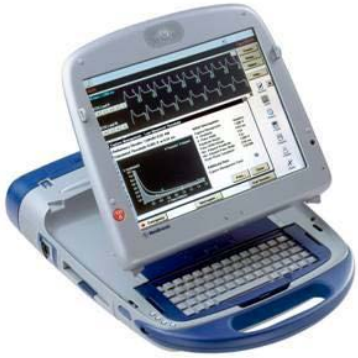


Figure 4: Medtronic 2090 Programmer

The Medtronic 2090 Programmer with the LINQ™ HF investigational RAMware will be used to download the LINQ™ HF investigational RAMware onto the LINQ™ device. LINQ™ HF investigational RAMware is required to activate additional sensors in the Reveal LINQ™ ICM. The LINQ™ HF investigational RAMware will be loaded onto the 2090 programmers designated for clinical use only. The 2090 programmer with the LINQ™ HF investigational RAMware will allow the ability to download and remove the RAMware into and from the device. In addition, the 2090 programmer will be used during the scheduled follow-up visits during the 6 minute hall walk test, as applicable [redacted]

5.5 Medtronic LINQ™ HF Investigational RAMware

[redacted]

[redacted]

5.6 Patient Assistant

The Reveal Patient Assistant is a battery operated, hand-held telemetry device that enables the subject, on experiencing symptoms potentially indicative of a cardiac event, to manually trigger the LINQ™ ICM to collect and store an ECG record.

The Reveal Patient Assistant is intended for unsupervised patient use away from a hospital or clinic. The Patient Assistant activates the data management feature in the Reveal LINQ™ ICM to initiate recording of cardiac event data in the implanted device memory.

The subjects will be asked to press the Patient Assistant whenever they feel increased shortness of breath compared to normal. In addition, the subjects will be asked to press the Patient Assistant device to mark the beginning and end of their 6 Minute Hall Walk test ONLY when the DR220 Holter is not used. Additionally, the LINQ™ HF RAMware enables the storage of a short segment of impedance signal when the Reveal Patient Assistant device is used.

Figure 5: Patient Assistant

5.7 MyCareLink® Home Monitor

The MyCareLink® Home Monitor is a device that enables the device diagnostic data (which includes ECG data) to be transmitted directly from the implanted Reveal LINQ™ device to the Medtronic CareLink® Network for review by the physician. The additional data that is stored in the device by the LINQ™ HF RAMware is also transmitted during a CareLink transmission but will not be available for review by the physician.

Figure 6: MyCareLink® Home Monitor

5.8 DR 220 Holter Monitor

The NorthEast Monitoring, Inc. DR220 Digital Recorder is a Holter monitor that is commercially available and designed to facilitate the ambulatory cardiac monitoring of those subjects who may benefit from such monitoring on order of a physician, including but not limited to those with complaints of palpitations, syncope, chest pains, shortness of breath, or those who need to be monitored to judge their current cardiac function, such as subjects who have recently received pacemakers. The DR220 Digital Recorder is intended for use with Medtronic System-B compatible implantable pulse generators, implantable cardiac defibrillators, and cardiac resynchronization therapy devices and implantable cardiac monitors. A Holter monitor is an external box used to record electrical heart signals from electrode patches attached to the skin (ECG) as well as from the cardiac device (EGM). There are no contraindications for the use of a DR220 Holter monitor. The Holter monitor will be used in accordance with its labeling. Only trained study personnel should apply the monitors.

The data obtained by monitoring is not analyzed at the time of recording. After the recording is complete, the data must later be downloaded to a compatible NorthEast Monitoring, Inc. Holter analysis system to be analyzed. No personal information will be entered and collected by DR220 recorder.

The DR220 Holter Recorder used in this study is a portable ECG device able to collect telemetry signals and marker channel information from any Medtronic device for up to 48 hours. The Holter Recorder has application for any subject with a Medtronic ICM. For the purposes of this study, the intended use of the Holter Recorder is to acutely uplink continuous [redacted] signals that will be collected by the LINQ™ HF RAMware in the Holter mode. Since only the device data uplink feature of the Holter will be used in this study, the device antenna will only be used and no ECG electrodes will be used.

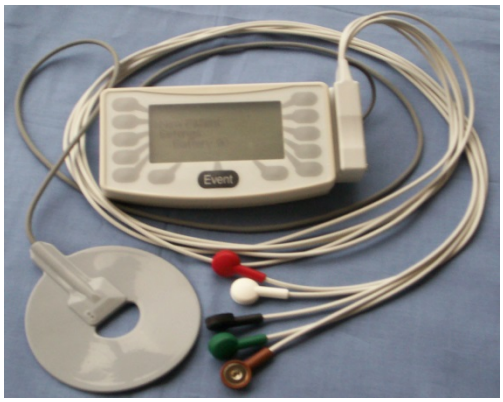


Figure 7: DR220 Holter

6 REGULATORY COMPLIANCE

6.1 Governing Regulations

The Reveal LINQ™ HF study is classified as a non-significant risk (NSR) IDE study.

The principles of the Declaration of Helsinki have been implemented in this study by means of the patient informed consent (PIC) process, IRB approval, study training and clinical trial registration. In the United States, the study will be conducted in compliance with 21 CFR Parts 11, 50, 54, 56 and 812. Also, local laws and regulations will be applicable in the countries where the study is conducted.

This study will be conducted in compliance with international ethical and scientific quality standards, known as good clinical practice (GCP). GCP includes review and approval by an independent IRB before initiating a study, continuing review of an ongoing study by IRBs, and obtaining and documenting the freely given informed consent of a subject before initiating the study.

The study will be publicly registered prior to first enrollment in accordance with the 2007 Food and Drug Administration Amendments Act (FDAAA) and Declaration of Helsinki on http://clinicaltrials.gov (PL 110-85, Section 810(a)

6.2 Institutional Review Board

Before enrolling subjects in the study, IRB approval of study documents including the CIP and PIC is required. IRB approval is required for all sites. IRB approval must be received in the form of a letter and provided to Medtronic before commencement of the study at a study center. The approval letter must contain enough information to identify the version or date of the documents approved.

6.3 CIP/CIP Amendments

Approval of the CIP is required from the following groups prior to any study procedures at a study center:

- Medtronic
- An independent institutional review board

Similarly, approval of subsequent revisions to the CIP is required at each study center from the above mentioned groups prior to implementation of the revised CIP at that center.

6.4 Subject Materials

Each center's IRB will also be required to approve any subject facing materials that may be used in the study, if applicable.

7 METHODOLOGY

7.1 Study Design

The Reveal LINQ™ HF study is a prospective, non-randomized, multi-center, observational, pre-market clinical study. The study is expected to be conducted at up to 30 centers in the United States. Up to 300 subjects will be enrolled to achieve approximately 40 heart failure events (no more than two per subject contribute to the cumulative total). Study subjects will be followed for up to 3 years post-insertion 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 4 years, representing approximately 1.5 years of patient enrollment and 2.5 years of subject follow-up. All Reveal LINQ™ system and procedure-related adverse events will be collected and reported per the study protocol.

7.2 Objective

7.2.1 Primary objective

The primary objective is to characterize Reveal LINQ™ derived data from patients with heart failure by assessing the relationship between changes in LINQ™ derived data and other physiologic parameters with subsequent ADHF events.

7.3 Subject Selection Criteria

Patients will be screened to ensure they meet all of the inclusion and none of the exclusion criteria prior to study enrollment. IRB approval of the Reveal LINQ™ Heart Failure (HF) Clinical Study including required documents (e.g. Clinical Investigation Plan, Patient Informed Consent Form, etc.) must be obtained prior to enrolling patients in the study.

7.3.1 Inclusion criteria

- Patient is 18 years of age or older
- 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 and Carelink transmissions
- Patient has NYHA Class III, per most recent assessment or at any time within 30 days prior to enrollment
- Patient had a HF event (HF event defined as meeting <u>any one of the following three criteria):</u>

  1. Admission with primary diagnosis of HF within the last **6 months**, OR

  2. Intravenous HF therapy (e.g. IV diuretics/vasodilators) or ultrafiltration at any one of the following settings within the last **6 months**:
     - Admission with secondary/tertiary diagnosis of HF
     - Emergency Department

- Ambulance
- Observation Unit
- Urgent Care
- HF/Cardiology Clinic
- Patient's Home, OR

3. Patient had the following BNP/NTpro-BNP within the last **3 months**:
   - If EF ≥ 50%, then BNP> 200 pg/m**l** or NTpro-BNP > 400 pg/m**l** OR
   - If EF is <50%, then BNP> 400 pg/m**l** or NTpro-BNP > 800 pg/m**l**

7.3.2 Exclusion criteria

- 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 severe valvular heart disease as defined by hemodynamically significant valve stenosis and/or prosthetic heart valve
- Patient has existing IPG, ICD, CRT-D or CRT-P device
- Patient has severe renal impairment (eGFR <25mL/min)

7.4 Minimization of Bias

Selection of subjects, treatment of subjects, and evaluation of study data are potential sources of bias. Methods incorporated in the study design to minimize potential bias include (but are not limited to):

- Patients will be screened to confirm eligibility for enrollment in keeping with the inclusion/exclusion criteria
- Subject demographics will be collected at baseline on possible differences that may affect the study results
- To ensure a widespread distribution of data between centers, the maximum number of enrollments per center is 60 subjects
- A maximum of two heart failure events per subject will be used towards the primary objective
- Regular monitoring visits will be conducted for adherence to the CIP and to verify source data
- All study clinicians, participating site personnel, and Medtronic personnel will be trained on their respective aspects of the study using standardized training materials
- All centers will use the same version of the Clinical Investigation Plan (CIP) and electronic Case Report Forms (eCRF)
- An independent Clinical Events Committee (CEC) will be used to regularly review and adjudicate reported adverse events, healthcare utilizations and deaths

In summary, potential sources of bias that may be encountered in this clinical study have been considered and minimized by careful study design.

8 STUDY PROCEDURES

Prior to performing study related procedures, all sites must have IRB approval as well as documentation from Medtronic of center readiness.

The study by design requires a close collaboration between the heart failure specialist and LINQ™ implanters at each participating center. All implanting physicians must be experienced in the handling of Reveal LINQ™ devices.

8.1 Investigator and Site Selection Criteria

All clinical investigators managing the subject's heart failure must be qualified practitioners and experienced in the management of patients with heart failure. All implanting physicians must be experienced in the handling of Reveal LINQ™ devices.

The role of the principal investigator is to implement and manage the day-to-day conduct of the clinical investigation as well as ensure data integrity and the rights, safety and well-being of the subjects involved in the clinical investigation.

The principal investigator shall:

- Be qualified by education, training, and experience to assume responsibility for the proper conduct of the clinical investigation
- Be experienced in the management of heart failure patients.
- Disclose potential conflicts of interest, including financial, that interfere with the conduct of the clinical investigation or interpretation of results

The principal investigator shall be able to demonstrate that the proposed investigational site:

- Has the required number of eligible subjects needed within the recruitment period
- Has one or more qualified investigators, a qualified investigational site research team and adequate facilities for the foreseen duration of the clinical investigation

Center personnel training will be completed prior to participation in this clinical study.

8.2 Site Activation

During the activation process (prior to subject enrollment), Medtronic will train site personnel on the clinical investigation plan, relevant standards and regulations, if needed, informed consent and on data collection and reporting tools. If new members join the study center team, they will receive training on the applicable clinical study requirements relevant to their role before contributing to the clinical study.

Prior to performing study related activities, all local regulatory requirements shall be fulfilled, including, but not limited to the following:

- IRB approval of study documents including the current version of the CIP and Patient Informed Consent.
- Regulatory authority approval or notification (as required per local law)
- Fully executed Clinical Trial Agreement (CTA)
- Financial Disclosure
- Curriculum Vitae (CV) of investigators

- Documentation of delegated tasks
- Documentation of study training

Additional requirements imposed by the IRB and regulatory authority shall be followed, if appropriate.

In addition, all participating site staff must be trained on the current version of the CIP and must be delegated by the principal investigator to perform study related activities.

Medtronic will provide each study center with documentation of study center/investigator readiness; this letter must be received prior to subject enrollment.

8.3 Equipment Requirements

The following equipment must be available at each center to support study activities:

- Computer with high speed internet access using Microsoft Internet Explorer for data entry (version 6 or 8 or other compatible version)
- Market-released Medtronic programmer (Model 2090)
- Blood draw including BNP or NT-proBNP analysis capabilities at a certified local lab

Medtronic will supply additional Patient Assistant devices for use at the in-office follow-up visits to mark the beginning and end of the 6 minute hall walk test ONLY when the DR220 Holter is not used.

8.4 Data Collection

Clinical data are collected at designated time points throughout the study. A web-based application tool, Remote Data Capture (RDC) will be used for data entry. This tool has Electronic Case Report Forms (eCRFs) which can be accessed via an Internet browser. Data will be processed using an electronic data management system for clinical studies. Data will be stored in a secure, password protected database which will be backed up on a daily basis. Data will be reviewed using programmed and manual data checks. Data queries will be made available to study centers for resolution. Study management reports will be generated to monitor data quality and study progress. The investigator is responsible for the preparation (review and signature) of the eCRFs. At the end of the study, the data will be frozen and retained indefinitely by Medtronic. The requirements for data collection and study visit schedules are summarized in Table 6.

Table 7: Data Collection and Study Procedure Requirements at Subject Visits

STUDY PROCEDURE	Baseline	LINQ Insertion	1 Mo Visit	6 Mo and 12 Mo Office Visit	Device Transmission/ HCU Monthly Call	Study Exit
Patient Informed Consent	X					
Inclusion/Exclusion Assessment	X					
Medical History	X					
Demographics	X					
Physical Exam	X		X	X		
Medication Assessment	X		X	X		X
Laboratory results	X			X		
Symptoms and Temperature (via ear is recommended)			X	X		
Final system configuration		X				
Insertion procedure information		X				
LINQ™ HF RAMware download onto LINQ™ device		X				
[redacted]		X				
Device Data		X	X	X	X	X
NYHA functional classification assessment			X	X		
6 minute hall walk test			X	X		
Holter (DR220) with 6 Minute Hall Walk Test (Recommended)				X*		
[redacted]			X	X		
LINQ™ HF RAMware removal from LINQ™ device						X
Adverse Event	As Occurs					
Healthcare Utilization						
Device Deficiency						
System Modification						
Study Deviations						
Death						

*DR220 Holter is recommended at the 6 Month Visits.

8.5 Role of the Sponsor Representatives

Medtronic personnel may provide support as required for the study under supervision of the Principal Investigator, including:

- Provide study training relevant and pertinent to the involvement of personnel conducting study activities and investigator responsibilities
- Technical support at device insertion and follow-up visits under the supervision of a study investigator, but no data entry on the case report forms, shall be performed by Medtronic personnel or their representatives at sites

- Monitoring and auditing activities

8.6 Patient Informed Consent Process

Patient informed consent (PIC) is defined as a legally effective documented confirmation of a subject's or their legally authorized representative voluntary agreement to participate in a particular clinical study after information has been given to the subject on all aspects of the clinical study that are relevant to the subject's decision to participate. This process includes obtaining a Patient Informed Consent Form and a/an Authorization to Use and Disclose Personal Health Information/Research Authorization/other privacy language as required by law that has been approved by the study center's IRB Committee and signed and dated by the subject or their legally authorized representative. A subject may only consent after information has been given to the subject on all aspects of the clinical investigation that are relevant to the subject's decision to participate. Informed consent may be given by the legally authorized representative only if a subject is unable to make the decision to participate in a clinical investigation. In such cases, the subject shall also be informed about the clinical investigation within his/her ability to understand.

Prior to enrolling subjects, each center's IRB will be required to approve the PIC Form and the Authorization to Use and Disclose Personal Health Information/Research Authorization/other privacy language as required by law. The document(s) must be controlled (i.e. versioned and/or dated) to ensure it is clear which version(s) were approved by the IRB. Any adaptation of the sample Patient Informed Consent Form must be reviewed and approved by Medtronic and the IRB reviewing the application prior to enrolling subjects.

The investigator must notify the subject or their legally authorized representative of any significant new findings about the study that become available during the course of the study which are pertinent to the safety and well-being of the subject, as this could impact a subject's willingness to participate in the study. If relevant, approval may be requested from subjects to confirm their continued participation.

Refer to Appendix D for the sample Patient Informed Consent Form Template.

Prior to initiation of any study-specific procedures, patient informed consent must be obtained from the subject or their legally authorized representative. Likewise, privacy or health information protection regulation may require subjects to sign additional forms to authorize centers to submit subject information to the study sponsor. The informed consent process must be conducted by the principal investigator or an authorized designee, and the Patient Informed Consent Form and Authorization to Use and Disclose Personal Health Information/Research Authorization/other privacy language as required by law must be given to the subject (or their legally authorized representative) in a language he/she is able to read and understand. The process of patient informed consent must be conducted without using coercion or undue improper influence on or inducement of the subject to participate by the investigator or other center personnel. The informed consent process shall not wave or appear to waive subject's legal right. The language used shall be as non-technical as possible and must be understandable to the subject and the impartial witness, where applicable.

The subject must have ample time and opportunity to read and understand the Patient Informed Consent Form, to inquire about details of the study, and to decide whether or

not to participate in the clinical study. All questions about the study should be answered to the satisfaction of the subject.

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

A copy of the Patient Informed Consent Form and the Authorization to Use and Disclose Personal Health Information/Research Authorization/other privacy language, signed and dated as required by law, must be provided to the subject.

If the Patient Informed Consent Form is obtained the same day the subject begins participating in study-related procedures, it must be documented in the subject's case history that consent was obtained prior to participation in any study-related procedures. It is best practice for the informed consent process to be documented in the subject's case history, regardless of circumstance.

In the event the subject cannot read and/or write, witnessed (impartial third party) patient informed consent will be allowed, provided detailed documentation of the process is recorded in the subject's case history and the witness signs and dates the Patient Informed Consent Form. The subject should "make his mark" (sign or otherwise physically mark the document so as to indicate consent) on the PIC as well. The Patient Informed Consent Form should document the method used for communication with the prospective subject and the specific means by which the prospective subject communicated agreement to participate in the study.

The original of the signed Patient Informed Consent Form must be filed in the hospital /clinical chart and/or with the subject's study documents.

The Patient Informed Consent Form and Authorization to Use and Disclose Personal Health Information/Research Authorization/other privacy language as required by law must be available for monitoring and auditing. Any Medtronic Field personnel who support the Reveal LINQ™ insertion must be able to review the subject's signed and dated Patient Informed Consent Form and verify its completeness prior to proceeding with the LINQ™ insertion/download. In the event the Medtronic Field personnel identify the patient informed consent as being incomplete, the Reveal LINQ™ insertion will not be allowed to occur until the consent of the subject can be adequately and appropriately obtained.

8.7 Enrollment

When a patient and the principal investigator or authorized designee have personally signed and dated the Patient Informed Consent Form, the patient is considered a subject enrolled in the study. The date the subject signed the Patient Informed Consent Form and data protection authorization must be documented in the subject's medical records.

8.8 Baseline

The Baseline visit can be a standalone visit or can be performed on the same day of LINQ™ Insertion prior to the LINQ™ Insertion procedure.

The following information is required to be collected at the baseline visit:

- Patient Informed Consent Form
- Inclusion/Exclusion Criteria assessment (including pregnancy test if the subject is of child bearing potential)
- Medical History including most recent EF (if available in the last 6 months) and previous heart failure events in the last 6 months.
- Demographics
- Physical exam
- Medications
- Laboratory results: BNP, eGFR, Blood Urea Nitrogen (BUN), Serum Creatinine, Sodium (Na), Potassium (K), Hemoglobin (Hb), Hematocrit (Hct), Troponin
- Any healthcare utilizations
- Study deviations

8.9 Insertion

Within 30 working days of the baseline assessment, the Reveal LINQ™ device will be inserted in the subject. The insertion procedure will be performed in accordance with the Medtronic Reveal LINQ™ implant instructions. After the Reveal LINQ™ device is inserted, the LINQ™ HF investigational RAMware will be downloaded to the device via the 2090 programmer. Use of the recommended implant locations is located in Figure 8 below. Physicians should follow the implant manuals when performing the Reveal LINQ™ implant.

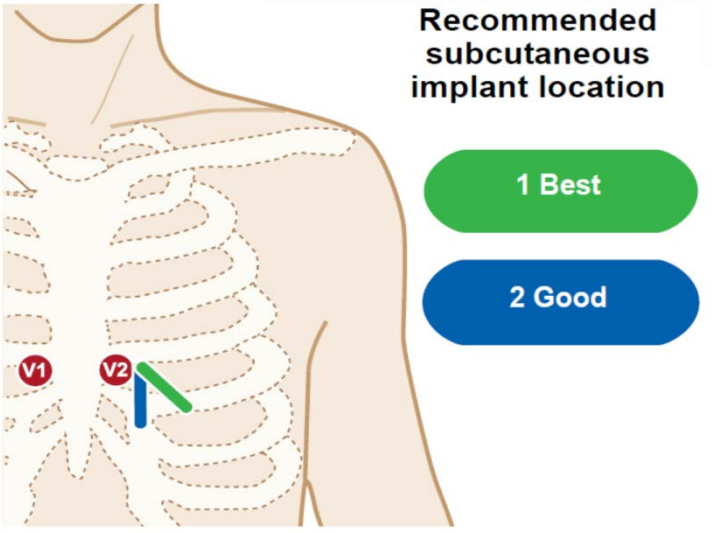


Figure 8: Recommended Insertion Locations

The following information is required to be collected at the insertion visit:

- Final system configuration
- Insertion procedure information
- LINQ™ HF Investigational RAMware download
- [redacted]
- Device interrogation (media/USB)
- Any Reveal LINQ™ system and procedure-related adverse events
- Any healthcare utilizations
- Any device deficiencies or study deviations

8.9.1 Programming Recommendations

Once the LINQ™ device is inserted into the subject, the physician is recommended to choose "AF management." This will automatically program the device to the nominal settings for the different detectors.

8.10 Scheduled Follow-up visits

After receiving notice of successful LINQ™ insertion, Medtronic will provide the target dates and windows for each visit to the implanting center. Should a subject miss a visit or the visit fall outside the pre-specified window, a study deviation must be reported and the original follow-up schedule maintained for subsequent visits.

Data analyses include follow-up visits, regardless of whether the visit occurs within the window. Therefore, a late visit is preferred over a missed visit but must be accompanied by a deviation. Follow-up visit windows are listed in Table 7 and are based on days post-insertion.

Table 8: Post-Insertion Follow-up Windows

Study Follow-up Visit	Window (Calculated days post-procedure attempt)		
	Window Start (# of days)	Target (# of days)	Window End (# of days)
1 month	30	30	37
6 month	163	183	203
12 month	345	365	385

The following information is required to be collected at the **1 Month** scheduled follow-up visits:

- Physical exam including temperature
- Symptoms review
- Medications
- NYHA assessment
- 6 Minute Hall Walk test
- [redacted]

- Device interrogation (media/USB)
- Any Reveal LINQ™ system and procedure-related adverse events
- Any healthcare utilizations
- Any device deficiencies or study deviations

The following information is required to be collected at the **6 Month and 12 Month** scheduled follow-up visits:

- Physical exam including temperature
- Symptoms review
- Medications
- NYHA assessment
- 6 Minute Hall Walk test *(DR220 Holter recommended to be used at 6 Month Visit Only during the 6 Minute Hall Walk test)*
- [redacted]
- Laboratory results: BNP, eGFR, Blood Urea Nitrogen (BUN), Serum Creatinine, Sodium (Na), Potassium (K), Hemoglobin (Hb), Hematocrit (Hct), Troponin
- Device interrogation (media/USB)
- Any Reveal LINQ™ system and procedure-related adverse events
- Any healthcare utilizations
- Any device deficiencies or study deviations

8.11 Device Transmission/ HCU Monthly Call (Start within Month 1)

There will be a Monthly Device Transmission eCRF to be completed starting within the first month from insertion. This visit will be conducted to ensure the subject manually transmitted the device data (see section 8.12 below). In addition, a HCU assessment will be completed in cases where the subject is contacted. Subjects should be contacted regularly (recommended at least every 3 months) regardless of manual transmission status to ensure complete and timely reporting of HCUs. Follow-up windows will vary based on the timing of the most recent device interrogation/transmission and will be provided by Medtronic as needed.

8.12 Monthly CareLink Transmissions

Subjects are required to perform a manual device transmission monthly from the time they are enrolled in the study until their Study Exit visit. [redacted] The subject will utilize the MyCareLink® Home Monitor to manually transmit the data. The subject will receive instructions on how to perform the manual transmission. Refer to Appendix G.

As described above, a Monthly Device Transmission eCRF will be required to be completed to ensure the subject manually transmitted. A study deviation will be required for any missed monthly manual Carelink transmissions, unless a device interrogation file for an interrogation occurring within the required timeframe is provided to Medtronic.

8.13 Device Interrogation

For all follow-up visits occurring in the office, a full “interrogate all” final device interrogation file (.pdd) must be obtained and saved in a digital format (USB). The original file must be stored at the site and a copy sent to Medtronic. It is recommended that data are not cleared during any interrogation. This should be conducted at the end of the visit.

8.14 Healthcare Utilization

Cardiovascular-related Health Care Utilizations (HCUs) (including hypervolemia and hypovolemia) will be collected. This includes the following:

- Unscheduled clinic visit (including subject-initiated phone calls if the subject is experiencing CV-related symptoms)
- Scheduled clinic visit (if the subject is experiencing CV-related symptoms)
- Hospital outpatient clinic visit
- Urgent care visit
- Other outpatient utilization with overnight stay
- Emergency department visit
- Inpatient hospitalization

HCU information should be reported upon center awareness and assessed at all visits including the monthly telephone visits. If multiple HCUs occur within the same day, data from all HCUs can be captured on one eCRF.

8.15 System Modification

A system modification will be reported in the event the device requires invasive modification (e.g., device explant, device reposition). In the event of a system modification, the follow-up schedule for the subject will remain unchanged. For a system modification the following activities are required:

- Complete the System Modification eCRF
- Device interrogation (media/USB)
- Any Reveal LINQ™ system and procedure-related adverse events
- Any healthcare utilizations
- Any device deficiencies or study deviations

If the device is taken out of service (e.g, explanted) and a replacement will not be implanted or the replacement is not a study approved device, the subject must be exited from the study after all device and/or procedure related AEs have been resolved or remain unresolved with no further action planned.

All explanted product (device) should be returned to Medtronic for analysis when permissible by local laws and regulations. See Section 9 for final product disposition details.

In the event that a subject has a re-attempt after a previous unsuccessful system modification, the subsequent attempt(s) must be reported via eCRF as separate system modifications.

8.16 Study Exit

A Study Exit eCRF is required for all subjects except in the case of death. Prior to exiting a subject from the study, it is recommended to follow the subject until all ongoing device and/or procedure related AEs are resolved or unresolved with no further actions planned. Following exit, subjects will continue to receive standard medical care. Upon exiting from the study, no further study data will be collected or study visits will occur for the subject. All data available through the time of the subject's exit will be used for analysis.

Subjects are urged to remain in the study as long as possible but may be exited from the study for any of the following situations and will be documented on the Study Exit eCRF:

- Subject did not meet inclusion/exclusion criteria
- Subject was not inserted with a Reveal LINQ™ device
- Reveal LINQ™ removal without re-implantation
- Implant attempted, however no Reveal LINQ™ was implanted
- Subject relocation to another geographic location
- Subject chooses to withdrawal
- Investigator chooses to withdraw a subject
- Subject lost to Follow-Up
- End of battery life of LINQ™ device
- Study Termination

The following information/procedure is to be collected/performed at study exit:

- Reason for exit
- Removal of the LINQ™ HF investigational RAMware from the LINQ™ device
- Medications
- Device interrogation (media/USB)
- Any Reveal LINQ™ system and procedure-related adverse events
- Any healthcare utilizations
- Any device deficiencies or study deviations

In the case that the subject is determined to be lost to follow-up, details of a minimum of two attempts and the method of attempt (e.g., one letter and one phone record or two letters) to contact the subject must be recorded. In addition, follow the regulations set forth by the governing IRB.

If discontinuation is because of safety or lack of effectiveness, the subject shall be asked to be followed for collecting safety data outside the clinical investigation.

8.17 Medications

Cardiovascular medications will be collected at the baseline assessment, 1 Month, 6 Month, 12 Month office visits and Study Exit. The name, dose, frequency and route of all cardiovascular medications will be collected. Changes to medications will be captured at healthcare utilizations.

There are no medications that are required for this study although some medications may be administered in treating specific conditions at the discretion of the physician. The only medications that are excluded from use during this study are investigational.

8.18 6 Minute Hall Walk Test

Subjects will be asked to perform a 6 Minute Hall Walk test at the 1 Month, 6 Month and 12 Month office visits. A Holter will be recommended to be worn during the 6 Minute hall walk at the 6 Month Visit only. In addition, the subjects will be asked to press the Patient Assistant device to mark the beginning and end of their 6 Minute Hall Walk test ONLY when the DR220 Holter is not used. Refer to Appendix C for more details.

[redacted]

[redacted]

8.21 Review of Data Recorded by the Reveal LINQ™ Device

Reveal LINQ™ data derived from the LINQ™ HF investigational RAMware will not be viewable to the site. The standard arrhythmia data from the LINQ™ device will be viewable via Carelink.

8.22 Holter

Subjects may be asked to have a Holter placed to collect some additional information from the LINQ™ device. The DR220 Holter Recorder used in this study is a portable ECG device able to collect continuously telemetered signals from any Medtronic device for up to 48 hours. The Holter Recorder has application for any subject with a Medtronic ICM. For the purposes of this study, the intended use of the Holter Recorder is to acutely uplink continuous [redacted] signals that will be collected by the LINQ™ HF RAMware in the Holter mode. The intended use of Holter mode is for a short duration of less than 30 minutes during the 6 minute hall walk test during an office visit.

Since only the device data uplink feature of the Holter will be used in this study, the device antenna will only be used and no ECG electrodes will be used. Please refer to Appendix C for more details.

9 INVESTIGATIONAL DEVICE/RAMWARE STORAGE, HANDLING AND TRACEABILITY

The following section details tracking of all clinical investigation study components. Study components will be distributed to a center only when Medtronic has received all required documentation and has notified the center of center activation.

Distribution of study components to study centers during the clinical study will be managed by Medtronic. All product must be stored in a secure location at the site. It is the responsibility of the investigator to correctly handle, store, and track the study products maintained at the site. Study components will be used only in the study according to the CIP.

Product Distribution logs may be located in the database and will be used for tracking of products during and after the study. The logs must be updated when product is received, opened, implanted, explanted, disposed of or returned to Medtronic. The disposition log tracks product information including, but not limited to, date, model/serial number, and expiration date for received product, subject ID of implanted subject, date implanted, date explanted (if applicable), date returned to Medtronic and reason for return (if applicable), reason for and method of destruction/disposal for explanted components not returned to Medtronic (if applicable), and name of person responsible for return or destruction/disposal (if applicable). Medtronic will perform periodic reconciliation of investigational product to ensure traceability.

The following products will be tracked on a disposition log:

- Reveal LINQ™ device
- 2090 Programmer with the LINQ™ HF investigational RAMware
- Patient Assistants provided to sites for use during in-office visits
- Holter DR220

The **2090 Programmers** used in the study are commercially available, however once the LINQ™ HF investigational RAMware is downloaded onto the 2090 Programmers in this study, the 2090 Programmer becomes investigational. The 2090 Programmer disposition logs will be located in the database and will be used for tracking of all programmers downloaded with LINQ™ HF investigational RAMware. When the LINQ™ HF investigational RAMware is installed on or removed from the programmer(s), the programmer disposition log must be updated.

The **Reveal LINQ™ device** used in this study are commercially available, however once the LINQ™ HF investigational RAMware is downloaded to the device, the device will be considered an investigational product. The investigational device will be tracked via device disposition logs in the database. When the LINQ™ HF investigational RAMware is installed on or removed from the device(s), these changes must be recorded on the applicable eCRF(s) (e.g. Insertion Procedure, Scheduled Follow-up or Study Exit eCRF).

9.1 Medtronic Supplied Equipment Accountability

All explanted product should be returned to Medtronic for analysis according to local laws and regulations. If the products are explanted but not returned, a justification is

required to be reported on the appropriate eCRF(s) and/or disposition log(s). The Product Distribution Logs must be updated for explanted devices. To receive a Returned Product Mailer Kit, please contact your local Medtronic personnel or Study Manager. All unused product must be returned to Medtronic upon study closure at the center.

The Product Disposition Logs must be updated with the final device disposition.

Table 9: Final Disposition of Products

Model Number	Component	Return to MDT at Center closure	Disposal after Each Use	LINQ™ HF Investigational RAMware Removal
LNQ11	Reveal LINQ™	X (Explant Only)		X (Study Exit)
24950	MyCareLink® Monitor	*Return Not Required – Market Released*		
96000	Patient Assistant*	*Return Not Required – Market Released**		
2090	2090 Programmer with LINQ HF Research System, Rev 1.0 RAMware (or subsequent version)	X[1]		X
DR220	Holter	X		
[1] If the 2090 programmer was supplied to the site for purposes of the study, the 2090 programmer should be returned to Medtronic. *All product returns will be contingent on local laws and regulations.* *All Investigational Product will be labeled Investigational.*				

*Patient Assistants that will be used at the sites are required to be returned to Medtronic at the end of the study.

9.1.1 Shipment of Study Components

Medtronic will only allow shipment of the study device and components to the hospital or investigator when Medtronic has received all required documentation and has notified the site of readiness. Products shall be used in these centers only and according to the CIP. Clinical investigational devices and components that are used for purposes of the study only will be provided at no cost by Medtronic. Distribution of the study device and components to centers during the study will be managed by Medtronic.

All investigational components must be stored in a secure location in which access is limited to authorized personnel only.

9.1.2 Storage and Handling of Study Device and Components

It is the responsibility of the investigator to store the study specific components and study specific equipment in a secured and temperature controlled area. The method of storage shall prevent the use of the study device and components for other applications. Opening sealed cases is forbidden for other than study use and must be reported to the Investigator and Sponsor upon detection.

10 STUDY DEVIATIONS

A study deviation is defined as an event within a study that did not occur according to the Clinical Investigation Plan or the Clinical Trial Agreement.

Prior approval by Medtronic is expected in situations where the investigator anticipates, contemplates, or makes a conscious decision to deviate. Prior approval is not required when a deviation is necessary to protect the safety, rights or well-being of a subject in an emergency or in unforeseen situations beyond the investigator's control (e.g. subject failure to attend scheduled follow-up visits, inadvertent loss of data due to computer malfunction, inability to perform required procedures due to subject illness).

For medically justifiable conditions which preempt a subject's ability to complete a study-required procedure, it may be permitted to report only one deviation which will apply to all visits going forward. This may also apply for other unforeseen situations (e.g. the subject permanently refuses to complete a study required procedure and the data will not contribute to the primary end point analysis). However, prior approval from Medtronic is required for such situations.

All study deviations must be reported on the Case Report Form regardless of whether medically justifiable, pre-approved by Medtronic, an inadvertent occurrence, or taken to protect the subject in an emergency. Multiple deviations of the same type at the same visit may be reported on one case report form. In the occurrence of a corrupted device interrogation file, Medtronic may request a deviation to document that a readable interrogation file is unavailable.

In the event the deviation involves a failure to obtain a subject's consent, or is made to protect the life or physical well-being of a subject in an emergency, the deviation must be reported to the IRB as well as Medtronic within five (5) working days. Reporting of all other study deviations should comply with IRB policies and/or local laws and must be reported to Medtronic as soon as possible upon the center becoming aware of the deviation. Reporting of deviations must comply with IRB policies, local laws, and/or regulatory agency requirements. Refer to Investigator Reports, Table 15 for deviation reporting requirements and timeframes for reporting to Medtronic and/or regulatory bodies.

Medtronic is responsible for analyzing deviations, assessing their significance, and identifying any additional corrective and/or preventive actions (e.g. amend the Clinical Investigation Plan, conduct additional training, terminate the investigation). Repetitive or serious investigator compliance issues may result in initiation of a corrective action plan with the investigator and site, and in some cases, necessitate suspending enrollment until the problem is resolved or ultimately terminating the investigator's participation in the study. Medtronic will provide center-specific reports to investigators summarizing information on deviations that occurred at the investigational site on a periodic basis.

11 ADVERSE EVENTS AND DEVICE DEFICIENCIES

Timely, accurate, and complete reporting and analysis of safety information for clinical studies are crucial for the protection of subjects. Reporting and analysis of safety data are mandated by regulatory authorities worldwide. Medtronic has established procedures in conformity with regulatory requirements to ensure appropriate reporting of safety information. This study is conducted in accordance with these procedures and regulations.

11.1 Adverse Event and Device Deficiency Definitions

Where the definition indicates “device”, it refers to any device used in the study. This might be the device under investigation, or any market released component of the system.

Table 10: Adverse Event Definitions

General	
Adverse Event (AE) (Adapted from ISO 14155:2011, 3.2)	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.
Adverse Device Effect (ADE) (ISO 14155:2011, 3.1)	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.
Device Deficiency (DD) (ISO 14155:2011, 3.15)	Inadequacy of a medical device with respect to its identity, quality, durability, reliability, safety or performance. NOTE 1: Device deficiencies include malfunctions, use errors and inadequate labeling
Relatedness	
Procedure Relatedness	An adverse event that occurs due to any procedure related to the insertion or surgical modification of the Reveal LINQ™ device
Reveal LINQ™ System Relatedness	An adverse event that results from the presence or performance of any component of the Reveal LINQ™ system (including the LINQ™ device, incision/insertion tools, patient assistant and programmer)
Seriousness	

Serious Adverse Event (SAE) (ISO 14155:2011, 3.37)	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 1: 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.
Serious Adverse Device Effect (SADE) (ISO 14155:2011, 3.36)	Adverse device effect that has resulted in any of the consequences characteristic of a serious adverse event.
Complication	An adverse event that includes the following is considered a complication: ☐ Results in death, ☐ Involves any termination of significant device function, or ☐ Requires an invasive intervention (21 CFR 812) Non-invasive: when applied to a diagnostic device or procedure, means one that does not by design or intention: ☐ Penetrate or pierce the skin or mucous membranes of the body, the ocular cavity, or the urethra, or ☐ Enter the ear beyond the external auditory canal, the nose beyond the nares, the mouth beyond the pharynx, the anal canal beyond the rectum, or the vagina beyond the cervical os. For purposes of this part, blood sampling that involves simple venipuncture is considered noninvasive, and the use of surplus samples of body fluids or tissues that are left over from samples taken for non-investigational purposes is also considered noninvasive.
Observation	Any adverse event that is not a complication.
Unanticipated Adverse Device Effect (UADE) *(21 CFR 812.3(s))*	Any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death, was not previously identified in a nature, severity, or degree of incidence in the investigational plan or application (including a supplementary plan or application), or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects.
Other	

<table>
<tr><td>Unavoidable Adverse Event</td><td>An Adverse Event inherent to a surgical procedure that is expected to occur in all subjects for a projected duration according to the Investigator’s opinion, including, but not limited to:
<table>
<tr><th>Event Description</th><th>Timeframe (hours) from the Surgical Procedure</th></tr>
<tr><td>Pocket site / Incisional pain</td><td>72</td></tr>
<tr><td>Mild to moderate bruising / ecchymosis</td><td>168</td></tr>
</table>
</td></tr>
</table>

11.2 Adverse Event and Device Deficiency Assessment

11.2.1 Adverse Events

Reveal LINQ™ system and procedure-related adverse events will be collected throughout the study duration, starting at the time of signing the Patient Informed Consent Form. Reporting of these events to Medtronic will occur on an Adverse Event (AE) Form, including a description of AE, date of onset of AE, date of awareness of site, treatment, resolution, assessment of both the seriousness and the relatedness to the investigational device. Each AE must be recorded on a separate AE Form. Subject deaths are also required to be reported on a Subject Death form. Refer to section 11.6 for Subject Death collection and reporting requirement

Documented pre-existing conditions are not considered AEs unless the nature or severity of the condition has worsened. The unavoidable Adverse Events, listed in Table 9 need not be reported unless the adverse event worsens or is present outside the stated timeframe post-implant. For AEs that require immediate reporting (refer to Table 11), initial reporting may be done by phone, fax, or on the eCRF completing as much information as possible. The AE eCRF must be completed as soon as possible.

11.2.2 Device Deficiencies

Device deficiency information will be collected throughout the study and reported to Medtronic. Note that device deficiencies that result in an adverse device effect (ADE) to the subject should be captured on an Adverse Event form only.

11.2.3 Processing Updates and Resolution

For any changes in status of a previously reported adverse event (i.e. change in actions taken, change in outcome, change in relatedness), an update to the original AE must be completed. All reported adverse events must be followed until the adverse event has been resolved, is unresolved with no further actions planned, the subject exits the study or until study closure, whichever occurs first.

In the event that a subject is exited from the study prior to study closure, all efforts should be made to continue following the subject until all unresolved procedure or system related adverse events, as classified by the investigator, are resolved or they are unresolved with no further actions planned.

At the time of study exit, all adverse events with an outcome of “Unresolved, further actions or treatment planned” must be reviewed and an update to the original AE must

be reported. At a minimum, if there are no changes to the description, relatedness, test and procedures or actions taken, the outcome must be updated to reflect “Unresolved at time of study closure.”

11.3 Adverse Events and Device Deficiency Classification

All reported adverse events and device deficiencies will be reviewed by a Medtronic representative. AEs will be classified according to the definitions provided.

Upon receipt of adverse events at Medtronic, a Medtronic representative will review the adverse event/device deficiency for completeness and accuracy and when necessary will request clarification and/or additional information from the Investigator. Medtronic will utilize MedDRA, the Medical Dictionary for Regulatory Activities, to assign a MedDRA term for each adverse event based on the information provided by the investigator.

Regulatory reporting of AEs and device deficiencies will be completed according to local regulatory requirements. Refer to Table 11 for a list of required investigator and Medtronic reporting requirements and timeframes. It is the responsibility of the investigator to abide by any additional AE reporting requirements stipulated by the IRB responsible for oversight of the study.

For emergency contact regarding a UADE and/or SAE, contact a clinical study representative immediately (refer to the study contact list provided in the center’s study documents binder/investigator site file or refer to the contact information provided in Table 1).

Adverse Events and Deaths will be classified according to the standard definitions as outlined below:

Table 11: Adverse Event Classification Responsibilities

What is classified?	Who classifies?	Classification Parameters
Relatedness	Investigator	Procedure, Reveal LINQ™ system
	Sponsor	Procedure, Reveal LINQ™ system
Seriousness	Investigator	SAE
	Sponsor	SAE, UADE
Diagnosis	Investigator	Based on presenting signs and symptoms and other supporting data
	Sponsor	MedDRA term assigned based on the data provided by Investigator
Death Classification	Investigator	Sudden Cardiac, Non-sudden Cardiac, Non-Cardiac, Unknown

An independent Clinical Events Committee (CEC) will review events and provide a final adjudication of the relatedness for all events as well as the complication/observation classification for system or procedure related events. Additionally, the CEC will provide an adjudication of the death classification for all reported deaths.

11.4 Adverse Event and Device Deficiency Reporting Requirements

Regulatory reporting of AEs / Device Deficiencies (DD) will be completed according to local regulatory requirements. Refer to Table 12 for a list of required investigator reporting requirements and timeframes, and of required Medtronic reporting requirements and timeframes.

The investigator is required to report UADE's to Medtronic immediately and to the IRB per local requirements. Medtronic is also required to report these events to the local regulatory authority based on their requirements. It is the responsibility of the investigator to abide by any additional AE/DD reporting requirements stipulated by the IRB responsible for oversight of the study.

For AEs/DDs that require immediate reporting, initial reporting may be done by contacting the study sponsor per the sponsor contact information provided in this document.

Regulatory reporting of AEs/DDs will be completed according to local regulatory requirements.

Table 12: Adverse Event Reporting Requirements

Unanticipated Adverse Device Effects (UADEs)	
Investigator submit to:	
Medtronic	Submit as soon as possible, but no later than within 10 working days after the investigator first learns of the event. (21 CFR 812.150(a)(1))
IRB	Submit as soon as possible, but no later than within 10 working days after the investigator first learns of the event. (21 CFR 812.150(a)(1))
Sponsor submit to:	
Regulatory authorities	Submit as soon as possible, but no later than within 10 working days after the investigator first learns of the event. (21 CFR 812.150(a)(1))
IRB	Submit as soon as possible, but no later than within 10 working days after the investigator first learns of the event. (21 CFR 812.150(a)(1))
All other reportable Adverse Events	
Investigator submit to:	
Medtronic	Submit in a timely manner after the investigator first learns of the event.
IRB	Submit to IRB per local reporting requirement.
Sponsor submit to:	
Regulatory authorities	Submit to regulatory authority per local reporting requirement.
IRB	Submit to IRB per local reporting requirement.
Device Deficiencies	
Investigator submit to:	
Medtronic	Submit in a timely manner after the investigator first learns of the event.
IRB	Submit to IRB per local reporting requirement.

11.5 Subject Death

11.5.1 Death Data Collection

All subject deaths must be reported by the investigator to Medtronic on a Subject Death form as soon as possible after the investigator first learns of the death.

In the event of a subject's death, the implanted system should be explanted and returned to Medtronic for analysis whenever possible. Local laws and procedures must be followed where applicable.

System Interrogation Data Recommendations:

- After the subject has died but prior to explant, the device shall be interrogated and a full summary interrogation (Interrogate All) performed when possible.
- Make the interrogation file before any programming to prevent overwriting information device's memory and/or distinguishing between events detected during versus before the explant procedure

If the device is not interrogated, an explanation must be entered on the Subject Death form. If any device is returned to Medtronic, internal return product reporting systems may be used to gather additional information about the returned device/component.

A copy of the death certificate, if available and allowed by state/local law, should be sent to the Medtronic clinical study team. When a death occurs in a hospital, a copy of the death summary report and all relevant hospital records should be sent to the Medtronic clinical study team, if available. If an autopsy is conducted, the autopsy report should also be sent to the Medtronic clinical study team if available and allowed by state/local law. When the death occurs at a remote site, it is the investigative center's responsibility to attempt retrieval of information about the death. Additionally, device disposition information should be updated. In summary, the following data will be collected:

- Date of death
- Detailed description of death
- Cause of death
- Relatedness to system and/or procedure
- Device interrogation (if available)
- Device disposition information
- Death summary/hospital records (if available and allowed by state/local law)
- Autopsy report (if available and allowed by state/local law)
- Death certificate (if available and/or allowed by state/local law)

11.5.2 Death Classification and Reporting

Sufficient information will be required in order to properly classify the subject's death. The Investigator shall classify each subject death per the following definitions:

Cardiac Death: A death directly related to the electrical or mechanical dysfunction of the heart.

Sudden Cardiac Death (SCD): Natural death due to cardiac causes, indicated by abrupt loss of consciousness within one hour of the onset of acute symptoms; preexisting heart disease may have been known to be present, but the time and mode of death are unexpected. If time of onset cannot be determined, SCD will alternatively be defined as any unexpected cardiac death occurring out of the hospital or in the emergency room as dead on arrival.

Non-sudden Cardiac Death: All cardiac deaths that are not classified as sudden deaths, including all cardiac deaths of hospitalized subjects on inotropic support.

Non-cardiac Death: A death not classified as a cardiac death.

Unknown Cardiac Classification: Unknown death classification is intended for use only when there is insufficient or inadequate information to classify the death.

Table 13: Subject Death Classification Responsibilities

What is classified?	Who classifies?	Classification Parameters
Relatedness	Investigator	Procedure, Reveal LINQ™ system
Death Classification	Investigator	Sudden Cardiac, Non-sudden Cardiac, Non-cardiac, Unknown

The Clinical Events Committee (CEC) will review deaths and provide a final adjudication of the primary cause of death, relatedness and cardiac classification.

Regulatory reporting of Subject Deaths will be completed according to local regulatory requirements. Refer to Table 11 for a list of required investigator and sponsor reporting requirements and timeframes.

11.6 Clinical Events Committee (CEC) review

At regular intervals, an independent Clinical Events Committee (CEC) will conduct a medical review of AEs, HCUs and deaths for subjects participating in the study.

The CEC will consist of a minimum of three (3) non-Medtronic employed physicians that are not participating investigators for the study, including a CEC chairperson. At a minimum, the CEC will adjudicate all adverse events, deaths, and HCUs as defined in section 14.2.5.

Medtronic personnel may facilitate and participate in a CEC meeting but will be non-voting members.

For adverse events and deaths reviewed by the CEC, Medtronic will provide the CEC with the Investigator's description and classification. The CEC is responsible for reviewing the Investigator's assessment and supportive documentation (when available), reviewing applicable definitions, and determining final classifications for all adjudication parameters. For adverse events, classification includes relatedness and complication or observation. Additionally, the CEC will provide an adjudication of the death classification for all reported deaths including primary cause of death, relatedness, and cardiac classification.

If the CEC disagrees with the investigator's classification of the event, the rationale will be provided to the investigator. If the investigator agrees with the CEC's adjudication, the case report form documenting the AE will be updated accordingly.

11.7 Product Complaint Reporting

In geographies where devices are market-released, product complaint reporting is applicable. This includes when an AE is related to a market-released device during the study. The reporting of product complaints is not part of the clinical study and should be

done in addition to the Adverse Event reporting requirements. Refer to local regulations for reporting requirements.

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 will notify the regulatory authorities, as applicable for the following incidents immediately upon learning of them:

- Any malfunction or deterioration in the characteristics and/or performance of a device, as well as any inadequacy in the labeling or instructions for use which led or might have led to the death or serious deterioration in the state of health of a patient, user, or other person.
- Any technical or medical reason resulting in withdrawal of a device from the market by the manufacturer.
- A serious deterioration in the state of heath includes:
    - Life-threatening illness or injury, or
    - Permanent impairment of a body structure function or a body function, or
    - In-patient or prolonged hospitalization, or
    - Medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function.

12 RISK ANALYSIS

Medtronic follows rigorous Quality Assurance and Control procedures throughout the research development process and for the duration of the clinical study. The risk analysis process for the LINQ™ Heart Failure (HF) study is being performed in accordance with ISO 14971, and ensures that the level of residual risk is reduced to as low as possible prior to starting the clinical study.

There are potential risks and side effects associated with a Reveal LINQ™ device implant and explant procedures:

- Allergenic reaction or device rejection phenomena including local tissue reaction
- Excessive device migration (internal pocket device movement as well as device externalization)
- Pocket infection
- Erosion through the skin
- Tissue / vascular trauma

Possible additional risks for participating in this study include the following (although others are possible):

- The Reveal LINQ™ device with the LINQ™ HF RAMware download is investigational and may be no more effective or less effective than a commercially available Reveal LINQ™ device system.
- [redacted]
- [redacted]
- There may be undesired device interactions with the LINQ™ HF investigational RAMware, potentially resulting in loss of or inaccurate Reveal LINQ™ data, and/or premature explant. Once the LINQ™ HF investigational RAMware feature set is executed, periodic data integrity checks are in place to ensure correct functionality.
- The Reveal LINQ™ device with the LINQ™ HF investigational RAMware download may present data that are different than anticipated due to unknown circumstances or medical conditions.
- There may be other discomforts and risks related to the Reveal LINQ™ device with LINQ™ HF investigational RAMware download and/or this study that are not foreseen at this time.

12.1 Risk Minimization

The potential risks associated with the LINQ™ HF investigational RAMware were identified, assessed, evaluated and effectively controlled. Any potential risks associated with this study are further minimized by selecting qualified investigators and training study personnel on the Clinical Investigation Plan.

In addition, investigators will be actively involved in the implantation and regular follow-up of the subjects implanted with the Reveal LINQ™ with investigational RAMware systems. At each office follow-up visit required per protocol (Table 6: Data collection and study procedure requirements at subject visits), the LINQ™ device will be interrogated, device data collected to verify appropriate device function and patient's health assessed for any adverse events.

Medtronic is further minimizing the possibility of risks by: performing required laboratory and pre-clinical testing prior to the clinical study, implementing quality control measures into production processes, providing guidelines for subject selection and evaluation, and providing adequate instructions and labeling.

Table 14: Potential Risks and Risk Minimization

Potential Risk	Minimization
ICM Pocket Infection from implant/ explant procedure or over duration of implant	• Industry standard sterilization and procedural processes will be followed to minimize the risk of infection • Wound check following implant, per site's practice
Allergenic reaction or ICM Rejection following implant procedure	• Assessment of subjects to ensure no allergenic or rejection reaction to materials used in incision/insertion tools, Reveal LINQ™ ICM exterior or incision closure method • Wound check following implant, per site's practice • Close monitoring with follow-up appointments • Investigator discretion to remove ICM and report study deviation • Use of biocompatible materials in the Incision/ Insertion Tools and Reveal LINQ™ ICM exterior patient-contacting surfaces
Excessive ICM Migration following implant procedure (internal device movement and externalization)	• Wound check following implant, per site's practice • Training and Information for User on the Reveal LINQ™ implant technique and incision closure techniques • Use of the implant tools to create small incision and tight pocket • Reveal LINQ™ ICM design includes anti-migration features on the header • Investigator discretion to remove if deemed medically necessary

Potential Risk	Minimization
Blunt Tissue Injury/Tissue or Vascular Trauma from implant/ explant procedure	• Insertion Tool has a stop position that prevents insertion of the probe beyond the distance required for prototype implant. • Training on the correct use of implant tools • Selection of experienced investigators
Pain, Scarring from implant/explant procedure	• Use of incision tool will produce the smallest incision possible for implant • Small device size minimizes the invasiveness of the implant and explant procedures
Undesired device interactions with the investigational RAMware	• Device interactions analysis to ensure there are no undesired interactions between the LINQ™ HF investigational RAMware and the Reveal LINQ™ device firmware. • LINQ™ HF investigational RAMware is designed to be automatically removed by the ROM code during POR processing
Premature/Unexpected ICM explant	• [redacted]
Electromagnetic interference	• Design consideration and precautions in place for the Reveal LINQ™ system remain effective to address EMI risks
[redacted]	[redacted]
Missing/Misleading information causing inappropriate medical intervention	• Data integrity checks have been implemented • Validation testing of the system set-up will be performed
Improper LINQ™ HF investigational RAMware access and activation	• Access code and preconditions are in place for appropriate activation • Data integrity checks have been implemented

12.2 Potential Benefits

The Reveal LINQ™ HF study may offer no direct personal benefit to individual subjects. Subjects may benefit from continuous arrhythmia monitoring with the Reveal ICM, as this monitoring could result in diagnosis of Atrial Fibrillation (or other arrhythmias) and comprehensive evaluation of symptoms on an earlier and more conclusive basis than what would be possible without an implantable cardiac monitor. Subjects may also benefit from being evaluated more frequently in the office according to the study visit schedule.

The information gained from this study could result in the improved management of other patients receiving a Reveal LINQ™ device in the future. Additionally, information collected from this study may assist in the design of new product(s)/therapy(ies) and/or instructions for use.

12.3 Risk-to-Benefit Analysis

Since the differences between the Reveal LINQ™ market-released device and the Reveal LINQ™ device with the LINQ™ HF investigational RAMware download are minimal, both devices are used in accordance with the Reveal LINQ™ implant manual and/or user manual, as applicable. The risks associated with the device are similar as would be the case if the subject received a Reveal LINQ™ device outside the study context. The risks introduced by the LINQ™ HF investigational RAMware are being evaluated and risk control measures being implemented to reduce the risk to as low as possible to minimize patient harm.

The study requirements for careful physician selection and training, and in-office visits carry potential benefits that might not be present if the subject was not enrolled in the study. Hence, for individual subjects, participation in the study may have greater benefit than risk. Moreover, the value of the knowledge to be gained by conducting this clinical study could help in the diagnosis of future patients. Lastly, the prospective benefit to LINQ™ HF subjects of having Reveal LINQ™ cardiac monitoring, with the potential to diagnose life-threatening arrhythmias, may provide the patient significant clinical benefit.

13 PLANNED STUDY CLOSURE, EARLY TERMINATIONOF STUDY OR STUDY SUSPENSION

13.1 Planned Study Closure

Study Closure is a process initiated by distribution of a study closure letter. Study closure is defined as closure of a clinical study that occurs 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. The study closure process is complete upon distribution of the Final Report or after final payments, whichever occurs last. Ongoing IRB oversight is required until the overall study closure process is complete. Refer to section 8.16 for additional information regarding study exit procedures.

13.2 Early Termination or Suspension

Early Termination of the Study is the closure of a clinical study that occurs prior to meeting defined endpoints. This is possible for the whole study or a single center. Study Suspension is a temporary postponement of study activities related to enrollment and distribution of the product. This is possible for the whole study or a single center.

13.2.1 Study-wide Termination or Suspension

Possible reasons for considering study suspension or termination of the study include but are not limited to:

- Adverse events associated with the system or product under investigation which might endanger the safety or welfare of the subject
- Observed/suspected performance different from the product's design intent
- Decision by Medtronic or regulatory body (where the study is operating under regulatory body authority)
- Technical issues during the manufacturing process

13.2.2 Investigator/center Termination or Suspension

Possible reasons for clinical investigator or center termination or suspension include but are not limited to:

- Failure to obtain initial IRB approval or annual renewal of the study
- Persistent non-compliance to the clinical investigation (e.g. failure to adhere to inclusion/exclusion criteria, failure to follow subjects per scheduled follow-ups)
- Lack of enrollment
- Noncompliance to regulations and the terms of the Clinical Trial Agreement (e.g. failure to submit data in a timely manner, failure to follow-up on data queries and monitoring findings in a timely manner, etc.)
- IRB suspension of the center
- Fraud or fraudulent misconduct is discovered (as defined by local law and regulations)
- Investigator request (e.g. no longer able to support the study)

13.3 Procedures for Termination or Suspension

13.3.1 Medtronic-initiated and Regulatory Authority-initiated

- Medtronic will promptly inform the clinical investigators of the termination or suspension and the reasons and inform the regulatory authority(ies) where required
- In the case of study termination or suspension for reasons other than a temporary IRB approval lapse, the investigator will promptly inform the IRB.
- In the case of study termination, the investigator must inform the subjects and may inform the personal physician of the subjects to ensure appropriate care and follow-up is provided
- In the case of a study suspension, subject enrollment must stop until the suspension is lifted by Medtronic
- In the case of a study suspension, enrolled subjects should continue to be followed out of consideration of their safety, rights and welfare

13.3.2 Investigator-initiated

- The investigator will inform Medtronic and provide a detailed written explanation of the termination or suspension
- The investigator will promptly inform the institution (where required per regulatory requirements)
- The investigator will promptly inform the IRB
- The investigator will promptly inform the subjects and/or the personal physician of the subjects to ensure appropriate care and follow-up is provided
- In the case of a study suspension, subjects enrolled should continue to be followed out of consideration of their safety, rights and welfare

13.3.3 IRB-initiated

- The investigator will inform Medtronic and provide a detailed written explanation of the termination or suspension within 5 business days
- Subject enrollment must stop until the suspension is lifted
- Subjects already enrolled should continue to be followed in accordance with IRB policy or its determination that an overriding safety concern or ethical issue is involved
- The investigator will inform his/her institution (where required per local requirements)
- The investigator will promptly inform the subjects, or legally-authorized designees and/or the personal physician of the subjects, with the rationale for the study termination or suspension.

14 STATISTICAL METHODS AND DATA ANALYSIS

14.1 General Considerations

Medtronic statisticians or designee will conduct all statistical analyses. The study is an event driven study with no formal statistical hypothesis planned. A separate Statistical Analysis Plan (SAP) will be developed and include a comprehensive description of the statistical methods and reports to be included in the final study report. 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.

14.2 Primary Objective

The primary objective is to characterize Reveal LINQ™ derived data from patients with heart failure by assessing the relationship between changes in LINQ™ derived data and other physiologic parameters with subsequent ADHF events.

14.2.1 Endpoint Definitions

why is the descriptive statistics redacted? (BN)

The ADHF events as adjudicated by the CEC that will be used in the primary analysis are those that are ≥30 days following implant in order to ensure sufficient LINQ™ derived data prior to the event onset are available. A second ADHF event within a subject may be used if the second ADHF event is >90 days following the first event. In the event a subject has > 2 qualifying ADHF events, only the first two will be used in the primary analysis. Additional analyses including all qualifying ADHF events may be conducted.

14.2.2 Analysis Methods

Physiologic data (including heart rate, bioimpedance, activity, blood pressure and weight), as well as blood samples (including serum BUN, creatinine, NT-proBNP, hemoglobin, hematocrit, troponin, eGFR and electrolytes), will be collected from subjects with acute decompensated heart failure. [redacted] Data will be collected from enrollment up to 3 years post-insertion. If a subject exits the study prematurely, data captured prior to exit will be included in the analysis. All data collected will be included in the analysis. Descriptive statistics (e.g. means, standard deviations, proportions) will be used to summarize the physiological and derived data recorded. Analyses will be conducted to assess changes in the physiologic and LINQ™ derived data in association with HF events.

14.2.3 Determination of Patients/Data for Analysis

All subjects with a successful insertion will be used in the analysis.

14.2.4 Sample Size

There are no sample size requirements as this is an observational study. The sample size was selected in order that data can be derived from an estimated 40 subjects with a

HF event within 12 months. This provides a conservative estimate of the required number of subjects. The CHAMPION study provides a 12 month KM estimate of HF hospitalization of 30% for Class III subjects.[17] To be conservative, it is assumed 25% of enrolled subjects will have at least one HF event within 12 months. If the estimate is used as a binomial proportion, a sample size of 300 subjects would accrue ≥40 subjects with event within 12 months with > 99% probability. If the proportion of subjects with HF event is lower than 25%, the probability of at least 40 subjects with at least one HF event is >91% if the underlying proportion of subjects with event is ≥16%. The projected enrollment number of 300 may be readjusted if the frequency of HF events is higher or lower than anticipated.

14.2.5 Heart Failure (HF) Event Definition

A heart failure event is 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

14.3 Interim Analysis

No interim analysis is planned in this study. Since there is no interim analysis planned, there are no criteria for early termination based on statistical evidence.

14.4 Missing Data

Missing data will not be imputed. In order to be included in the primary analysis, an ADHF event must have complete LINQ™ data downloads prior to the event. If device data is missing, the event will not be included in the primary analysis.

14.5 Subgroup Analysis

No subgroup analysis is planned in this study.

15 DATA AND QUALITY MANAGEMENT

Data will be collected using an electronic data management system for clinical studies. CRF data will be stored in a secure, password-protected database which will be backed up nightly. Data will be reviewed using programmed and manual data checks. Data queries will be made available to centers for resolution. Study management reports may be generated to monitor data quality and study progress. At the end of the study, the data will be frozen and will be retained indefinitely by Medtronic.

All records and other information about subjects participating in this study will be treated as confidential. Data will be transferred and processed by Medtronic or a third party designated by Medtronic in a key coded form, unless it's impossible to make it anonymous, for instance, where the subject's name cannot be removed from the data carrier.

Procedures in the CIP require source documentation. Source documentation will be maintained at the site. Source documents, which may include worksheets, patient medical records, programmer printouts, and interrogation files, must be created and maintained by the study center.

The data reported on the eCRFs shall be derived from source documents and be consistent with these source documents, and any discrepancies shall be explained in writing.

Device data from transmissions will be uploaded to secure servers. Media/USB data collected at office visits will be sent to Medtronic. Upon receipt, device data will be maintained with databases and retrieved for analysis and reporting.

The sponsor or a regulatory authority may audit or inspect the study center to evaluate the conduct of the study. The clinical investigator(s)/institution(s) shall allow study related monitoring, audits, IRB review and regulatory inspection by providing direct access to source data/documents.

16 WARRANTY/INSURANCE INFORMATION

16.1 Warranty

Warranty information is provided in the product packaging for the LINQ™ ICM. Additional copies are available upon request.

17 MONITORING

It is the responsibility of Medtronic to ensure proper monitoring of this clinical study. Trained Medtronic personnel or delegates appointed by Medtronic may perform study monitoring at the study center or via remote monitoring in order to ensure that the study is conducted in accordance with the CIP, the Clinical Trial Agreement, and applicable regulatory and local requirements. Medtronic, or delegates, must therefore be allowed access to the subjects' case histories (clinic and hospital records, and other source data/documentation) upon request as per the Patient Informed Consent Form, Research Authorization (where applicable) and Clinical Trial Agreement. The principal investigator should also be available during monitoring visits.

17.1 Monitoring Visits

Frequency of monitoring visits may be based upon subject enrollment, duration of the study, study compliance, number of adverse events, number of deviations, findings from previous monitoring visits and any suspected inconsistency in data that requires investigation. Regulatory documents may be reviewed at each study center. Monitoring for the study, including site qualification visits, site initiation visits, interim monitoring visits, and closeout visits will be done in accordance to the Reveal LINQ™ HF monitoring plan.

Monitoring visits may be conducted periodically to assess site study progress, the investigator's adherence to the CIP, regulatory compliance including but not limited to IRB approval and review of the study, maintenance of records and reports, and review of source documents against subject eCRFs. Monitors review site regulatory and study compliance by identifying findings of non-compliance and communicating those findings along with recommendations for preventative / corrective actions to site personnel. Monitors may work with study personnel to determine appropriate corrective action recommendations and to identify trends within the study or at a particular center.

17.2 Access to the Site and Study Materials

The investigator will permit study related monitoring, audits, IRB review and regulatory inspections by providing direct access to source data and source documents.

18 REQUIRED RECORDS AND REPORTS

18.1 Investigator Records

The investigator is responsible for the preparation and retention of the records cited below. All of the below records, with the exception of case history records and case report forms, should be kept in the Investigator Site File (i.e., the study binder provided to the investigator) or Subject Study Binder. CRFs must be maintained and signed electronically within the electronic data capture system during the study. The following records are subject to inspection and must be retained for a period of two years (or longer as local law or hospital administration requires) after the date on which the investigation is terminated.

- All correspondence between the IRB, sponsor, monitor, FDA, regulatory authority and the investigator that pertains to the investigation, including required reports.
- Subject's case history records, including:
  - Signed and dated Patient Informed Consent Form
  - Observations of adverse events/adverse device effects/device deficiencies
  - Medical history
  - LINQ™ Insertion and follow-up data
  - Documentation of the dates and rationale for any deviation from the protocol
- List of investigation sites
- Financial disclosure
- Normal value(s)/range(s) for clinical laboratory tests
- Lab certificate (if applicable)
- Investigational product traceability records
- Non implantable product traceability records (if applicable)
- All approved versions of the CIP, PIC and Report of Prior Investigation Summary
- Signed and dated Clinical Trial Agreement
- Current curriculum vitae principal investigators
- Documentation of delegated tasks
- IRB approval documentation. Written information that the investigator or other study staff, when member of the IRB, did not participate in the approval process. Approval documentation must include the IRB composition, where required per local law
- Regulatory authority notification, correspondence and approval, where required per local law
- Study training records for site staff
- Any other records that FDA and local regulatory agencies require to be maintained (e.g financial disclosure)
- Final Study Report including the statistical analysis

18.2 Investigator Reports

The investigator is responsible for the preparation (review and signature) and submission to the sponsor of all case report forms, adverse events and adverse device effects (reported per the country-specific collection requirements), device deficiencies, deaths, and any deviations from the clinical investigation plan. If any action is taken by an IRB with respect to this clinical study, copies of all pertinent documentation must be forwarded to Medtronic in a timely manner. Reports are subject to inspection and to the retention requirements as described above for investigator records.

Safety data investigator reporting requirements are listed in section 11.The investigator shall prepare and submit in a complete, accurate and timely manner the reports listed in this section.

If any action is taken by an IRB with respect to this clinical study, copies of all pertinent documentation must be forwarded to Medtronic in a timely manner.

Table 15: Investigator Reports per Medtronic Requirements

Report	Submit to	Description/Constraints
Withdrawal of IRB approval	Sponsor and Relevant Authorities, if applicable	The investigator must report a withdrawal of approval by the reviewing IRB of the investigator's part of the investigation within 5 working days.
Study deviations	Sponsor and IRB	Notice of deviations from the CIP to protect the life or physical wellbeing of a subject in an emergency shall be given as soon as possible, but no later than 5 working days after the emergency occurred. Except in such emergency, prior approval is required for changes in the plan or deviations. If the deviation may affect the scientific soundness of the plan or the rights, safety and welfare of the subjects, the deviation must be approved by Medtronic, the IRB, and the FDA/applicable regulatory authorities. If the deviation does not affect these issues then only Medtronic must approve it. *(21 CFR 812.150(a)(4))*
Withdrawal of IRB approval (either suspension or termination)	Sponsor	The investigator must report a withdrawal of approval by the reviewing IRB of the investigator's part of the investigation within 5 working days. *(21 CFR 812.150(a)(2))*
Progress report	Sponsor and IRB	The investigator must submit this report to the sponsor and IRB at regular intervals, but in no event less than yearly. *(21 CFR 812.150 (a)(3))*.
Failure to obtain informed consent prior to investigational device use	Sponsor and IRBs	If an investigator uses a device without obtaining informed consent, the investigator shall report such use within 5 working days after device use. *(21 CFR 812.150(a)(5))*
Final report	Sponsor and IRBs	This report must be submitted within 3 months of study completion or termination of the investigation or the investigator's part of the investigation. *(21 CFR 812.150(a)(6))*

18.3 Sponsor Records

Medtronic shall maintain the following accurate, complete, and current records which include, but are not limited to:

- All correspondence which pertains to the investigation
- Signed Investigator Trial Agreements, financial disclosure and curriculum vitae of principal investigator and delegated task list
- All approved informed consent templates, and other information provided to the subjects and advertisements, including translations
- Copies of all IRB approval letters and relevant IRB correspondence and IRB voting list/roster/letter of assurance, if applicable
- Names of the institutions in which the clinical study will be conducted
- Regulatory authorities correspondence, notification and approval as required by national legislation
- Names/contact addresses of monitors
- Statistical analyses and underlying supporting data
- Final report of the clinical study
- The Clinical Investigation Plan, Report of Prior Investigations summary and study related reports, and revisions
- Study training records for site personnel and Medtronic personnel involved in the study
- Any other records that local regulatory agencies require to be maintained
- Investigational product traceability records
- Non-implantable product traceability records

18.4 Sponsor Reports

Medtronic shall prepare and submit the following complete, accurate, and timely reports listed in the table below. In addition to the reports listed below, Medtronic shall, upon request of reviewing IRB and/or regulatory agency provide accurate, complete and current information about any aspect of the investigation. Safety data Medtronic reporting requirements are listed in Table 11 of the Adverse Event section.

Table 16: Sponsor Reports

Report	Submit to	Description/Constraints
Withdrawal of IRB approval	Investigators, IRB	Notification within five working days. *(21 CFR 812.150(b)(2))*
Progress Reports	IRB	Progress reports will be submitted at least annually. *(21 CFR 812.150(b)(5), 812.36(f)*
Recall and device disposition	Investigators, IRB	Notification within 30 working days and will include the reasons for any request that an investigator return, repair, or otherwise dispose of any devices. *(21 CFR 812.150(b)(6))*
Final report	Investigators, IRB	A final report will be submitted to investigators and IRBs within six months after completion or termination of this study. *(21 CFR 812.150(b)(7))*
Study Deviation	Investigators	Ensure that all deviations from the Clinical Investigation Plan are reviewed with the appropriate clinical investigator(s), are reported on the case report forms and the final report of the clinical investigation. Site specific study deviations will be submitted to investigators periodically.
Significant risk device determination	FDA	If an IRB determines that the device is a significant risk device, the sponsor shall submit to FDA a report of the IRB's determination within 5 working days after sponsor learns of the determination. *(21CFR 812.150(b)(9))*

Medtronic records and reports will be stored in a password-protected document management system.

The sponsor and principal investigator shall maintain the clinical investigation documents as required by the applicable regulatory requirement(s). They shall take measures to prevent accidental or premature destruction of these documents. The principal investigator or sponsor may transfer custody of records to another person/party and document the transfer at the investigation site or at the sponsor's facility.

Appendix A: Data Collection Elements (Case Report Forms)

A copy of the Case Report Forms for the Reveal LINQ™ Heart Failure (HF) Study is available under separate cover. Final CRFs will be provided to sites via the electronic data management system after the site has fulfilled all requirements for database access.

Appendix B: Preliminary Publication Plan

Publications from the Reveal LINQ™ Heart Failure (HF) Study will be handled according to Medtronic's Standard Operating Procedures and as indicated in the Clinical Trial Agreement.

Publication Committee

Medtronic may form the Reveal LINQ™ Heart Failure (HF) Publication Committee from study investigators. Medtronic personnel may serve as members of the committee. This committee will manage study publications with the goal of publishing findings from the data. The Publication Committee will develop the final Publication Plan as a separate document.

The Publication Committee's role is to: 1) manage elements addressed in the publication plan as outlined in this appendix, 2) develop the final Publication Plan under separate cover, 3) execute the Publication Plan, 4) oversee the publication of primary and ancillary study results, 5) review and prioritize publication proposals, 6) provide input on publication content, and 7) determine authorship. In addition, the committee will apply and reinforce the authorship guidelines set forth in the Publication Plan.

Membership in the Publication Committee does not guarantee authorship. The committee will meet as needed.

Management of Primary and Ancillary Publications

The Publication Committee reviews, prioritizes, and manages all publications including primary and ancillary publications. Primary publications are those that address analyses of the primary objective as specified in the Clinical Investigation Plan.

An ancillary publication is any publication that does not address the primary study objective identified in the Clinical Investigation Plan. They include publications proposed and developed by the Publication Committee, other Medtronic departments or entities, clinicians participating in this clinical study, and clinicians not participating in this clinical study. The committee will work with Medtronic to ensure that requests do not present conflicts with the primary results, other proposals, are not duplicative, and to determine which ancillary publication proposals, if any, will be supported.

The committee may decide that no publications, including abstracts, will be published prior to the end of the study or with individual center data. Requests for publications on study objectives utilizing subset data (e.g., regional) will be evaluated for scientific validity and the ability of Medtronic to provide resources.

Criteria for Determining Authorship

Publications will adhere to authorship criteria defined by the International Committee of Medical Journal Editors (ICMJE, Uniform requirements for manuscripts submitted to biomedical journals, www.icmje.org). Individual authorship criteria defined by the target journal or conference will be followed when it differs from ICMJE criteria.

Authors, including Medtronic personnel, must at a minimum meet all of the conditions below:

- Substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data for the work; AND
- Drafting the work or revising it critically for important intellectual content; AND
- Final approval of the version to be published; AND
- Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Decisions regarding authorship and contributor-ship will be made by the committee according to a priori ranking system. The selected authors will be responsible for drafting the publication. All selected authors must fulfill the authorship conditions stated above to be listed as authors

All investigators not listed as co-authors will be acknowledged as the “Medtronic Reveal LINQ™ Heart Failure (HF) Clinical Study Investigators” and will be individually listed according to the guidelines of the applicable scientific journal when possible and affiliation. Any other contributors will be acknowledged by name with their specific contribution indicated.

Transparency

Transparency of study results will be maintained by the following means:

- a final report, describing the results of all objectives and analysis, will be distributed to all investigators and IRBs.
- registering and posting the study results on ClinicalTrials.gov based on the posting rules stipulated
- submitting for publication the primary study results after the study ends
- disclosing conflicts of interest (e.g., financial) of the co-authors of publications according to the policies set forth by the corresponding journals and conferences
- making an individual centers study data accessible to the corresponding investigator after the completion of the study, if requested

Appendix C: LINQ™ HF Study Procedure Handbook

A LINQ™ HF Study Procedure handbook that will provide instructions on how to use the DR220 Holter during the 6 Minute Hall Walk test and [redacted]

Appendix D: Patient Informed Consent Form Template

Patient Informed Consent Form will be provided under separate cover.

Appendix E: Participating Investigators and Institutions

A complete list of participating investigators and institutions where study activities will be conducted will be provided under separate cover.

This information will be updated throughout the course of the study. The updated list will be maintained at Medtronic and will be available upon request.

Appendix F: IRB Committee List

A complete list of participating IRBs and the Chairperson(s) will be provided under separate cover.

This information will be updated throughout the course of the study. The updated list will be maintained at Medtronic and will be available upon request.

Appendix G: Labeling

Labeling for the LINQ™ HF investigational RAMware will be provided under separate cover. Labeling for all other market approved system components can be found with each package insert.

In addition, the subject may receive an Instructions manual on how to perform the manual device transmission. This will be provided under separate cover, if applicable.

Appendix H: Bibliography

A complete bibliography and summary of relevant literature, summary and results of preclinical testing and summary and results of previous clinical investigational is provided in the Report of Prior Investigation (RPIS).

[1] Jencks SF, Williams MV, Coleman EA (2009) Rehospitalizations among Subjects in the Medicare Fee-for-Service Program. New England Journal of Medicine 360(14): 1418-1428.

[2] Ahmed A, Allman R, Fonarow G, Love TE, Zannad F, Dell'Italia LJ, White M, Gheorghiade M. (2008) Incident Heart Failure Hospitalization and Subsequent Mortality in Chronic Heart Failure: A Propensity-Matched Study. Journal of Cardiac Failure 1 4(3): 211-218.

[3] Solomon SD, Dobson K, Pocock S, Skali H, McMurray JJV, Granger CB, Yusuf S, Swedberg K, Young JB, Michelson EL, Pfeffer MA and for the Candesartan in Heart failure: Assessment of Reduction in Mortality and mortality (CHARM) Investigators (2007) Influence of Nonfatal Hospitalization for Heart Failure on Subsequent Mortality in Subjects with Chronic Heart Failure. Circulation 116(13):1482-1487.

[4] Fonarow GC, Stough WG, Abraham WT, Albert NM, Gheorghiade M, Greenberg BH, O'Connor CM, Sun JL, Yancy CW, Young JB (2007) Characteristics, Treatments, and Outcomes of Subjects with Preserved Systolic Function Hospitalized for Heart Failure: A Report from the OPTIMIZE-HF Registry. Journal of the American College of Cardiology 50(8): 768-777.

[5] Whellan, David, et. al. *Combined Heart Failure Device Diagnostics Identify Patients at Higher Risk of Subsequent Heart Failure Hospitalizations*. Journal of American College of Cardiology, Vol. 55, No. 17, 2010.

[6] Cowie, Martin, et. al. *Development and validation of an integrated algorithm derived from parameters monitored in implantable devices for identifying patients at risk for heart failure hospitalization in an ambulatory setting*. European Heart Journal, 2013.

[7] Auricchio, Angelo, et.al. *Assessment of a novel device-based diagnostic algorithm to monitor patient status in moderate-to-severe heart failure: rationale and design of the CLEPSYDRA Study*. European Journal of Heart Failure, 2010.

[8] Boehmer, John, et. al. *Rationale and Design of the Multisensor Chronic Evaluations in Ambulatory Heart Failure Patients (MultiSENSE) Study*. Cardiac Rhythm Management, 6:2137-2143, 2015.

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[10] Adamson, et. al. *Continuous Autonomic Assessment in patients with symptomatic heart failure: Prognostic Value of Heart Rate variability measured by an Implantable Cardiac Resynchronization Device*, Circulation 110:2389-2394, 2004.

[11] Goetze, Stephan, et. al. *Ambulatory respiratory rate trends identify patients at higher risk of worsening heart failure in implantable cardioverter defibrillator and biventricular device recipients: a novel ambulatory parameter to optimize heart failure management*. J Inter Card Electrophysiol, 43:21-29, 2015.

[12] Katra, Rodolphe, Niranjan Chakravarthy, *Remote At-Home Detection and Monitoring of Functional Chronotropic Incompetence in Heart Failure Patients*. J of Cardiovasc Trans. Res. 4:14-20, 2011.

[13] Yu CM, Wang L, Chau E, et al. Intrathoracic impedance monitoring in patients with heart failure: correlation with fluid status and feasibility of early warning preceding hospitalization. Circulation 2005;112(6):841-8.

[14] Roy-Chaudhury, P, Williamson, DE, Tumlin, JA, Kher, VK, Prakash, K, Charytan DM, Tiwari, SC, Pokhariyal, S, Podoll, AS. "Monitoring in Dialysis (MiD) Study: Exploring the Timeline and Etiology of Increased Arrhythmias in Hemodialysis (HD) Patients." J Am Soc Nephrol; 2015: Late Breaking Clinical Trial Poster (SA-PO1112).

[15] Ekman, I., et. al. *Symptoms in patients with heart failure are prognostic predictors: insights from COMET. Journal of Cardiac Failure*. 11, 288–292, 2005.

[16] Silva, L., et. al. *Persistent orthopnea and the prognosis of patients in the heart failure clinic*. Congestive Heart Failure, 10, 177–180, 2004.

[17] Philip B. Adamson, William T. Abraham, Robert C. Bourge, Maria Rosa Costanzo, Ayesha Hasan, Chethan Yadav, John Henderson, Pam Cowart, and Lynne Warner Stevenson. Wireless Pulmonary Artery Pressure Monitoring Guides Management to Reduce Decompensation in Heart Failure With Preserved Ejection Fraction. Circ Heart Fail. 2014;7:935-944.

Appendix I: Pre-clinical Testing

A summary and results of pre-clinical testing is provided in the LINQ™ HF Report of Prior Investigations Summary (RPIS).

Appendix J: Previous Clinical Investigations

A summary and results from previous clinical investigations related to the LINQ™ HF study or devices with similar features is provided in the Report of Prior Investigations Summary (RPIS).

Appendix K: Committees

The Reveal LINQ™ Heart Failure (HF) study will utilize a Clinical Events Committee (CEC) for the assessment of Adverse Events, Healthcare Utilizations and Deaths.

The Reveal LINQ™ Heart Failure (HF) study may utilize a Publication Committee aiming to manage study publications.

A Data Monitoring Committee (DMC) is not needed for this study. This decision was made based on the following criteria: fast enrollment in this trial (approximately 18 months) making a DMC impractical, and it is felt there are no additional benefits of a DMC reviewing the data in addition to the Clinical Events Committee (CEC).

The updated member lists will be maintained at Medtronic and will be made available upon request.

Appendix L: Summary of Changes

Version	Summary of Changes	Author
1.0	Initial Release	Jennifer Seamans, Principal Clinical Research Specialist
2.0	Section 1.2: Updated sponsor contact information in Table 1 to reflect change in worldwide study leader.	Aimee Laechelt, Senior Clinical Research Specialist
	Section 1.4: Added Steering Committee membership and contact information since committee is now established.	
	Sections 2 and 5: Updated Tables 4 and 6 to allow for subsequent versions of the investigational RAMware to be utilized since an updated version is expected to be released, with clarifying language beneath table.	
	Sections 2 and 7.3: Updated inclusion criteria to clarify window allowed for the NYHA III criterion.	
	Sections 2 and 7.3: Updated BNP/NTpro-BNP inclusion criterion to clarify categorization for patients with EF=50, to clarify that the 3-month window applies to the BNP/NTpro-BNP measurement, and to specify units for BNP/NTpro-BNP.	
	Section 8.11: Updated to clarify recommended frequency for phone calls to subjects to ensure complete and timely reporting of HCUs, and to clarify timing of follow-up windows and how they will be provided to sites.	
	Section 8.12: Updated to clarify that a deviation form will not be required for a missed monthly transmission if a device interrogation performed within the window is provided to Medtronic, since the device interrogation would capture all of the required data.	
	Section 8.14: Clarified scope of types of HCUs to be reported, and reformatted for further clarity.	
	Section 9: Removed statement that study components can only be ordered by Medtronic, since sites can place an order directly to Medtronic (which is acceptable since Medtronic manages distribution of product).	
	Section 9: Added clarification that only the patient assistants kept at the site need to be tracked since they need to be returned to Medtronic at the end of the study (the patient assistants provided to the study subjects don't	

	need to be tracked since not investigational and don't need to be returned).	
	Section 9: Removed requirement for CareLink monitors to be tracked since they are not investigational and don't need to be returned to Medtronic.	
	Section 9: Updated language to clarify documentation requirements associated with installation/removal of the investigational RAMware from the devices and programmers.	
	Section 9.1: Updated Table 9 to include subsequent versions of the investigational RAMware since the CIP now allows for subsequent versions of the RAMware to be utilized in the study.	
	Section 11: Added SADE definition to Table 10 for completeness.	
	Section 11: Updated Table 10 to remove note that only system or procedure related AEs will be classified as a complication or observation, since these are the only types of AEs being collected in the study.	
	Section 11.2.1: Added clarification that deaths will be reported via a Subject Death form.	
	Section 11.2.2: Added clarification that device deficiencies that result in an ADE should be captured on an AE form.	
	Section 11.3: Updated Table 11 to correct "Severity" to "Seriousness", and to remove language stating that SAEs and UADEs would be adjudicated as complications/observations by the sponsor, since this will be performed by the CEC.	
	Section 11.6: Clarified scope of CEC adjudication.	
	Section 14.2.4: Corrected HF event probability (due to error in CIP v1.0).	
	Section 18.1: Removed "Subject screening log (if applicable)" from list of investigator records, since not required to be maintained for this study.	
	Section 18.1: Added "if applicable" to requirement for maintaining non implantable product traceability records, since not required in all cases (e.g. CareLink monitors and patient assistants provided to subjects are not required to be tracked).	
	Section 18.4: Updated Table 16 to remove requirements for reporting to FDA, since the study is classified as a non-significant risk IDE	

	and therefore the study was not submitted to FDA.	
	Appendix A: Updated text to remove “draft” since final version of CRFs now available.	
	Appendix E: Removed statement that site confirmation was not finalized since now complete, and clarified that a site list would be provided under separate cover.	
	Appendix F: Removed statement that site confirmation was not finalized since now complete, and clarified that an IRB list would be provided under separate cover. Also added statement that information will be updated throughout study and updated listing will be available upon request.	
	Appendix L: Updated Summary of Changes to include changes reflected in CIP v2.0.	
	Minor updates to punctuation, grammar and formatting throughout document for accuracy, clarity and consistency.	

Statistical Analysis Plan

Clinical Investigation Plan Title	Reveal LINQ HF
Clinical Investigation Plan Version	1.0
Sponsor/Local Sponsor	Medtronic, Inc. 8200 Coral Sea Street NE Mounds View, MN U.S.A. 55112 1-800-328-2518
Document Version	1.0

Table of Contents

1. Version History

Version	Summary of Changes	Author(s)/Title
1.0	• Not Applicable, New Document	Lou Sherfesee, Sr. Principal Statistician

2. List of Abbreviations and Definitions of Terms

Abbreviation	Definition
AE	Adverse Event
ADHF	Acute decompensated heart failure
AF	Atrial Fibrillation
AHF	Acute Heart Failure
CEC	Clinical Events Committee
CIP	Clinical Investigational Plan
CRF	Case Report Form
CRT	Cardiac Resynchronization Therapy
ECG	Electrocardiogram
EF	Ejection Fraction
HCU	Healthcare Utilization
HF	Heart Failure
ICD	Implantable Cardioverter-Defibrillator
ICM	Insertable Cardiac Monitor
IPG	Implantable Pulse Generator
NYHA	New York Heart Association
RAMware	Software downloaded onto LINQ™ device
RR	R-wave to R-wave interval
SAE	Serious Adverse Event

3. Introduction

Medtronic, Inc. is sponsoring the Reveal LINQ™ Heart Failure (HF) study, a prospective, non-randomized, multi-center, observational, pre-market clinical study. The purpose of this clinical study is to characterize Reveal LINQ™ derived data from patients with heart failure by assessing the relationship between changes in LINQ™ derived data and other physiologic parameters with subsequent acute decompensated heart failure events (ADHF).

The study is utilizing the Reveal LINQ™ device with an investigational LINQ™ HF RAMware. [redacted] Additionally, the device will collect the standard information collected in the market released LINQ™ device such as atrial fibrillation burden, average ventricular rate during atrial fibrillation (AF), night and day heart rate and heart rate variability. The study will also collect information regarding HF related clinical events during the same period.

The data collected via the LINQ HF investigational RAMware will not be provided to sites for the treatment of the subjects. Following insertion of the LINQ™ device and download of the LINQ HF investigational RAMware, subjects will be followed for up to 3 years post-insertion 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 Reveal LINQ HF Study design and the planned analyses to be included in a final report.

4. Study Objectives

The primary objective is to characterize Reveal LINQ™ derived data from patients with heart failure by assessing the relationship between changes in LINQ™ derived data and other physiologic parameters with subsequent ADHF events.

5. Investigation Plan

The LINQ™ HF study is a Non-Significant Risk Investigational Device Exemption (IDE) study. The study is utilizing the Reveal LINQ™ device with an investigational LINQ™ HF RAMware download. The LINQ™ HF RAMware enables [redacted]

The single-arm observational study is expected to be conducted at up to 30 centers in the United States. Up to 300 subjects will be enrolled to achieve approximately 40 ADHF events (no more than two per subject will contribute to the cumulative total). Study subjects will be followed for up to 3 years post-insertion 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. The expected study duration is approximately 4 years representing 1.5 years of enrollments and 2.5 years of follow-up.

The subject population for the LINQ™ HF study is patients with heart failure with a New York Heart Association (NYHA) Class III. Inclusion and Exclusion criteria are listed below.

INCLUSION CRITERIA

- Patient is 18 years of age or older
- 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 and Carelink transmissions.
- Patient is NYHA Class III
- Patient had a HF event (HF event defined as meeting any one of the following three
- criteria):
  1. Admission with primary diagnosis of HF within the last **6 months**, OR
  2. Intravenous HF therapy (e.g. IV diuretics/vasodilators) or ultrafiltration at any one of the following settings within the last **6 months**:
     - Admission with secondary/tertiary diagnosis of HF
     - Emergency Department
     - Ambulance
     - Observation Unit
     - Urgent Care
     - HF/Cardiology Clinic
     - Patient's Home, OR
  3. Patient had the following within the last **3 months**: EF > 50%, then BNP> 200 ng/L or NTpro-BNP > 400 ng/L OR If EF is <50%, then BNP> 400 ng/L or NTpro-BNP > 800 ng/L

EXCLUSION CRITERIA

- 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 severe valvular heart disease as defined by hemodynamically significant valve stenosis and/or prosthetic heart valve
- Patient has existing IPG, ICD, CRT-D or CRT-P device
- Patient has severe renal impairment (eGFR <25mL/min)

Subjects will have in-office visits at 1 month post-insertion, as well as 6 and 12 months post-insertion. These in-office visits will include NYHA assessment, 6 minute hall walk, [redacted], physical exam, medication assessment, and collection of symptoms and temperature. Blood tests will be performed at the 6 and 12 month visits. Following the 12 month visit, there will be no further required in-office visit until the exit visit in which the RAMware is removed from the device. In addition to in-office visits, subjects will perform monthly manual CareLink transmissions. [redacted]

[redacted]

6. Determination of Sample Size

There are no sample size requirements as this is an observational study. However, 40 ADHF events with LINQ device data available for the most recent 30 days prior to the event will be collected; up to two events per subject may be used in the analysis, and these events must be at least 90 days apart. While any ADHF event with the requisite device data that occurs prior to a subject's exit may be used in the analysis, the sample size was selected in order that data can be derived from an estimated 40 subjects with a ADHF event within 12 months. This provides a conservative estimate of the required number of subjects. The CHAMPION study provides a 12 month KM estimate of HF hospitalization of 30% for Class III subjects[1]. To be conservative, it is assumed 25% of enrolled subjects will have at least one ADHF event within 12 months. If the estimate is used as a binomial proportion, a sample size of 300 subjects would accrue ≥40 subjects with event within 12 months with > 99% probability. If the proportion of subjects with ADHF event is lower than 25%, the probability of at least 40 subjects with at least one ADHF event is >88% if the underlying proportion of subjects with event is ≥16%. The projected enrollment number of 300 may be readjusted if the frequency of ADHF events is higher or lower than anticipated.

7. Statistical Methods

7.1. Study Subjects

7.1.1. Disposition of Subjects

This is a single-arm study. Subjects who are consented will undergo a planned standard of care surgical procedure. At enrollment, subjects consent to have a Reveal LINQ inserted and investigational LINQ HF RAMware downloaded. Subjects will then return for 1, 6, and 12 month visits and an exit visit. A STROBE diagram will show each of these stages of follow-up through 12 months, with categories for missed visit, death, exit, and early study closure as reasons subjects did not complete a visit. If the study continues beyond 12 months for one or more subjects, there will be a final box with categories for death, exit, and study closure as reasons for study discontinuation beyond 12 months.

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, how many occurrences there were in the study, and the number of subjects experiencing each type of deviation. Inclusion/exclusion violations will not result in subjects being excluded from analysis of objectives. [redacted]

[redacted]

7.1.3. Analysis Sets

All enrolled subjects who undergo a LINQ insertion and investigational LINQ HF RAMware download will be included in the analysis of the primary objective. Subjects who do not experience ADHF events used in the analysis will still have their data summarized as a reference.

7.2. General Methodology

Data analysis will be performed by a Medtronic statistician or designee, and will be performed once at least 40 ADHF events (as adjudicated by the CEC) occurring at least 30 days post-Reveal LINQ implant have been obtained from subjects who received the downloaded RAMware and have data for the most recent 30 days prior to the event. No more than two events per subject will be included in the analysis, and those two events must be at least 90 days apart.

All analyses will be performed on an "As Treated" basis.

The cohort will include all enrolled subjects who received the downloaded investigational LINQ HF RAMware and experienced ADHF events at least 30 days post-implant. Subjects who do not experience ADHF events may also be included as a reference dataset for baseline readings of measurements (i.e. profile of measurements that do not precede ADHF events).

Any tests of treatment effects will be conducted at a two-sided alpha level of 0.05 unless otherwise stated.

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 Data and Dropouts

Missing data will not be imputed. In order to be included in the primary analysis, an ADHF event must have LINQ™ data downloads for at least the most recent 30 days prior to the event. If device data are missing, the event will not be included in the primary analysis.

7.5. Adjustments for Multiple Comparisons

No adjustment for multiple comparisons will be made. This is a single arm study.

7.6. Demographic and Other Baseline Characteristics

Descriptive statistics will be used to summarize baseline and demographic characterstics. For categorical data such as gender and New York Heart Association classification, 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 receive a LINQ device.

7.7. Treatment Characteristics

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

- Time from procedure check-in to subject discharge
- Pre-procedure preparation time
- Procedure time (time subject enters the room to time subject leaves procedure room)
- Insertion time (time from firt incision to skin closure)
- Pre-procedure preparation location
- Procedure location
- Location of inserted device (e.g. parallel to sternum over 4th intercostal space)
- Whether device was sutured
- Closure method used (e.g. staple(s), suture(s))
- Local anesthesia used
- Antibiotic agent(s) administered pre-procedure and post-procedure
- Location of subject education on their Reveal LINQ system, and total education time

Additionally, the percentage of subjects on CV medications will be assessed as of each follow-up visit. This will be done separately for relevant classes such as beta blockers, diuretics, and ACE-Inhibitors/ARBs.

7.8. Interim Analyses

No interim analyses are planned for this study. Since there is no interim analysis planned, there are no criteria for early termination based on statistical evidence. Once the requisite number of ADHF events have been obtained (a minimum of 40 occurring ≥ 30 days post-implant among subjects with the RAMware downloaded to the subject's LINQ device, with no more than two ADHF events per subject), follow-up in the study may be terminated and all subjects exited.

7.9. Evaluation of Objectives

The primary objective is to characterize Reveal LINQ™ derived data from patients with heart failure by assessing the relationship between changes in LINQ™ derived data and other physiologic parameters with subsequent ADHF events.

7.9.1. Hypothesis

Due to the feasibility nature of this trial, there are no hypotheses for this objective.

7.9.2. Performance Requirements

Performance requirements are not pre-specified for this objective. The ADHF events as adjudicated by the CEC that will be used in the primary analysis are those that are ≥30 days following implant in order to ensure sufficient LINQ™ derived data prior to the event onset are available. A second ADHF event within a subject may be used if the second ADHF event is >90 days following the first event. In the event a subject has > 2 qualifying ADHF events, only the first two will be used in the primary analysis. Additional analyses including all qualifying ADHF events may be conducted.

A heart failure event is 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

7.9.3. Rationale for Performance Criteria

This is a feasibility study, and so this objective is for the purpose of gathering data for [redacted] this data will be used later for potential hypothesis generation regarding the predictive nature of one or more of these data elements for ADHF outcomes.

7.9.4. Analysis Methods

Physiologic data (including heart rate, bioimpedance, activity, blood pressure and weight), as well as blood samples (including serum BUN, creatinine, NT-proBNP, hemoglobin, hematocrit, troponin, eGFR and electrolytes), will be collected from subjects with acute decompensated heart failure. [redacted]

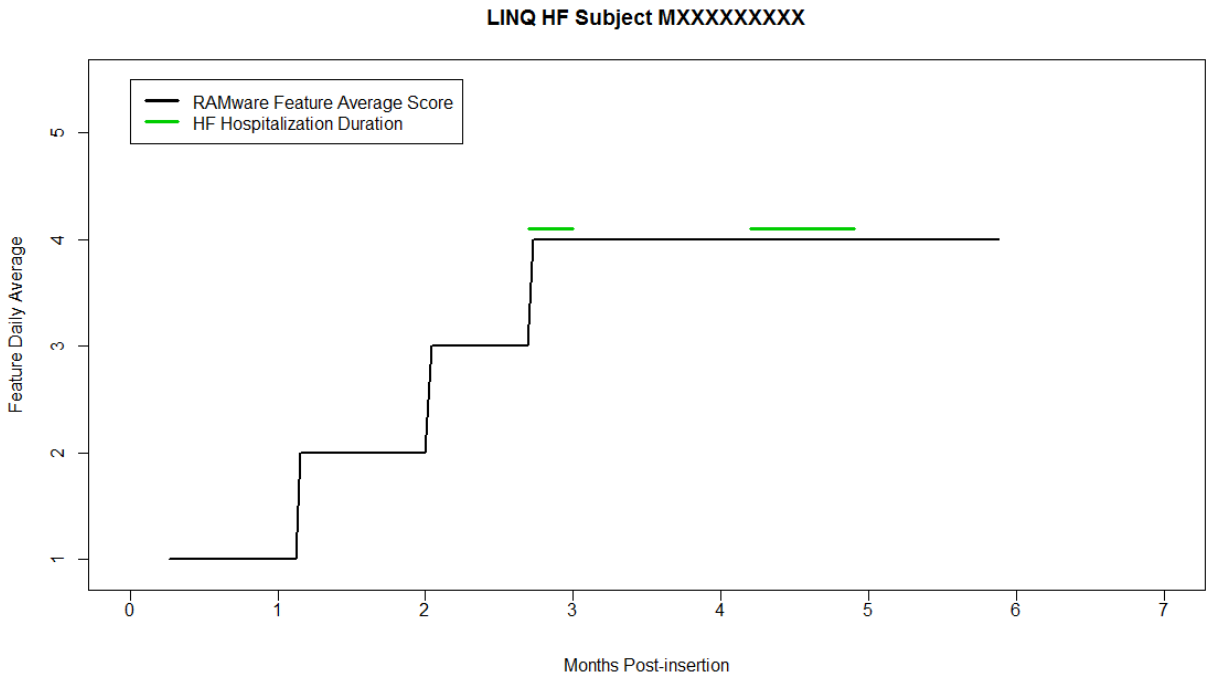
The following table lists out the RAMware features and frequency of measurements.

[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]
	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

Data will be collected from enrollment up to 3 years post-insertion. If a subject exits the study prematurely, data captured prior to exit will be included in the analysis. All data collected will be included in the analysis. Descriptive statistics (e.g. means, standard deviations, proportions) will be used to summarize the physiological and derived data recorded. Analyses will be conducted to assess changes in the physiologic and LINQ™ derived data in association with HF events.

For each subject whose device contains the downloaded RAMware, the measurements in the table above will be averaged to produce one mean value for each feature for each day. Then for subjects who experience at least one ADHF event, the daily mean values will be averaged across subjects for each day leading up to the first event per subject and each day following that event for a minimum of 14 days on either side of admission. For example, if 40 subjects have at least one ADHF event, then for each of the 14 days prior to that event, the 40 subjects' mean values for that day will be averaged. The same will be done for the 14 days following ADHF admission. This will be done for each of the features above.

For subjects who have multiple ADHF events, plots may be produced with time on the x-axis, and daily average value for a particular feature on the y-axis, with periods in which the ADHF events occurred noted as well. The graph may have the following format. Because the lack of required follow-up visits beyond 12 months may result in ADHF events going unreported, a summary of the plot of a single subject's readings over time should include a marker at 12 months to denote the point at which required follow-up visits ended for this subject.



Subjects who do not experience an ADHF event included in the analysis will have their daily data averaged across these subjects for each day post-insertion and plotted as reference for comparison with the data summaries described above.

7.9.5. Determination of Patients/Data for Analysis

All subjects with a successful insertion will be used in the analysis. See section 7.4 for handling of missing data.

7.9.6. Sample Size

Due to the feasibility nature of this trial, there is no sample size requirement for this objective. A maximum of 300 subjects is allowed. See section 6 for rationale.

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) or Unanticipated Serious Adverse Defice Effect (USADE), 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. A second column in the table will include similar statistics for the number of serious adverse events for each corresponding MedDRA term, and the number of subjects experiencing those serious adverse events. 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.

If any adverse event is classified by the CEC as an Unanticipated Adverse Device Effect, it will be summarized.

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-procedure, 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. Health Outcomes Analyses

Healthcare utilizations will be adjudicated by the CEC. A summary table will be generated showing the prevalence of each HCU type. The format of the table will be as presented below. All HCUs will be included in the table below. Because multiple HCU's occurring on the same day will be recorded on one HCU form, only the most severe HCU type (using the hierarchy in the table below) will be taken for each form. For example, if a subject presented at the Emergency Department and then is admitted to an inpatient hospitalization, that HCU will be considered an inpatient hospitalization for purposes of analysis.

Healthcare Utilization Type	**Number of HCUs (Number, % of Subjects With HCU)**	
	All HCUs	**HF-related HCUs**
Inpatient Hospitalization	X (Y, %)	X (Y, %)
Emergency Department Visit	X (Y, %)	X (Y, %)
Hospital Outpatient Clinic Visit	X (Y, %)	X (Y, %)
Other Outpatient Utilization with overnight stay	X (Y, %)	X (Y, %)
Urgent Care visit	X (Y, %)	X (Y, %)
Clinic Visit	X (Y, %)	X (Y, %)
Scheduled	X (Y, %)	X (Y, %)
Unscheduled	X (Y, %)	X (Y, %)
Phone Call	X (Y, %)	X (Y, %)
Total Events	**X (Y, %)**	**X (Y, %)**

Additionally, the monthly rate of heart failure-related HCUs will be determined, allowing for multiple events per subject. The monthly rates will be calculated for each month post-insertion. For each month (e.g. 0-30 days, 31-61 days, etc.), the number of HF-related HCUs occurring in that interval will be divided by the total number of follow-up months for that interval (each subject can contribute a minimum

of 0 months and a maximum of 1 month for each interval). The intervals for month K (K=1,2,…,30) will be determined by multiplying 30.44 days by K-1 and K and rounding each to the nearest whole number. As described above, if multiple HCU types are recorded on one HCU form, this will count as one total HCU.

7.12. Changes to Planned Analysis

No changes from the CIP-specified analysis are planned, though additional analyses are described in this document.

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 healthcare outcomes and adverse events. Level II validation may occur for programs summarizing baseline demographics, study deviations, follow-up compliance, and study exits.

9. References

1. Philip B. Adamson, William T. Abraham, Robert C. Bourge, Maria Rosa Costanzo, Ayesha Hasan, Chethan Yadav, John Henderson, Pam Cowart, and Lynne Warner Stevenson. Wireless Pulmonary Artery Pressure Monitoring Guides Management to Reduce Decompensation in Heart Failure With Preserved Ejection Fraction. Circ Heart Fail. 2014;7:935-944.