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Medtronic Global Form	056-F154, Version 4.0 **Clinical Study Document Approval Form**

Medtronic **Clinical Study Document Approval Form**	
Study Name/Identifier	ReLINQuish (**R**elationship b**e**tween **LINQ**™ s**u**bcutaneous **i**mpedance and right-**s**ided **h**emodynamic measurements)
Document Name	ReLINQuish Clinical Investigation Plan, Version 2.0
Document Reference Number	

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Medtronic Clinical Investigation Plan	
Clinical Investigation Plan/Study Title	ReLINQuish (**R**elationship b**e**tween **LINQ** s**u**bcutaneous **i**mpedance and right-**s**ided **h**emodynamic measurements)
Study Product Name	Reveal LINQ™
Sponsor/Local Sponsor	Medtronic , Inc. 8200 Coral Sea Street NE Mounds View, MN 55112
Document Version	2.0
Lead Principal Investigator(s)	[redacted]
Coordinating Investigator	[redacted]

Table of Contents

Contents

1. Glossary

Term	Definition
AE	Adverse Event
ADHF	Acute decompensated heart failure
AF	Atrial fibrillation
CEC	Clinical Events Committee
CIP	Clinical Investigational Plan
CRF	Case Report Form
CRT	Cardiac Resynchronization Therapy
CRT-D	Cardiac Resynchronization Therapy – Defibrillation
CTA	Clinical Trial Agreement
eCRF	Electronic Case Report Form
ePAD	Estimated pulmonary artery diastolic pressure
ECG	Electrocardiogram
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HCU	Healthcare utilization
HF	Heart failure
ICD	Implanted Cardioverter-Defibrillator
ICM	Insertable Cardiac Monitor
IRB	Institutional Review Board
LV	Left ventricle

Term	Definition
LVAD	Left Ventricular Assist Device
MDT	Medtronic
NYHA	New York Heart Association
PAP	Pulmonary artery pressure
PIC	Patient Informed Consent
RAMware	Software downloaded onto LINQ™ device
RDC	Remote data capture
RHC	Right heart catheterization
RV	Right ventricle
SAE	Serious Adverse Event
SCD	Sudden Cardiac Death

2. Synopsis

Title	ReLINQuish (**R**elationship b**e**tween **LINQ**™ s**u**bcutaneous **i**mpedance and right-**s**ided **h**emodynamic measurements)
Clinical Study Type	Feasibility
Product Name	Reveal LINQ™
Sponsor	Medtronic
Local Sponsor	Medtronic, Inc. 8200 Coral Sea Street, NE Mounds View, MN 55112
Indication under investigation	Reveal LINQ™ impedance and hemodynamic measurements in patients with heart failure
Investigation Purpose	The purpose of the ReLINQuish study is to characterize the relationship between subcutaneous impedance and hemodynamic measurements in patients with heart failure. Additionally, the relationship between changes in subcutaneous impedance and other physiologic parameters during acute decompensated HF events will be characterized.
Product Status	

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 (v1.1 or later)	Medtronic	Investigational
PA96000	Patient Assistant	Medtronic	Market-Released
24950	MyCareLink® Home Monitor	Medtronic	Market-Released
DR220	Holter	NorthEast Monitoring, Inc.	Market-Released

	*The Reveal 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.
Primary Objective(s)	The primary objective is to characterize the relationship between changes in Reveal LINQ™ subcutaneous impedance and cardiopulmonary hemodynamic measurements, resulting from: 1) short-term vasodilator and/or exercise challenges during right heart catheterization procedures or 2) long-term daily trends of physiologic data, in patients with heart failure.
Ancillary Objective	To characterize the relationship between changes in Reveal LINQ™-derived data and other physiologic parameters with any acute decompensated heart failure (ADHF) events.
Study Design	The study is a prospective, non-randomized, observational clinical study to be conducted at up to 5 centers in the US. Up to 30 subjects will be enrolled in the study. Study subjects will be followed for up to 18 months post-insertion or 3 right heart catheterization procedures, whichever comes first. The expected study duration is approximately 3 years representing 18 months of enrollments and 18 months of follow-up.
Sample Size	Up to 30 subjects will be enrolled.

Inclusion/ Exclusion Criteria	<u>Inclusion Criteria:</u>
	• Patients meeting at least 1 of 3 criteria will be included in the study:
	  ○ Patients with symptomatic systolic or diastolic heart failure who in the clinician's judgment have a high likelihood of undergoing serial right heart catheterizations to aid in clinical management of their heart failure
	  ○ Patients with dyspnea on exertion in whom exercise hemodynamics is indicated to diagnose diastolic dysfunction
	  ○ Patients who have or will be implanted with a pulmonary artery pressure monitor
	• 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.
	<u>Exclusion Criteria:</u>
	• Patient has an existing Medtronic implantable cardiac device

	• Patient has a left ventricular assist device (LVAD) • 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
Study Procedures and Assessments	After enrollment, baseline data will be collected and a Reveal LINQ™ device with LINQ-HF investigational RAMware will be inserted. Subjects will be enrolled for 18 months and undergo scheduled follow-up visits at 6 and 12 months. Subjects may forego a scheduled follow-up visit if they have had a right heart catheterization (RHC) procedure within the follow-up visit window. If the subject has an implantable pressure monitor, data will be collected from the monitor at the follow up visits. For subjects undergoing clinically indicated RHCs as determined by physician judgment, a two-month blanking period post-insertion to allow for pocket maturation would be preferred. Prior to each RHC procedure, Holter mode will be enabled on the Reveal LINQ™ device using a 2090 programmer with investigational software, and a Holter monitor applied to the subject to collect high-resolution impedance and ECG. After placement of the PA catheter (Swan-Ganz), a standardized procedure will be followed to ensure appropriate placement of the pressure reference transducer. The RHC will be performed according to the participating institution's procedure. ECG and hemodynamic data will be recorded on the lab recording system, a copy of which will be provided to Medtronic. Lab and Holter data will be synchronized by introduction of noise on the ECG signal which will be common to both systems (e.g., briefly disconnecting or tapping on an electrode). As part of the standard procedure, subjects may be administered a vasodilator or exercise challenge. Holter mode will be disabled at the conclusion of the procedure. These subjects may exit prior to 18 months after the completion of three RHC procedures. Starting one month post-insertion, the subject will utilize the MyCareLink Home Monitor to manually transmit data on a monthly basis. The subjects will be asked to press the Patient Assistant whenever they feel increased shortness of breath compared to normal. Health Care Utilizations (HCUs) (including hospitalizations, emergency department visits, outpatient treatment involving overnight stay, urgent care, or clinic visits) will be collected and reported on a HCU Case Report Form. Cardiovascular-related (including hypervolemia and hypovolemia) HCU information should be reported upon center awareness and assessed at all visits.
Safety Assessments	There are no defined safety endpoints in the ReLINQuish Study. Relevant Adverse Events (AEs), Device Deficiencies (DDs), and Health Care Utilizations will be

	collected throughout the study duration and will be assessed and reported per regulatory requirements
Statistics	ReLINQuish is an observational characterization study and therefore will not have powered endpoints. Analysis will include descriptive comparisons between LINQ™ impedance and hemodynamic measurements.

3. Introduction

3.1. Background

Filling pressures are considered to be an important diagnostic parameter in management of heart failure (HF) patients. Higher filling pressures are associated with higher risk for hospitalizations and mortality.[1, 2] Monitoring and adjusting therapy based on pressures may improve patient symptoms and has been shown to reduce HF events.[5] The first generation implantable pressure sensor (Chronicle, Medtronic Inc. MN) consisted of a pressure sensor at the end of a lead that resided in the right ventricle.[3] The measured pressures were used to estimate pulmonary artery diastolic pressure (ePAD). The pivotal human clinical trial, COMPASS-HF, using this sensor failed to achieve the primary outcome of reducing HF-related events compared to the standard of care arm.[4] The newer generation pressure sensors are leadless and are fully contained in one of the major right-sided vessels in the heart. Following a successful outcome trial,[5] FDA recently approved the first ever implantable sensor to measure filling pressures. The CardioMEMS pulmonary artery (PA) pressure sensor is an integral component of the FDA-approved CardioMEMS HF system (St. Jude Medical, MN). The sensor is implanted in a branch of the pulmonary artery and provides on-command PA pressure waveforms, pressure readings, and trend data over time (e.g. over a week). The clinician can remotely access these data and incorporate them in patient management. For example, a diuretic or another medication intervention may be made if the patient's PA pressure is out of the normal range. In fact such PA pressure-guided interventions were hallmark of the successful CHAMPION trial.[5] The trial showed that PA pressure-guided HF management was associated with a 28% reduction in HF hospitalization rate at 6 months, and 37% after an average follow-up of 15 months relative to the control arm in which subjects were managed using clinical assessment alone.

Intrathoracic impedance is another HF management tool that has been available for over a decade in patients with implantable devices (ICD and CRT-D).[6] Impedance is measured across the RVcoil-to-can vector, and a declining trend in impedance and corresponding rise in derived OptiVol index signifies higher risk of an HF event. Intrathoracic impedance is inversely correlated with pulmonary capillary wedge pressure (PCWP).[6] Both intrathoracic impedance and OptiVol index have been shown to be associated with higher risk of HF hospitalization and mortality.[7-9]

The Reveal LINQ™ insertable cardiac monitor is a leadless device that is inserted in the region of the thorax. Two electrodes on the body of the device continuously monitor the subject's subcutaneous ECG and, with investigational software, impedance. Subcutaneous impedance derived from the Reveal LINQ™ insertable cardiac monitor may be of similar utility in patients without implantable devices.

The Monitoring in Dialysis (MiD) study was conducted in renal failure patients implanted with a Reveal LINQ™ insertable cardiac monitor. The results indicated subcutaneous impedance trends upwards with fluid removal during dialysis sessions and downwards between dialysis sessions. Therefore, the preliminary data show that continuous subcutaneous impedance monitoring has a direct inverse relationship to patient fluid status in both a detailed analysis and long-term trending analysis.[10]

The LINQ HF study is utilizing the Reveal LINQ™ device with an investigational LINQ HF RAMware download (version 1.1 or later). The commercially available Reveal LINQ™ device records and stores only subcutaneous ECG and activity from a single axis accelerometer. The LINQ HF RAMware enables the hardware to record and store impedance, temperature, activity, RR interval, R-wave amplitude, posture change count (based on z-axis accelerometer values) and x, y, and z-axis accelerometer measurements periodically. The download also has a Holter mode in which continuous impedance and ECG signals will be collected acutely and recorded on a DR220 Holter Recorder. 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.

Understanding the relationship between cardiopulmonary pressure and subcutaneous tissue impedance is of scientific interest, and could also be of potentially clinical utility. Understanding the correlation between the two parameters (or lack thereof) would help to determine treatment strategies when certain impedance values/trends are noted in patients with LINQ impedance data available (but no pressure data).

The current proposal is to utilize the LINQ HF RAMware download to investigate the relationship between LINQ impedance and direct hemodynamic measurements in patients with heart failure. Additionally, the relationship between changes in LINQ impedance and other physiologic parameters during acute decompensated HF events will be characterized. Monthly downloads will be performed, and device data from the LINQ and PA pressure monitor (where applicable) will be collected at scheduled follow-up visits occurring 6, 12 and 18 months post-insertion of the LINQ device. In subjects undergoing right heart catheterization procedures, a Holter Recorder will be applied to collect continuous impedance and ECG during the procedure . Similar to the LINQ HF clinical study, information regarding HF-related clinical events will be collected while the patient is enrolled. The study will be conducted in three patient populations:

1. Patients with symptomatic systolic or diastolic heart failure who in the clinician's judgment have a high likelihood of undergoing serial right heart catheterizations (RHC) to aid in clinical management of their heart failure
2. Patients with dyspnea on exertion in whom exercise hemodynamics is indicated to diagnose diastolic dysfunction
3. Patients who have or will be implanted with a pulmonary artery pressure monitor

3.2. Purpose

The purpose of the ReLINQuish study is to characterize the relationship between subcutaneous impedance and direct hemodynamic measurements in patients with heart failure to assess cardiac function. Additionally, the relationship between changes in subcutaneous impedance and other physiologic parameters during acute decompensated HF events will be characterized.

4. Objectives and Endpoints

4.1. Objectives

4.1.1. Primary Objective

The primary objective is to characterize the relationship between changes in Reveal LINQ™ subcutaneous impedance and right heart hemodynamic measurements, resulting from: 1) short-term drug and/or exercise challenges during right heart catheterization procedures or 2) long-term daily trends of physiologic data, in patients with heart failure.

4.1.2. Ancillary Objective

To characterize the relationship between changes in Reveal LINQ™-derived data and other physiologic parameters with any acute decompensated heart failure (ADHF) events.

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

4.2. Endpoints

It will be of interest to characterize the relationship between changes in Reveal LINQ™ subcutaneous impedance and right heart hemodynamic measurements, resulting from: 1) short-term drug and/or exercise challenges during right heart catheterization procedures or 2) long-term daily trends of physiologic data, in patients with heart failure.

It will also be of interest to characterize the relationship between changes in Reveal LINQ™-derived data and other physiologic parameters with any acute decompensated heart failure (ADHF) events.

4.2.1. Primary Endpoint

As a feasibility study, ReLINQuish is not powered to meet any endpoints.

5. Study Design

The ReLINQuish study is a prospective, non-randomized, observational clinical study to be conducted at up to 5 centers. Up to 30 subjects will be enrolled in the study. After enrollment, baseline data will be collected and a Reveal LINQ™ device with LINQ-HF investigational RAMware will be inserted.

Subjects will be enrolled for 18 months and undergo scheduled follow-up visits at 6 and 12 months. Subjects may forego a scheduled follow-up visit if they have had a right heart catheterization (RHC) procedure within the follow-up visit window.

For subjects undergoing clinically indicated RHCs as determined by physician judgment, a two-month blanking period post-insertion to allow for pocket maturation would be preferred. The subject will remain enrolled for up to 18 months or 3 right heart catheterization (RHC) procedures, whichever comes first. The intent is to capture up to 3 RHCs per patient as performed as standard of care at the investigator's institution. In this observational study, physicians will be asked to collect right heart pressures during clinically indicated RHC procedures as determined by the treating physician. The RHC will be performed according to the participating institution's procedure. There are no study-related requirements around the performance or timing of the procedures, other than measures to collect comprehensive data and assure quality.

Prior to each RHC procedure, Holter mode will be enabled on the LINQ device using a 2090 programmer with investigational software, and a Holter monitor applied to the subject to collect high-resolution impedance and ECG. A standardized procedure will be followed to ensure appropriate placement of the pressure transducer. ECG and hemodynamic data will be recorded on the lab recording system, a copy of which will be provided to Medtronic. Lab and Holter data will be synchronized by introduction of noise on the ECG signal which will be common to both systems (e.g., briefly disconnecting or tapping on an electrode). As part of the standard procedure, subjects may be subjected to a drug or exercise challenge. Holter mode will be disabled at the conclusion of the procedure.

Starting one month LINQ post-insertion, the subject will utilize the MyCareLink Home Monitor to manually transmit data on a monthly basis. Site personnel will monitor for compliance with monthly transmissions and call the subject as needed with a reminder to transmit the data monthly. The subjects will be asked to press the Patient Assistant whenever they feel increased shortness of breath compared to normal. Health Care Utilizations (HCUs) (including hospitalizations, emergency department visits, outpatient treatment involving overnight stay, urgent care, or clinic visits) will be collected and reported on a HCU Case Report Form. Cardiovascular-related (including hypervolemia and hypovolemia) HCU information should be reported upon center awareness and assessed at all contacts with the subjects.

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 elibility for enrollment in keeping with the inclusion/ exclusion criteria
- 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

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

5.1. Duration

Study subjects will be followed for up to 18 months post-insertion or 3 right heart catheterization procedures, whichever comes first. The expected study duration is approximately 3 years representing 18 months of enrollments and 18 months of follow-up.

5.2. Rationale

Filling pressures are considered to be an important diagnostic parameter in management of heart failure (HF) patients. Higher filling pressures are associated with higher risk for hospitalizations and mortality.[1, 2] Monitoring and adjusting therapy based on pressures may improve patient symptoms and has been shown to reduce HF events.[5]

The Reveal LINQ™ insertable cardiac monitor is a minimally invasive, leadless device that is inserted in the region of the thorax. Subcutaneous impedance measured between two electrodes on the body of the device, in addition to other sensor data derived from the Reveal LINQ™ insertable cardiac monitor, may be of similar utility in patients without implantable devices and allow for HF management with less invasive measurements.

The Monitoring in Dialysis (MiD) study was conducted in renal failure patients implanted with a Reveal LINQ™ insertable cardiac monitor. The results indicated impedance trends upwards with fluid removal during dialysis sessions and downwards between dialysis sessions. Therefore, the preliminary data show that continuous impedance monitoring has a direct inverse relationship to patient thoracic fluid status in both a detailed analysis and long term trending analysis.[10]

In the ReLINQuish study, the follow-up duration of 18 months, combined with selection of subjects with the likelihood of undergoing serial RHCs or an implanted PA pressure sensor, will allow for the assessment of correlation between pulmonary artery pressures (as surrogates of left side cardiac pressures) and subcutaneous impedance over time. Physiologic parameters captured during any ADHF events occurring while the subject is enrolled will further provide insight into correlations with LINQ impedance.

Acute changes in subcutaneous impedance

Preclinical data have shown that, while OptiVol impedance coincides with changes in LV end-diastolic pressure upon acute volume overload, the subcutaneous impedance lags (Figure 1). To account for any lag in subcutaneous impedance resulting from the acute drug or exercise challenge during the RHC, the Holter recorder will continue to obtain high resolution impedance data during the approximate 1-hour recovery period following the RHC procedure.

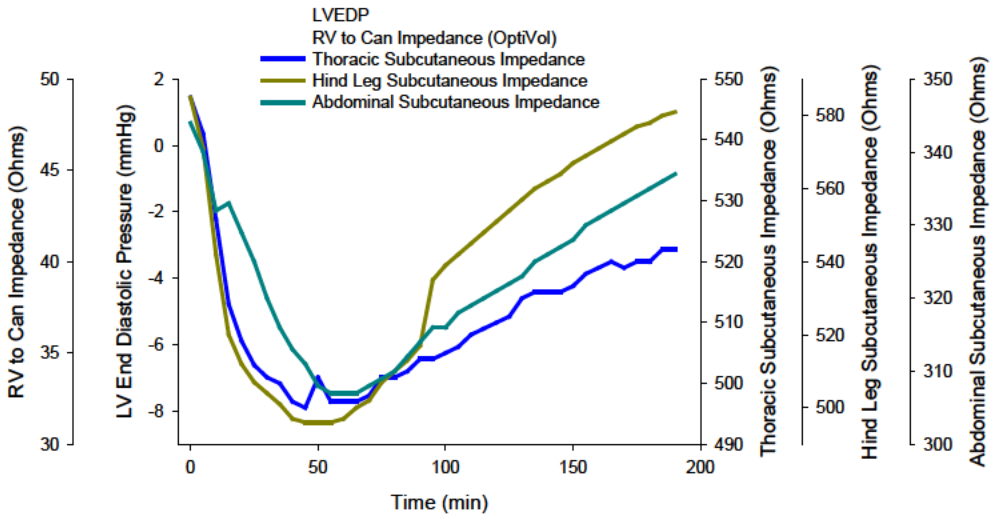
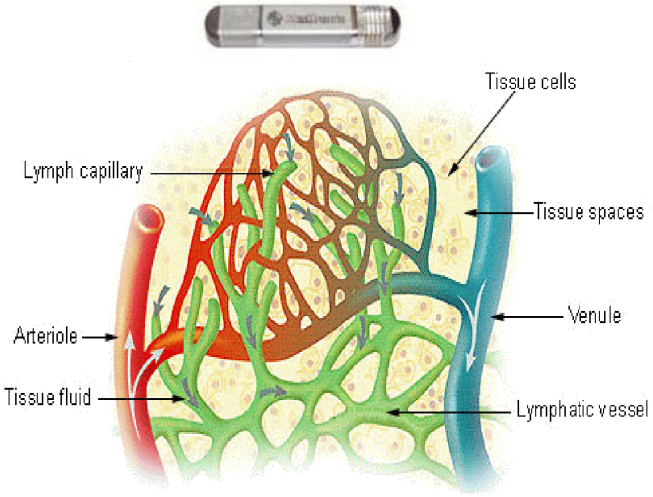


Figure 1. Preclinical data showing the response to fluid overload. Subcutaneous impedance measured from multiple locations mirrors but lags the changes to LV end-diastolic pressure and thoracic impedance.[11]

Despite the subject remaining euvolemic during the RHC, there are physiologic bases behind the hypothesis that changes in subcutaneous impedance may be observed as a result of an acute intervention during the RHC:

- Capillary bed fluid dynamics: Under normal physiologic conditions, 90% of fluid that leaves the arterial capillary bed is reabsorbed by the venous capillary bed according to conventional microcirculation fluid dynamics. Any physiologic anomaly such as increased central venous pressure (or decreased systemic arterial resistence) would reduce the volume absorption by the venous side and as a result the lymphatic system would have to compensate for the additional fluid volume shift. Considering that the lymphatic system drains into the venous system, this leads to subsequent fluid accumulation in the extravascular space, resulting in subcutaneous edema.



- Hypermia: Increased cardiac output or relaxation of the arterioles as a result of the interventions may lead to generalized increased tissue perfusion which may be sensed subcutaneously.

6. Product Description

6.1. General

The study is utilizing the Reveal LINQ™ device with an investigational LINQ HF RAMware download. The LINQ HF RAMware enables high-resolution impedance and ECG to be streamed to a Holter monitor during a right heart catheterization procedure. Surface ECG and hemodynamic data Swan-Ganz catheter will be continuously recorded on the lab system. Additionally, the RAMware enables the hardware to record and store impedance, temperature, activity, RR interval, R-wave amplitude, posture change count (based on z-axis accelerometer values) and x, y, and z-axis accelerometer measurements periodically. These data will be captured in monthly uploads via the MyCareLink Home Monitor. The system components that will be used in this study are listed in the table below.

Table 1: ReLINQuish Study System Components

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 1.1 or later)	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.

6.2. Manufacturer

Products are manufactured by Medtronic.

Medtronic, Inc.
710 Medtronic Parkway
Minneapolis, MN 55432-5604 - USA
www.medtronic.com
Tel. +1-763-514-4000
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6.3. Packaging

Standard Medtronic practice is not to re-package, re-label or sticker commercially-release devices used in clinical studies.

Instructions for use and current labeling of the Reveal LINQ™, MyCareLink® Monitor, Medtronic Patient Assistant and 2090 Programmer, which are CE-marked in all geographies, are provided in the device user manuals in local language. Although these devices are commercially-released, they will be used outside of the approved indications.

The labelling of the investigational software will be in English.

User manuals and labeling for the study devices will be provided under a separate cover.

6.4. Intended Population

Patients with dyspnea on exertion or symptomatic systolic or diastolic heart failure who have a high likelihood of undergoing serial right heart catheterizations (RHC) to aid in clinical diagnosis and/or

management of their heart failure, or patients who have or will be implanted with a pulmonary artery pressure monitor, will be included in the study.

6.5. Equipment

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 subject'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.

Figure 2: Reveal LINQ™ ICM.

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 3: Incision Tool

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 4: Insertion Tool

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.

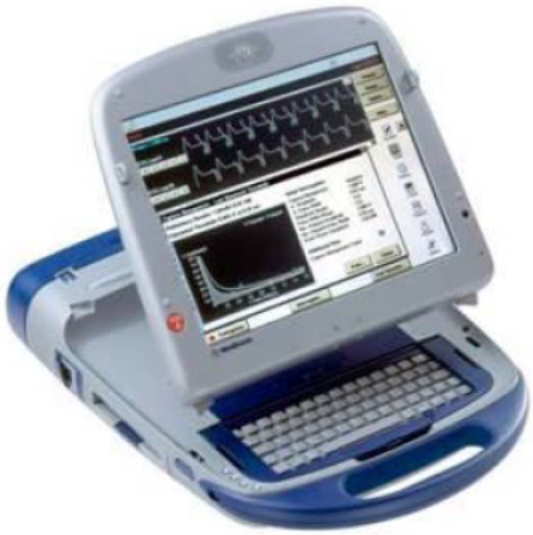


Figure 5: Medtronic 2090 Programmer

The Medtronic 2090 Programmer with the LINQ HF investigational RAMware will be used to download the LINQ HF investigational RAMware onto the Reveal 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.

Medtronic LINQ HF Investigational RAMware

The LINQ HF investigational RAMware (ver 1.1 or later) will provide the ability to enable the Reveal LINQ™ hardware for the collection and storage of Reveal LINQ™ sensor data. The LINQ HF RAMware enables the hardware to record and store impedance, temperature, activity, RR interval, R-wave amplitude, posture change count (based on z-axis accelerometer values) and x, y, and z-axis accelerometer measurements periodically. The device will collect and store this data every 60 minutes for impedance, temperature, activity, R-wave amplitude and every 5 minutes for RR intervals, posture change count, and x, y, and z-axis accelerometer values. In addition, impedance measurements are collected nightly and when the Patient Assistant is used.

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 Reveal 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 6: Patient Assistant

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 7: MyCareLink® Home Monitor

DR220 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 impedance and ECG 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.

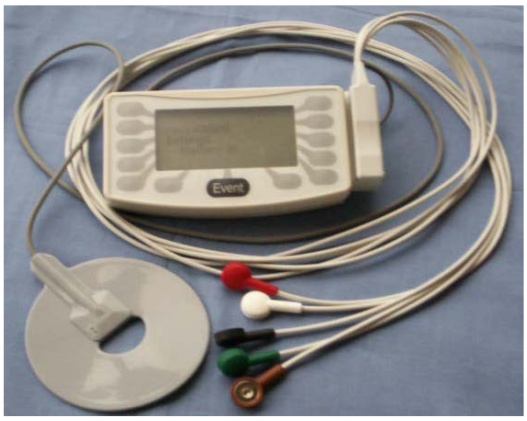


Figure 8: DR220 Holter

6.6. Product Use

The Reveal LINQ™ device is a programmable cardiac monitor that continuously monitors a patient's ECG and other physiological parameters.

It will be implanted in all the subjects enrolled in the study and the device implant procedure will be performed as per routine practice according to the Clinician Manual. After implant, the investigational software will be downloaded onto the device making it interventional. In order to complete this installation, an ad-hoc 2090 Programmer, with the investigational software on it will have to be provided to the site before study start.

The subject will be provided of:

- A Patient Assistant that will allow him/her to record (mark) heart rhythm in case he/she experiences any specific symptoms that could be related to his/her cardiac condition, such as but not limited to fainting, palpitations, dizziness, and shortness of breath.
- A Carelink Monitor that will allow him/her to perform automatic daily transmissions and manual transmissions once a month.

At every follow-up visit, a device interrogation will be performed in order to download on a USB flash drive information recorded by the device on subcutaneous impedance values and standard LINQ™ information such as ECGs and Trends (Cardiac Compass, Histograms, and Longest AF).

6.7. Product Training Requirements

Prior to investigation site initiation or subsequent involvement in study activities, Medtronic will provide study training relevant and pertinent to the involvement of personnel conducting study activities and investigator responsibilities, AE reporting, as well as device training.

As a minimum the CIP, PIC, use of data collection tools, applicable local regulations, as well as device training are required. Study-specific training will be documented prior to investigation site initiation.

Table 2 below lists the requirements for study personnel prior to conducting any study procedures:

Table 2: Training Requirements

Study personnel	Documented Study Training	Database training	Authorization by PI through Delegated Task List	CV
Principal Investigator	X	X		X
Co-Investigator	X		X	X
General Study Personnel (coordinators, technicians, etc.)	X	X	X	
Medtronic staff	X			

6.8. Product Receipt and Tracking

Investigational device Traceability record containing Model numbers of devices, shipping date and name and address of person that received shipped device, Location (if different than person shipped to), transfer and receipt by Medtronic dates shall be maintained accurate, complete and current.

6.9. Product Storage

The disposable (Reveal LINQ™) and non-disposable devices (MyCareLink® Monitor, Medtronic Patient Assistant and 2090 Programmer) used during the clinical study are commercially available. However, when the investigational software is installed on the programmer(s), the study devices become investigational devices.

From that moment on full disposition must be performed.

All investigational products must be controlled by Medtronic and/or trained study center personnel. Investigational product will be stored in a secure location at the study center. The method of storage shall prevent the use of investigational devices/products for other applications than mentioned in this Clinical Investigation Plan. It is the responsibility of the investigator to correctly handle, store, and track the investigational products.

6.10. Product Return

Investigator agrees to use the study devices solely for the purpose of the study. Medtronic will retain all rights of possession and ownership in the study device and Investigator will acquire no rights of possession and ownership in the Study Devices pursuant to the Clinical Trial Agreement or otherwise. Upon the termination or expiration of this Agreement, Investigator will immediately return any unused disposable Study Devices and all non-disposable devices to Medtronic at Medtronic's cost.

Any disposable investigational product needs to be returned to Medtronic in case of device deficiency during the implant procedure or during the follow-up visits. In that case they should be returned as soon as possible for investigation.

Mailer kits with prepaid US postage are available for use within the United States to send CRT, ICD, IPG, and leads to Medtronic's CRHF Returned Product Analysis Lab. These mailers are sized to accommodate the devices and leads from a single patient or clinical event and are designed to meet US postal regulations for mailing biohazard materials. To receive a kit, please contact your local field person or a study team member.

6.11. Product Accountability

Documentation of investigational product allocation and tracking is required at each step of the process via the Product Accountability Log. It is the responsibility of the investigator to correctly handle, store, and track the investigational products. The investigational Product Accountability Log is provided to the center and will be used for tracking of all investigational products. The log must be maintained at the center and updated when the investigational product is received, used, disposed or returned to Medtronic.

7. Selection of Subjects

7.1. Study Population

Patients with dyspnea on exertion or symptomatic systolic or diastolic heart failure who have a high likelihood of undergoing serial right heart catheterizations (RHC) to aid in clinical diagnosis and/or management of their heart failure, or patients who have an implanted pulmonary artery pressure monitor, will be included in the study.

7.2. Subject Enrollment

Patients must sign the patient informed consent form and meet all of the inclusion and none of the exclusion criteria prior to being enrolled.

7.3. Inclusion Criteria

- Patients meeting 1 of 3 criteria will be included in the study:
  1. Patients with symptomatic systolic or diastolic heart failure who have a high likelihood of undergoing serial right heart catheterizations (RHC) to aid in clinical management of their heart failure
  2. Patients with dyspnea on exertion in whom exercise hemodynamics is indicated to diagnose diastolic dysfunction
  3. Patients who have or will be implanted with a pulmonary artery pressure monitor
- 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

7.4. Exclusion Criteria

- Patient has an existing Medtronic implantable cardiac device.
- Patient has a left ventricular assist device (LVAD).
- 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

8. Study Procedures

8.1. Schedule of Events

8.1.1. Data Collection

Table 3: Data Collection

STUDY PROCEDURE	Baseline	LINQ insertion	Right heart catheterization	Monthly LINQ device transmission	6M and 12M visits	Exit
Patient informed consent	X					
Inclusion/Exclusion assessment	X					
Medical history	X					
Demographics	X					
Physical exam, including pitting edema measurement assessment	X		X		X	
Medication assessment	X		X		X	X
Chemistry panel + NT-proBNP	X				X	
Symptoms and temperature (via ear is recommended)			X		X	
Hemodynamic measurements			X			
Final system configuration		X				
Insertion procedure information		X				
LINQ HF RAMware download onto LINQ device		X				
LINQ device data		X	X	X	X	X
Implanted PA pressure monitor device data		X	X		X	X
NYHA functional classification assessment			X		X	
Holter (DR220)			X			
Limited posture test		X				
Posture test			X		X	

STUDY PROCEDURE	Baseline	LINQ insertion	Right heart catheterization	Monthly LINQ device transmission	6M and 12M visits	Exit
LINQ HF RAMware removal from LINQ device						X
6 minute hall walk test (optional)					X	
Adverse event	As needed					
Healthcare utilization						
Device transmission/HCU call						
Device deficiency						
System modification						
Study deviations						
Echo reports (optional)						

8.2. Subject Screening

Patients will be screened to ensure they meet all of the inclusion and none of the exclusion criteria prior to study enrollment.

8.3. Prior and Concomitant Medications

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

8.4. Subject Consent

Informed consent is defined as a legally effective documented confirmation of a subject's 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 subject's informed consent through the subject signing and dating an Informed Consent Form that has been approved by the study center's IRB, and the subject signing and dating an Authorization to Use and Disclose Personal Health Information/Research Authorization/other privacy language as required by law. The Informed Consent Form should also be signed and dated by

the Principal Investigator or an authorized designee. 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.

Prior to enrolling subjects, each site must have documented IRB approval of the Informed Consent Form (IC Form) and an Authorization to Use and Disclose Personal Health Information/Research Authorization/other privacy language as required by law. Any changes to a previously approved Informed Consent Form throughout the course of the study must be reviewed and approved by Medtronic and the IRB reviewing the application before being used to obtain consent or re-consent a study subject. 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.

The investigator must notify the subject 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 continuing informed consent in writing.

The process of obtaining informed consent shall:

- Ensure that the Principal Investigator, or an authorized designee, obtains the informed consent.
- Include all aspects of the clinical study that are relevant to the subject's decision to participate throughout the clinical study.
- Avoid any coercion or undue improper influence on, or inducement of the subject to participate.
- Not waive or appear to waive the subject's legal rights.
- Ensure the Informed Consent Form and an Authorization to Use and Disclose Personal Health Information/Research Authorization/other privacy language, as required by law, are given to the subject in a non-technical language the subject is able to read and understand.
    - Provide ample time and opportunity for the subject to read and understand the Informed Consent Form, to inquire about details of the study, and to consider participation. All questions about the study should be answered to the satisfaction of the subject.
- Include a personally dated signature of the subject acknowledging that their participation in the study is voluntary.
- Include a personally dated signature by the principal investigator or authorized designee responsible for obtaining the informed consent, as required by local law.
- Provide the subject with a copy of the Informed Consent Form and an Authorization to Use and Disclose Personal Health Information/Research Authorization/other privacy language as required by law.
    - Ensure subjects are notified 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 informed consent 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) informed consent will be allowed, provided detailed documentation of the process is recorded in the subject's case

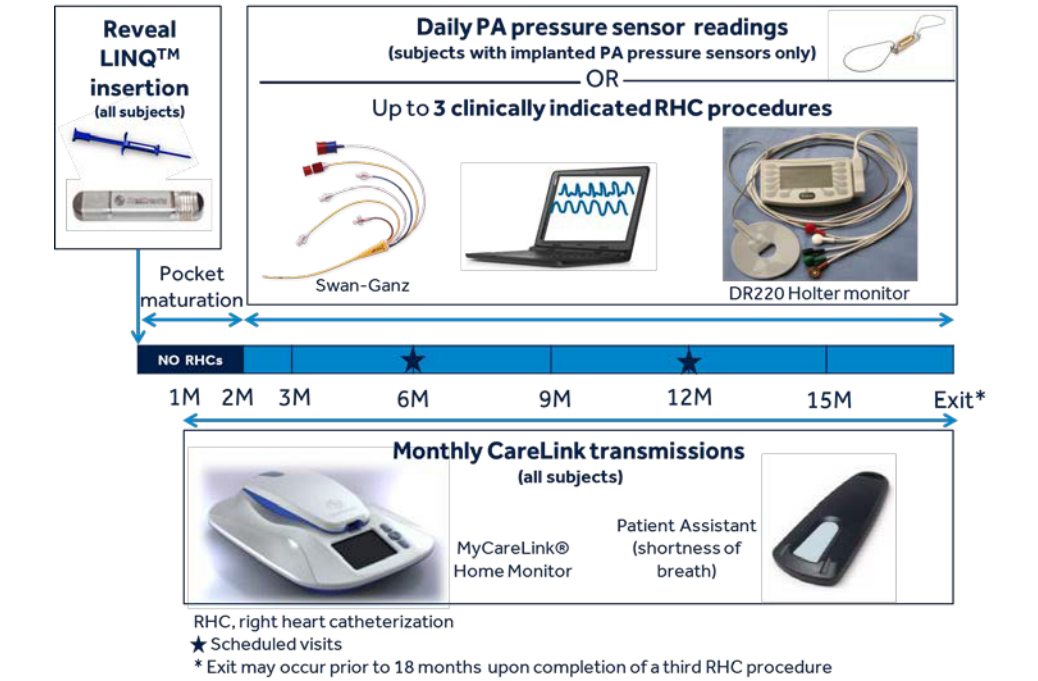
history and the witness signs and dates the Informed Consent Form. Informed consent shall be obtained through a supervised oral process. An independent witness must be present throughout the process. The Informed Consent Form and any other information must be read aloud and explained to the prospective subject, if allowed by local law. The witness signs and personally dates the Informed Consent Form attesting that the information was accurately explained and that informed consent was freely given. The subject should "make his mark" (sign or otherwise physically mark the document so as to indicate consent) on the Informed Consent Form as well. The 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 Informed Consent Form must be filed in the hospital/clinical chart and/or with the subject's study documents.

The 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, auditing, and regulatory inspections. Any Medtronic Field personnel who support the ReLINQuish study must be able to review the subject's signed and dated Informed Consent Form and Authorization to Use and Disclose Personal Health Information/Research Authorization/other privacy language, as required by law and verify its completeness prior to proceeding with any study procedures. In the event the Medtronic Field personnel identify the Informed Consent Form or Authorization to Use and Disclose Personal Health Information/Research Authorization/other privacy language, as required by law, as being incomplete, the ReLINQuish study procedures will not be allowed to occur until the informed consent of the subject can be adequately and appropriately obtained.

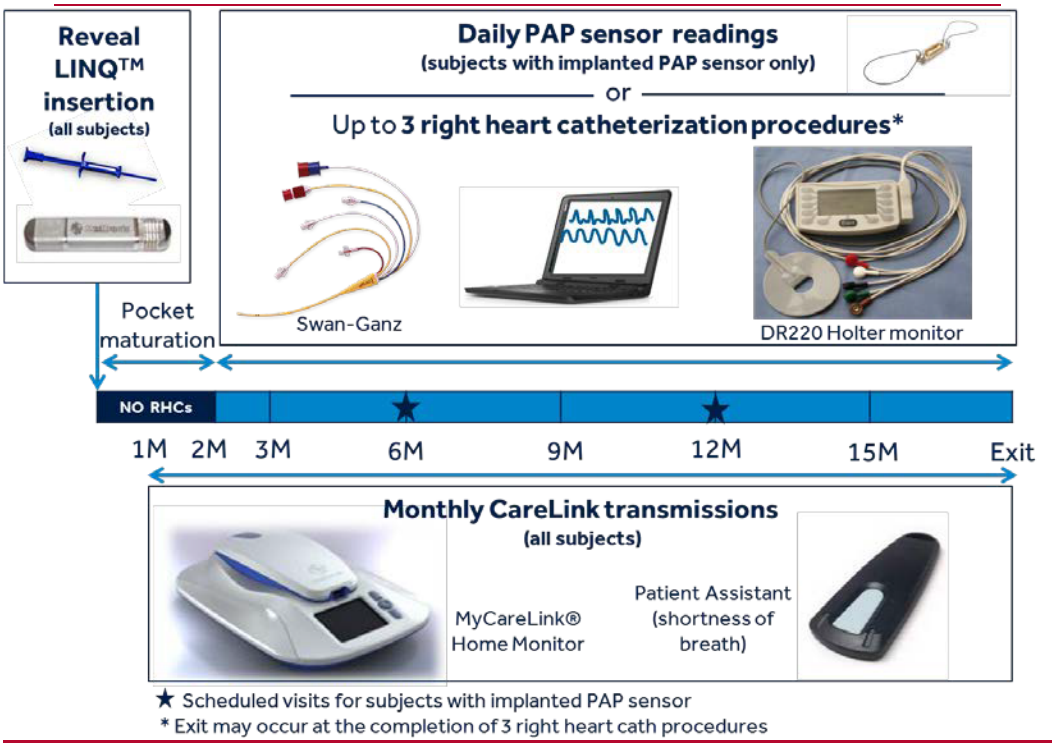
When a patient and the Principal Investigator or authorized designee, as required, have personally signed and dated the Informed Consent Form and Authorization to Use and Disclose Personal Health Information/Research Authorization/other privacy language, as required by law, the patient is considered a subject enrolled in the study. The date the subject signed the Informed Consent Form and Authorization to Use and Disclose Personal Health Information/Research Authorization/other privacy language as required by law, must be documented in the subject's medical records.

8.5. Study Procedures

Data will be collected at the Baseline Visit, Insertion, 6 and 12-month follow-up visits, RHC procedures, and monthly CareLink transmissions. A two-month blanking period post-insertion is recommended but not required. Subjects may be exited upon completion of 3 RHCs.



RHC, right heart catheterization
★ Scheduled visits
* Exit may occur prior to 18 months upon completion of a third RHC procedure



★ Scheduled visits for subjects with implanted PAP sensor
* Exit may occur at the completion of 3 right heart cath procedures

Figure 9: Schedule of Events

8.5.1. Baseline

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

The following information is required to be collected in the CRF at the baseline visit prior to performing the device implant:

- Informed consent
- Inclusion/exclusion criteria
- Medical history
- Demographics
- Physical examination, including pitting edema measurement assessment
- Medication assessment
- Standard chemistry panel plus NT-proBNP
- Symptoms and temperature (via ear is recommended)

8.5.2. Insertion

Following the baseline visit, a Reveal LINQ™ device will be implanted in the subject. The implant procedure will be performed in accordance with the hospital's standard implant practice and in accordance with the Medtronic Reveal LINQ™ implant instructions.

Use of the recommended implant locations is located in Figure 10 below. Physicians should follow the Clinician Manual when performing the Reveal LINQ™ implant.

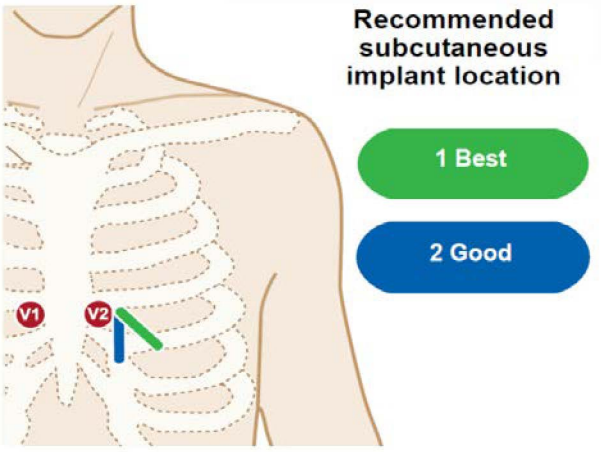


Figure 10: Recommended implant locations

After the implant procedure, the investigational software will be downloaded onto the implanted LINQ device.

The following information will be collected:

- Final system configuration, including LINQ, Patient Assistant and Carelink Monitor serial numbers
- Insertion procedure information, including location of inserted device
- Device interrogation (save to media)
- Limited posture test

8.5.3. Right Heart Catheterization Procedure

A two-month blanking period post-insertion to allow for pocket maturation would be preferred prior to the first right heart catheterization (RHC) procedure.

Prior to each RHC procedure, Holter mode will be enabled on the LINQ device using a 2090 programmer with investigational software, and a DR220 Holter Recorder will be applied to the subject to collect high-resolution impedance and ECG. See Appendix C for more information on applying the Holter.

The RHC will be performed according to the participating institution's procedure. There are no study-related requirements around the performance or timing of the procedures, other than measures to collect comprehensive data and assure quality. A standardized procedure will be followed to ensure appropriate placement of the pressure transducer. The location of the pressure transducer will be measured from the substernal notch down and recorded at the first procedure. This measurement will be used to ensure consistent placement of the pressure transducer at subsequent procedures. Both the proximal and distal ports of the Swan-Ganz catheter will be connected for continuous recording of right atrial and pulmonary artery pressures. Cardiac output and systemic blood pressure will be measured frequently throughout the procedure and at least every 2 minutes during the drug or exercise challenge and recovery. ECG and hemodynamic waveform data will be recorded on the lab recording system, a copy of which will be provided to Medtronic. Lab and Holter data will be synchronized by introduction of noise on the ECG signal which will be common to both systems (e.g., briefly disconnecting or tapping on an electrode).

As part of the standard procedure, subjects may be administered an acute drug or exercise challenge. Alternatively, subjects with an implanted PA pressure monitor may undergo a right heart catheterization procedure without any associated drug or exercise challenge. The Holter will continue to record data throughout the recovery/observation period with the subject remaining supine or with moderate head elevation if necessary. The timing and description of any positional changes will be noted in the CRFs. At the conclusion of the recovery period, the posture test will be performed, the Holter recorder will be removed, and Holter mode will be disabled (see Appendix C for more information).

The following information will be collected *prior to* each right heart catheterization procedure:

- Physical examination, including pitting edema measurement assessment
- Medication assessment
- Standard chemistry panel plus NT-proBNP (only if the procedure visit is substituting for the 6- or 12-month scheduled follow-up visit)
- Symptoms and temperature (via ear is recommended)
- NYHA functional classification assessment

The following additional information will be collected at each right heart catheterization procedure:

- Device data
- Posture test
- Hemodynamic measurements
- Holter (DR220) data

8.5.4. 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 3 and are based on days post-insertion.

Table 4. Post-Insertion Follow-Up Visit Windows

Scheduled follow-up visit	Window (Calculated days post-insertion)		
	Window Start	Target	Window End
6 month	163	183	203
12 month	335	365	395
Exit*	518	548	578

*Subjects will exit at approximately 18 months, or after completing 3 right heart catheterization procedures, whichever comes first. It will not be considered a study deviation if the date of exit of a subject completing 3 RHCs occurs outside of the Exit visit window.

The subject can forego a scheduled follow-up visit if he/she had a right heart catheterization procedure in the same window.

The following information is to be collected at the 6-month and 12-month follow-up visits:

- Physical examination, including pitting edema measurement assessment
- Medication assessment
- Standard chemistry panel plus NT-proBNP
- Symptoms and temperature (via ear is recommended)
- LINQ device data
- Implanted PA pressure monitor data (if applicable)
- NYHA functional classification assessment
- Posture test
- 6MHW (optional)

The following information is to be collected at Exit:

- Reason for exit
- HCU and AEs
- Medication assessment
- LINQ device data
- Implanted PA pressure monitor data (if applicable)
- LINQ HF RAMware removal from LINQ device

8.5.5. Monthly CareLink Transmissions

Starting one month post-insertion, the subject will utilize the MyCareLink Home Monitor to manually transmit data on a monthly basis. Site personnel will monitor that the monthly transmissions are occurring and call the subject as needed with a reminder to transmit the data monthly. Health Care Utilizations (HCUs) (including hospitalizations, emergency department visits, outpatient treatment involving overnight stay, urgent care, or clinic visits) will be collected and reported on a HCU Case Report Form. Cardiovascular-related (including hypervolemia and hypovolemia) HCU information should be reported upon center awareness and assessed at all visits.

8.5.6. 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 experienceing 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.

8.5.7. Limited Posture Test

A limited posture test will be conducted at the Reveal LINQ™ insertion. Subjects will be requested to be put in two different postures: standing and supine on back. During each posture, the Medtronic 2090 Programmer with the LINQ HF investigational RAMware will be used to store the x, y, and z-axis accelerometer values to calibrate the posture measurements. Refer to Appendix C for more details.

8.5.8. Posture Test

A posture test will be conducted at each right heart catheterization procedure, and at 6 Month and 12 Month scheduled visits in subjects with implanted PAP sensors. Subjects will be requested to be put in four different postures: standing, supine on back, lying down on left side and lying down on right side. During each posture, the Medtronic 2090 Programmer with the LINQ HF investigational RAMware will be used to store the x, y, and z-axis accelerometer values to calibrate the posture measurements. Refer to Appendix C for more details.

8.6. Assessment of Safety

There are no defined safety endpoints in the ReLINQuish Study. Relevant Adverse Events (AEs), Device Deficiencies (DDs), and Health Care Utilizations will be collected throughout the study duration and will be reviewed by the Medtronic Safety Representative for reporting per regulatory requirements. Further information on the collection of AEs and DDS is discussed in Section 11.

8.7. Recording Data

Source data is all information, original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents. Examples of these original documents, and data records include: hospital records, clinical and office charts, laboratory notes, memoranda, subjects' diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments such as hospital monitoring equipment and implantable devices, Holter PDF reports, SD cards, copies or transcriptions certified after verification as being accurate and complete, microfiches, photographic negatives, microfilm or magnetic media, x-rays, subject files, and records kept at the pharmacy, at the laboratories, and at medico-technical departments involved in the clinical trial.

The investigator will clearly mark clinical records to indicate that the subject is enrolled in this clinical study.

Study worksheets may be used and are considered as source documentation.

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. If applicable, the eCRF may be considered source for the following data collection elements but not limited to:

- Enrollment Notification
  - Site assigned patient reference
- Baseline
  - Administrative Information
  - Cardiac Disease Classification
- Deviations

The site is responsible to record all trial related source data enabling the sponsor to reconstruct the complete course of the clinical trial. Source data will be transcribed to and reported through the CRF accordingly. A source data identification list will be provided to the sponsor for approval prior to commencing the clinical part of the trial. The list will be filed in the investigator site file.

Where copies of the original source document as well as print outs of original electronic source documents are retained, these shall be signed and dated by a member of the investigation site team with a statement that it is a true reproduction of the original source document.

8.8. Deviation Handling

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 a study 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. The deviation must be recorded with an explanation. Multiple deviations of the same type at the same visit may be reported on one case report form if they occur at the same date/visit and they have the same root cause.

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 Institutional Review Board (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.

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, and 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.

8.9. Study Exit

At study exit, a CRF 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 system and/or procedure related AEs are resolved or unresolved with no further actions planned. Following exit, subjects will continue to receive standard medical care with their primary/enrolling physician. Upon exiting from the study, no further study data will be collected and no further study visits will occur for the subject. All data available through the time of the subject's exit will be used for analysis.

Subjects will remain in the study until 18 months, or upon completing 3 right heart catheterization procedures, whichever comes first.

The subject may also be exited from the study for any of the following situations:

- Subject has completed follow-up
- Subject lost to follow-up
- Subject death
- Subject has an explant without the intent to re-implant
- Subject did not meet inclusion/exclusion criteria
- Subject did not provide consent or data use protection authorization
- Subject chooses to withdraw (e.g., consent withdrawal, relocation to another geographic location)
- Investigator deems withdrawal necessary (e.g., medically justified, inclusion/exclusion criteria not met, failure of subject to maintain adequate study compliance)
- Lead or generator replacement

If subject is not lost to follow up, the following information/procedure is required to be collected/performed at exit (where available):

- Reason for exit HCU and AEs

- LINQ device data
- Implanted PA pressure monitor data (if applicable)
- Medication assessment
- LINQ™ HF RAMware removal from LINQ™ device

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.

9. Risks and Benefits

9.1. Potential Risks

The potential risks associated with the ReLINQuish study were identified and have been successfully mitigated. 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, the LINQ™ device will be interrogated, device data collected to verify appropriate device function and patient's health assessed for any adverse events.

Medtronic has further minimized the possibility of risks by performing pre-clinical testing prior to the ReLINQuish clinical study, implementing quality control measures into software development processes, providing guidelines for subject selection and evaluation, and providing adequate training instructions and labeling.

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.
- There may be stimulation effects from the impedance measurements being taken across the Reveal LINQ™ device electrodes. The amount of current injected as part of the impedance measurements has been minimized to very low levels to prevent patient harm.
- The LINQ™ HF investigational RAMware feature set will cause current drain on the Reveal LINQ™ ICM device battery. Risk control measures have been implemented and the current projected longevity of a LINQ™ device with investigational LINQ™ HF RAMware shows a 5 month decrease in average projected service life compared to a LINQ™ device without the RAMware. The exact service life of the LINQ™ device will vary depending on each subject's use.
- 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 RAMwaredownload 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.

Table 5: Risk and Risk Reduction Strategy

Risk	Mitigations/ Risk Controls
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
Allergic reaction of ICM rejection following implant procedure	• Assessment of subjects to ensure no allergic 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 biocompatiple 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 a small incision and tight pocket. • Reveal LINQ™ ICM design includes anti-migration features on the header • Investigator discretion to remove if deemed medically necessary
Blunt tissue injury/trauma or vascular trauma from implant/explant procedure	• Insertion tool has a stop position the prevents insertion of the probe beyond the distance required for implant • Training on the correct use of implant tools • Selection of experienced investigator
Pain or scarring from implant/explant procedure	• Use of incision tool will produce the smallest incision possible for implant • Small devices 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™ firmware • LINQ HF investigational RAMware is designed to be automatically removed by the ROM code during POR processing
Premature/unexpected ICM explant	• The projected longevity of Reveal LINQ™ device with investigational LINQ HF RAMware shows a 5 month decrease in average projected service life compared to a device without the RAMware. The exact service life of each device will vary depending on each subject's use.
Electromagnetic interference	• Design consideration and precautions in place for the Revela LINQ™ system remain effective to address EMI risks

Pain or stimulation effects from impedance measurements over duration of implant	• The amount of current injected as part of the impedance measurements has been minimized to prevent subject harm • Design controls in place to protect against fault conditions
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
Undesirable interaction of LINQ HF impedance measurement with concomitant implanted cardiac device (IPG/ICD/ CRT-P/D) therapy delivery	• Pre-clinical testing prior to the ReLINQuish clinical study
Undesirable interaction of Tel-B with concomitant implanted devices	• Pre-clinical testing prior to the ReLINQuish clinical study • Exlcusion of Medtronic IPGs, ICDs, and CRTs

9.2. Potential Benefits

The ReLINQuish study may offer no benefit to the subject. 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.

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.

9.3. Risk-Benefit Rationale

Since the differences between the Reveal LINQ™ market-released device and the Reveal LINQ™ device with the LINQ 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 implements to reduce the risk to as low as possible to minimize subject harm.

The study requirements for careful physician selection and training carry potential benefits that may 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 subjects of having Reveal LINQ™ cardiac monitoring, with the potential to diagnose life-threatening arrhythmias, may provide the subject with clinical benefit.

10. Adverse Event Assessments

10.1. Definitions/Classifications

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. In addition, all serious adverse events (SAEs) leading to death should be reported, regardless of relatedness.

Reporting of these events to Medtronic will occur on an AE Form, including date of AE, treatment, resolution, assessment of both the seriousness of the AE and the relatedness to the device or procedure. Each AE must be recorded on a separate AE eCRF. Documented pre-existing conditions are not considered AEs unless the nature or severity of the condition has worsened. Unavoidable AEs, listed in Table 6, need not be reported unless the AE worsens or is present outside the stated timeframe post-insertion.

For AEs that require immediate reporting (see Table 6), initial reporting may be done by contacting the study sponsor per the sponsor contact information. The original completed AE CRF must be submitted to Medtronic as soon as possible.

Any medication, whether cardiovascular or not, associated with the treatment of an AE must be reported. Medication changes that are not related to adverse events will not be collected.

Subject deaths are also required to be reported. Refer to Section 11.4 for Subject Death collection and reporting requirements.

10.1.1. Device Deficiencies

Device deficiency (DD) information will be collected throughout the study and reported to Medtronic. Note that DDs that result in an Adverse Device Effect (ADE) to the subject should be captured ason an AE CRF only.

10.1.2. Event Updates and Resolution

For any changes in status of a previously reported AE (i.e. change in actions taken, change in outcome, change in relatedness), information needs to be updated on, or added to the original AE

form. All AEs must be followed until the AE has been resolved, the subject dies or exits the study, or until study closure, whichever occurs first.

At the time of study exit, all collected AEs with an outcome of "Unresolved" 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 exit".

10.2. Definitions/Classifications

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, and includes but is not restricted to: the Reveal LINQ™, the programmer, and insertion tools.

Table 6: Adverse Event and Device Deficiency Definitions

General	
Adverse Event (AE)	Any untoward medical occurrence, unintended disease or injury, or untoward clinical signs (including abnormal laboratory findings) in subjects, users or other persons, whether or not related to the investigational medical device NOTE 1: This definition includes events related to the investigational medical device or the comparator. NOTE 2: This definition includes events related to the procedures involved.
Adverse Device Effect (ADE)	Adverse event related to the use of an investigational medical device NOTE 1: This definition includes adverse events resulting from insufficient or inadequate instructions for use, deployment, implantation, installation, or operation, or any malfunction of the investigational medical device. NOTE 2: This definition includes any event resulting from an error use or from intentional misuse of the investigational medical device.
Device Deficiency (DD)	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 Related	An Adverse Event that is directly related to the insertion or surgical modification of the system. NOTE: In general, this excludes events that are inherent to any surgical procedure (e.g. anesthesia complications) as well as indirect subsequent consequences of the procedure (e.g. reaction to pain medication).

Reveal LINQ System Related (includes all implantable components and features, associated introduction tools, operational and installed software and programmers as defined in the Clinical Investigation Plan)	An adverse event that results from the presence or performance of any component of the system. Device-related: An adverse event that results from the presence or performance (intended or otherwise) of the device. RAMware-related: An adverse event that results from the presence or performance (intended or otherwise) of the RAMware. Programmer Related: An adverse event that results from the presence or performance (intended or otherwise) of the programmer Insertion Tool Related: An adverse event that results from the presence or performance (intended or otherwise) of the iinsertion tool. Holter Related: An adverse event that results from the presence or performance (intended or otherwise) of the implant tool.
Cardiovascular Related	An Adverse Event relating to the heart and the blood vessels or the circulation (e.g. Atrial Fibrillation, Myocardial Infarction, stroke, perivascular disease)

Not Related	Relationship to the device or procedures can be excluded when: ▪ The event is not a known side effect of the product category the device belongs to or of similar devices and procedures; ▪ The event has no temporal relationship with the use of the device or the procedures; ▪ The serious event does not follow a known response pattern to the medical device (if the response pattern is previously known) and is biologically implausible; ▪ The discontinuation of medical device application or the reduction of the level of activation/exposure – when clinically feasible – and reintroduction of its use (or increase of the level of activation/exposure) do not impact the serious event; ▪ The event involves a body-site or an organ not expected to be affected by the device or procedure; ▪ The serious event can be attributed to another cause (e.g., an underlying or concurrent illness/clinical condition, an effect of another device, drug, treatment, or other risk factors); ▪ The event does not depend on a false result given by the device used for diagnosis (when applicable); ▪ Harms to the subject are not clearly due to use error; ▪ In order to establish the non-relatedness, not all the criteria listed above might be met at the same time, depending on the type of device/procedures and the event.
Unlikely	The relationship with the use of the device seems not relevant and/or the event can be reasonably explained by another cause, but additional information may be obtained.
Possible	The relationship with the use of the investigational device is weak but cannot be ruled out completely. Alternative causes are also possible (e.g. an underlying or concurrent illness/ clinical condition or/and an effect of another device, drug or treatment). Cases were relatedness cannot be assessed or no information has been obtained should also be classified as possible.
Probable	The relationship with the use of the investigational device seems relevant and/or the event cannot reasonably explained by another cause, but additional information may be obtained.

Causal Relationship	The event is associated with the device or study procedures beyond reasonable doubt when: ▪ The event is a known side effect of the product category the device belongs to or of similar devices and procedures; ▪ The event has a temporal relationship with device use/application or procedures; ▪ The event involves a body-site or organ that the device or procedures are applied to or the device or procedures have an effect on; ▪ The serious event follows a known response pattern to the medical device (if the response pattern is previously known); ▪ The discontinuation of medical device application (or reduction of the level of activation/exposure) and reintroduction of its use (or increase of the level of activation/exposure) impact on the serious event (when clinically feasible); ▪ Other possible causes (e.g., an underlying or concurrent illness/clinical condition or/and an effect of another device, drug, or treatment) have been adequately ruled out; ▪ Harm to the subject is due to error in use; ▪ The event depends on a false result given by the device used for diagnosis (when applicable); ▪ In order to establish the relatedness, not all the criteria listed above might be met at the same time, depending on the type of device/procedures and the serious event.
Seriousness	

Serious Adverse Event (SAE)	Adverse event that a) led to death, b) led to serious deterioration in the health of the subject, that either resulted in 1) a life-threatening illness or injury, or 2) a permanent impairment of a body structure or a body function, or 3) in-patient or prolonged hospitalization, or 4) medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function, c) led to fetal distress, fetal 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. (ISO 14155:2011, 3.37)
Serious Adverse Device Effect (SADE)	Adverse device effect that has resulted in any of the consequences characteristic of a serious adverse event. (ISO 14155:2011, 3.36)
Other	
Unanticipated Adverse Device Effect (UADE)	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. (21 CFR 812.3(s))
Acute Decompensated Heart Failure (ADHF) Event	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

<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>

10.3. Reporting of Adverse Events

10.3.1. Adverse Events and Device Deficiency Classification

All reported AEs and DDs will be reviewed by a Medtronic representative. Adverse Events will be classified according to the definitions provided.

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

For emergency contact regarding a UADE or SAE, contact a ReLINQuish Study representative immediately (refer to the study contact list provided in the site's study documents binder/investigator site file or refer to the Sponsor Contact Information section provided in the CIP).

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

Table 7: Adverse Event Classification Responsibilities

What is classified?	Who classifies?	Classification Parameters
Relatedness	Investigator	Device, Insertion Tool(s), RAMware, Programmer, Holter, Procedure,
	Sponsor	Device, Insertion Tool(s), RAMware, Programmer, Holter, Procedure
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

10.3.2. Adverse Events and Device Deficiency Reporting Requirements

Regulatory reporting of AEs and device deficiencies will be recorded and reported according to local regulatory requirements. It is the responsibility of the Investigator to abide by the adverse event reporting requirements stipulated by local law and the site's IRB/EC.

Table 8: 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))
Regulatory authorities	Submit to regulatory authority per local reporting requirement
Ethics Committee	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 within 10 working days after first receives notice of the effect. (21 CFR 812.150(b)(1))
Ethics Committee	Submit within 10 working days after first receives notice of the effect. (21 CFR 812.150(b)(1))
Investigators	Submit within 10 working days after first receives notice of the effect. (21 CFR 812.150(b)(1))
All other reportable Adverse Events	
Investigator submit to:	
Medtronic	Submit in a timely manner after the investigator first learns of the event.
Regulatory authorities	Submit to regulatory authority per local reporting requirement.
Ethics Committee	Submit to Ethics Committee per local reporting requirement.
Device Deficiencies	
Investigator submit to:	
Medtronic	Submit or report as required per local reporting requirements.
Regulatory authorities	Submit to regulatory authority per local reporting requirement.
Ethics Committee	Submit to Ethics Committee per local reporting requirement.
Sponsor submit to:	
Regulatory authorities	Submit to regulatory authority per local reporting requirement.
Ethics Committee	Submit to Ethics Committee per local reporting requirement.

10.4. Subject Death

10.4.1. Death Data Collection

All subject deaths must be reported by the investigator to Medtronic on an AE form (AE with outcome of fatal) as soon as possible after the investigator first learns of the death. In case of death, there should be one SAE with the outcome of death reported.

In the event of a subject's death, it is recommended that the implanted system be explanted and returned to Medtronic for analysis whenever possible per local process. Local laws and procedures must be followed where applicable.

System Interrogation Data Recommendations:

- After the subject has died but prior to explant, it is strongly recommended that the system be interrogated and a full summary interrogation (Interrogate All) performed when possible, and saved in a digital format. Store one copy of the save-to-media at the site and send a copy to Medtronic.
- Make the device interrogation/save-to-media file before any programming to prevent overwriting information in the device's memory and/or distinguishing between events detected during versus before the explant procedure.
- Recommend obtaining the exact date and time of death as lower temperatures after death can cause ERI and other "event flags" to be stored in the device memory.

If the system is not interrogated, an explanation must be entered on the AE form. If any system component 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 ReLINQuish 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 ReLINQuish Study team, if available. If an autopsy is conducted, the autopsy report should also be sent to the Medtronic ReLINQuish Study team if available and allowed by state/local law. When the death occurs at a remote site, it is the investigative site'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 and Save-to-Media (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 allowed by state/local law)

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

Table 9: Subject Death Classification Responsibilities

What is classified?	Who classifies?	Classification Parameters
Death Classification	Investigator	Sudden Cardiac, Non-sudden Cardiac, Non-cardiac, Unknown

Regulatory reporting of Subject Deaths will be completed according to local regulatory requirements.

10.5. 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 Clinical 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.

11. Data Review Committees

The purpose of the study is to characterize the relationship between subcutaneous impedance and hemodynamic measurements in patients with heart failure. Additionally, the relationship between changes in subcutaneous impedance and other physiologic parameters during acute decompensated HF events will be characterized. Since this study will not provide effectiveness and/or safety data, an independent Adverse Event Advisory Committee (AEAC) will not be utilized. Qualified Medtronic personnel will review all adverse events. A Data Monitoring Committee (DMC) will not be utilized to monitor data collected in the study since there are no safety endpoints or planned interim analysis.

12. Statistical Design and Methods

This feasibility study is not powered to formally test a hypothesis. However, it is expected that a sample of up to 30 subjects will be sufficient to determine whether this approach warrants further study.

13. Ethics

13.1. Statement(s) of Compliance

The ReLINQuish 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 and obtaining and documenting the freely given informed consent of a subject before initiating the study.

The ReLINQuish study was designed to reflect the GCP principles outlined in ISO 14155:2011. These include the protection of the rights, safety and well-being of human subjects, controls to ensure the scientific conduct and credibility of the clinical investigation and the definition of responsibilities of the sponsor and investigators. In accordance with the ISO standard, the sponsor shall avoid improper influence on, or inducement of, the subject, monitor, any investigator(s) or other parties participating in, contributing to, the clinical investigation. All investigators shall avoid improper influence on or inducement of the subject, sponsor, monitor, other investigator(s) or other parties participating in or contributing to the clinical investigation.

The study will be conducted according to federal, national and local laws, regulations, standards, and requirements of the countries/geographies where the study is being conducted. The principles of the Declaration of Helsinki have been implemented through the patient informed consent (PIC) process, IRB approval, study training, clinical trial registration, preclinical testing, risk-benefit assessment and publication policy.

All investigators are required to complete financial disclosure, as outlined in 21 CFR Part 54 and all sites will need to comply with:

- 21 CFR Part 11
- 21 CFR Part 50
- 21 CFR Part 56
- 21 CFR Part 812(b)

The study will be publicly registered on http://clinicaltrials.gov prior to first enrollment in accordance with the 2007 Food and Drug Administration Amendments Act (FDAAA) (PL 110-85, Section 801(a)) and the Declaration of Helsinki.

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

- Medtronic
- An Institutional Review Board at each individual study center

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.

14. Study Administration

14.1. 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 site in order to ensure that the study is conducted in accordance with the CIP, the Clinical Trial Agreement or Work Order, 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 Informed Consent Form and Authorization to Use and Disclose Personal Health Information/Research Authorization/other privacy language (data protection authorization) as required by law and Clinical Trial Agreement or Work Order. The principal investigator should also be available during monitoring visits.

Monitoring for the study will be done in accordance to the study-specific 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/EC 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 site. Regulatory documents may be reviewed at each study site.

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.

14.2. Data Management

Data will be collected using a 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 is impossible to make it anonymous, for instance, where the patient's name cannot be removed from the data carrier, such as fluoroscopy images.

Procedures in the CIP require source documentation. Source documentation will be maintained at the site. Source documents, which may include, but not limited to, worksheets, patient medical records, lab results, ECGs, programmer printouts, and interrogation files, must be created and maintained by the investigational site team. In some cases, the data reported in the CRFs may be considered source, as long as there is evidence of it in the subject's record. The CRF may serve has the primary source for the following data points but is not limited to the list below (refer to the study-specific monitoring plan for complete listing).

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

14.3. Direct Access to Source Data/Documents

All study investigator(s)/institution(s) will permit study-related monitoring, audits, IRB/IEC review, and regulatory inspection(s), providing direct access to source data/documents as required in accordance with ReLINQuish CIP and the investigator agreement.

14.4. Confidentiality

All records and other information about subjects participating in this study will be treated as confidential. The identity of a subject will never be disclosed in the event that study data are published.

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

Study data may be made available to third parties, e.g. in the case of an audit performed by regulatory authorities, provided the data are treated confidentially and that the subject's privacy is guaranteed. Sites will maintain subject privacy according to local and national regulations and institutional requirements.

14.5. CIP Amendments

Amendments to this Clinical Investigation Plan shall be agreed upon between Medtronic and clinical investigator(s) and be recorded with a justification for the amendments.

14.6. Record Retention

The investigator must retain the Investigator Site File, subject medical files and CRFs in accordance with local law and regulations for a minimum period of 2 year (or longer if local laws require) after market-release in his/her region. The investigator should take measures to prevent accidental or early destruction of the clinical study related materials.

14.7. Publication and Use of Information

Publications and presentations referring to this clinical study will be coordinated by Medtronic to allow the use of all available data. The following publication policy will have to be adhered to by all participating investigation sites:

Medtronic may intend to publish the results of the study in scientific journals and congresses.

There are no plans to form a publication committee. Publication activities will be assessed after the study is completed and any collaboration with the investigator will be determined at that time.

Authorship on any publication(s) resulting from this clinical study will be assigned according to substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data, drafting the article or revising it critically for important intellectual content and final approval of the version to be published. This is in accordance with the Vancouver principles (The Uniform Requirements for Manuscripts Submitted to Biomedical Journals: Writing and Editing for Biomedical Publication, Latest ICMJE Recommendations ("Recommendations for the Conduct, Reporting, Editing, and Publication of Scholarly Work in Medical Journals", 2013), as agreed upon by the editors of all major medical journals.

The number of authors will be dependent on the regulations of the concerning journal.

Based on the principle that Medtronic owns the data of this clinical study, a single investigation site may access and use the data provided by itself for scientific publications following prior approval by Medtronic.

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

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

Participating subjects will not be identified by name in any published reports about the clinical study.

14.8. Suspension or Early Termination

14.8.1. 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 10.9 for additional information regarding study exit procedures.

14.8.2. 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.

14.8.3. 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

14.8.4. 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).

14.8.5. Procedures for termination or suspension

14.8.5.1. 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

14.8.5.2. 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

14.8.5.3. 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 or guardians and/or the personal physician of the subjects, with the rationale for the study termination or suspension

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16. Appendices

Appendix A: Patient Informed Consent Form Template

Appendix B: Draft data collection forms (Case Report Forms)

Appendix C: ReLINQuish Handbook

Appendix D: Site Information

Appendix A: Patient Informed Consent Form Template

Template informed consent form will be provided under separate cover.

Appendix B: Draft data collection forms

Draft data collection forms will be provided under separate cover.

Appendix C: ReLINQuish Study Procedure Handbook

The ReLINQuish Study Procedre Handbook will be provided under separate cover.

Appendix D: Site Information

Center and Mailing Address
[redacted]
[redacted]

17. Version History

Version	Summary of Changes	Author(s)/Title
1.0	• Initial Release	[redacted] Clinical Research Specialist [redacted] Principal Scientist
	• Updated risks section. The following risks were added: Electromagnetic interference Pain or stimulation effects from impedance measurements over duration of implant Missing/Misleading information causing inappropriate medical intervention Improper LINQ™ HF investigational RAMware access and activation Undesirable interaction of LINQ HF impedance measurement with concomitant implanted cardiac device (IPG/ICD/ CRT-P/D) therapy delivery Undesirable interaction of Tel-B with concomitant implanted devices	[redacted] Clinical Research Specialist