Medtronic **Clinical Investigation Plan**	
Clinical Investigation Plan/Study Title	Reveal LINQ™ for Chronic Obstructive Pulmonary Disease (COPD)
Clinical Investigation Plan Identifier	MDT19019
Study Product Name	Reveal LINQ™ Insertable Cardiac Monitor (ICM) System
Sponsor/Local Sponsor	**Sponsor:** Medtronic, Inc US 8200 Coral Sea Street NE Mounds View, MN U.S.A. 55112 Phone: 1-800-328-2518
Document Version	5.0
Version Date	1-DEC-2022
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1. Administrative Information

1.1 Sponsor Contact Information

Medtronic contact information is provided below. This information is subject to change during the clinical study. Periodic updates to study contact information will be sent to the centers as needed.

Table 1: Sponsor Contact Information

Study Manager Contacts
Worldwide clinical study leader/US contact
Monitoring Contacts
Worldwide monitoring leader/US contact

2. Glossary

Term	Definition
ADE	Adverse device effect
ADHF	Acute Decompensated Heart Failure
AE	Adverse event
AF	Atrial Fibrillation
ALLEVIATE-HF RAMware	Investigational software downloaded to the LINQ™ TruRhythm device in study subjects
BCSS	Breathlessness, Cough, and Sputum Scale
BNP	Brain natriuretic peptide
CFR	Code of Federal Regulations
CIP	Clinical Investigation Plan

Term	Definition
COPD	Chronic Obstructive Pulmonary Disease
CRF	Case report form
CRO	Contract Research Organization
CRT-D	Cardiac resynchronization therapy-defibrillator
CRT-P	Cardiac resynchronization therapy-pacemaker
CTA	Clinical trial agreement
CV	Cardiovascular
DD	Device deficiency
DMC	Data Monitoring Committee
EAC	Event Adjudication Committee
EC	Ethics Committee
ECG	Electrocardiogram
eCRF	Electronic case report form
EGM	Electrogram
EP	Electrophysiologist
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act
FEV1	Forced Respiratory Volume
GCP	Good Clinical Practice
GOLD	Global Initiative for Chronic Obstructive Lung Disease
HF	Heart failure
HIPAA	Health Insurance Portability and Accountability Act
ICD	Implantable cardioverter-defibrillator

Term	Definition
ICF	Informed consent form
ICM	Insertable cardiac monitor
ICMJE	International Committee of Medical Journal Editors
IDE	Investigational Device Exemption
IFU	Indications for Use
IPG	Implantable pulse generator
IRB	Institutional Review Board
LAR	Legally authorized representative
LINQ HF RAMware	Investigational software downloaded to the LINQ™ Pre-TruRhythm device in study subjects
MCT	Mobile cardiac telemetry
MedDRA	Medical Dictionary for Regulatory Activities
MiD	Monitoring in Dialysis
NSR	Non-significant Risk
NT-proBNP	N-terminal brain natriuretic peptide
PRN	'pro re nata' – as needed
RDC	Remote data capture
RR	Respiration rate
SADE	Serious adverse device effect
SAE	Serious adverse event
SAP	Statistical analysis plan
SC	Steering Committee
SCD	Sudden Cardiac Death
SDN	Software Distribution Network

Term	Definition
SGRQ	St. George's Respiratory Questionnaire
UADE	Unanticipated Adverse Device Effect
UAE	Unavoidable Adverse Event
US	United States
USB	Universal Serial Bus
WO	Work order

3. Synopsis

Title	Reveal LINQ™ for COPD
Clinical Study Type	Prospective, non-randomized, multi-center, observational, pre-market clinical study.
Product Name	LINQ™ Insertable Cardiac Monitor (ICM) System with either LINQ HF or ALLEVIATE-HF investigational RAMware download
Sponsor / Local Sponsors	**Sponsor:** Medtronic, Inc US 8200 Coral Sea Street NE Mounds View, MN U.S.A. 55112 Phone: 1-800-328-2518
Indication under investigation	The study is utilizing investigational RAMware, either LINQ HF OR ALLEVIATE-HF, that will be downloaded onto the subject's market-released Medtronic Reveal LINQ ICM. The investigational RAMware enables the hardware to record and store additional sensor data. The market-released indication is provided below: The Reveal LINQ ICM is an insertable automatically activated and patient activated monitoring system that records subcutaneous ECG and is indicated in the following cases: • Patients with clinical syndromes or situations at increased risk of cardiac arrhythmias • Patients who experience transient symptoms such as dizziness, palpitation, syncope, and chest pain that may suggest a cardiac arrhythmia The device has not been tested specifically for pediatric use.
Investigation Purpose	The purpose of the LINQ™ for COPD study is to characterize Reveal LINQ™ derived data from patients with COPD by assessing the relationship between changes in LINQ™ derived data

<table>
<tr><td></td><td>with COPD exacerbation events. The study will also collect information regarding COPD related clinical events during the same period.</td></tr>
<tr><td>Product Status</td><td>
<table>
<tr><th>Model Number</th><th>Component</th><th>Manufacturer</th><th>Investigational or Market-released</th></tr>
<tr><td>LNQ11</td><td>Reveal LINQ™ Insertable Cardiac Monitor</td><td>Medtronic</td><td>Market-Released*</td></tr>
<tr><td>LNQ11</td><td>Incision Tool</td><td>Medtronic</td><td>Market-Released</td></tr>
<tr><td>LNQ11</td><td>Insertion Tool</td><td>Medtronic</td><td>Market-Released</td></tr>
<tr><td>SW026</td><td>2090 Programmer</td><td>Medtronic</td><td>Market-Released*</td></tr>
<tr><td>Not Applicable</td><td>LINQ HF RAMware, Version 1.1 and subsequent versions as they are released**</td><td>Medtronic</td><td>Investigational</td></tr>
<tr><td>Not Applicable</td><td>LINQ HF Software, Rev 1.1 and subsequent versions as they are released</td><td>Medtronic</td><td>Investigational</td></tr>
<tr><td>Not Applicable</td><td>ALLEVIATE-HF RAMware, Version 1.32 and subsequent versions as they are released**</td><td>Medtronic</td><td>Investigational</td></tr>
<tr><td>ALVT22</td><td>ALLEVIATE-HF Software, Rev 1.1 and subsequent versions as they are released</td><td>Medtronic</td><td>Investigational</td></tr>
<tr><td>PA96000</td><td>Patient Assistant</td><td>Medtronic</td><td>Market-Released</td></tr>
<tr><td>24950</td><td>MyCareLink® Home Monitor</td><td>Medtronic</td><td>Market-Released</td></tr>
<tr><td>DR220</td><td>Holter</td><td>NorthEast Monitoring, Inc.</td><td>Market-Released</td></tr>
<tr><td>IP-9260</td><td>QS+CARE™ Bed Monitor</td><td>EMFIT</td><td>Market-Released</td></tr>
</table>
*The LINQ™ device and the 2090 programmer are market-released, but once the investigational Software or RAMware is downloaded into the devices, they are considered investigational.
**Subjects will receive the most current approved version of the investigational RAMware at the time of their device insertion.
</td></tr>
<tr><td>Study Objective</td><td>The study objective is to characterize Reveal LINQ™ derived data from patients with COPD by assessing the relationship between changes in LINQ™ derived data with COPD events collected during the study.</td></tr>
<tr><td>Study Design</td><td>The Reveal LINQ™ for COPD study is a Non-significant Risk IDE, observational, non-randomized, multi-center, clinical study. The study is expected to be conducted at up to 10</td></tr>
</table>

	centers in the United States and up to 100 subjects will be enrolled, with no more than 20 subjects enrolled per site. All enrolled subjects will be implanted with a Reveal LINQ™ Insertable Cardiac Monitor (ICM) with either the investigational LINQ HF or ALLEVIATE-HF RAMware download, and will be followed until the last subjects' 6-month follow-up visit is completed or until official study closure, defined as when Medtronic and/or regulatory requirements have been satisfied per the Clinical Investigation Plan and/or by a decision by Medtronic or regulatory authority, whichever occurs first. Accordingly, the expected total study duration is approximately 33 months, representing approximately 26 months of patient enrollment, at least 6 months of follow-up with 1 month between enrollment and insertion. All LINQ™ system and procedure-related adverse events (AEs), all serious adverse events (SAEs), all Pulmonary related AEs and all Cardiovascular related AEs will be collected throughout the study duration of a subject's participation in the study, beginning at the time of informed consent.
Sample Size	The study may enroll approximately 100 subjects
Inclusion/Exclusion Criteria	**Inclusion Criteria** • Patient is ≥ 45 years old • Patient (or patient's legally authorized representative) is willing and able to provide written informed consent • Patient is willing and able to comply with the protocol, including follow-up visits, diary submissions and CareLink transmissions • FEV_1 (post bronchodilator) ≤ 70% of predicted • Current or former smoker with lifetime cigarette consumption of ≥ 10 pack-years • One COPD exacerbation in the previous 12 months requiring hospitalization, urgent care or emergency department visit for respiratory illness OR Two COPD exacerbations within the previous 12 months requiring antibiotics and/or corticosteroids for respiratory symptoms • The patient's medical records must be accessible by the enrolling site over the follow-up period **Exclusion Criteria** • Less than 30 days from diagnosis of a COPD exacerbation as defined as taking antibiotics and/or corticosteroids for respiratory symptoms, hospitalization, urgent care or emergency department visit for respiratory illness. * • Less than 30 days from diagnosis of a HF event as defined as any cardiovascular-related (including hypervolemia) Health Care Utilizations (HCUs) for any one of the following events: Admission with primary diagnosis of HF or 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, or HF/Cardiology Clinic • Active respiratory infection being treated with antibiotics and/or corticosteroids • Class IV heart failure • Clinical diagnosis of unstable angina, bronchiectasis, or cystic fibrosis

	• Any concomitant condition that might endanger the patient through participation in the study or interfere with study procedures, as assessed by the investigator • Patient is pregnant (all females of child-bearing potential must have a negative pregnancy test within 1 week of enrollment) • Patient is enrolled in another study that could confound the results of this study, without documented pre-approval from a Medtronic study manager • Patient has an existing or planned implantation of Medtronic IPG, ICD, CRT-D or CRT-P device in the near future • Patient has an existing and active insertable cardiac monitor, regardless of manufacturer.# • Concurrent disease with life expectancy less than 1 year * This exclusion criterion has been removed as documented in the Intended CIP deviation dated 13-OCT-2021 # This exclusion criterion has been updated to "Patient has an active non-Medtronic insertable cardiac monitor" in the Intended CIP deviation dated 13-OCT-2021
Study Procedures and Assessments	When a patient or Legally authorized representative (LAR) and the principal investigator have signed, and dated the Patient Informed Consent Form, the patient is considered a subject enrolled in the study. Following consent, a baseline assessment will be completed, and subjects will undergo a Reveal LINQ™ device insertion including either the LINQ HF or ALLEVIATE-HF investigational RAMware download within 30 calendar days of enrollment. All subjects will be provided with a MyCareLink Patient Monitor, enrolled in the Medtronic CareLink network, and instructed on how to set up their monitor to ensure automatic nightly transmission of their device data. Subjects will complete a weekly diary entry or when their symptoms change, comprising of the BCSS Questionnaire and documentation of any PRN medications. Additionally, subjects will complete telephone follow-up visits every three months post device insertion (visits may also be conducted in-person if desired). The optional in-office follow-up visit however can be conducted at any time during study participation, except within 30 days post insertion of the device. All enrolled subjects will be followed until study closure. Data collection and procedures are summarized below: Baseline: Informed consent, inclusion/exclusion assessment, medical history, subject demographics, SGRQ, Baseline Measurements, Medication Assessment, subject diary enrollment, Labs, Spirometry tests (pre and post bronchodilator), adverse events, study deviations LINQ Insertion Visit: LINQ™ insertion, LINQ HF OR ALLEVIATE-HF RAMware download, device interrogation (save to media via USB), system and procedure information, adverse events, device deficiencies, study deviations Subject Diary (weekly): BCSS Questionnaire, PRN medication assessment Scheduled Phone Follow-up Visits (every 3 months): Medication assessment, adverse events, device deficiencies, study deviations

	Scheduled In-office Follow-up Visit (optional): Baseline Measurements, medication assessment, device interrogation (save to media via USB) (pre and post visit procedures), spirometry tests with Holter, patient assistant activity, Chest x-ray, adverse events, device deficiencies, study deviations Study Exit Visit: Reason for exit, removal of LINQ HF or ALLEVIATE-HF RAMware from LINQ™ device, device interrogation (save to media via USB), opting out of the subject diary, SGRQ, Medication assessment, labs, adverse events, device deficiencies, study deviations Additionally, up to 20 subjects will be asked to place an EMFIT monitor under their bed for the length of their study participation, with no more than 10 subjects per site. Furthermore, LINQ™ device data will be collected bi-weekly via CareLink manual transmissions as well as system modifications and subject deaths will be collected.
Safety Assessments	All LINQ™ system and procedure-related adverse events (AEs), all serious adverse events (SAEs), all Pulmonary related AEs and all Cardiovascular related AEs will be collected throughout the study duration of a subject's participation in the study, beginning at the time of informed consent. An Event Adjudication Committee (EAC) will conduct a medical review of all adverse events classified by the investigator or Medtronic as Pulmonary related and all AEs with a fatal outcome. The EAC will consist of non-Medtronic employed physicians that are not participating investigators for the study.
Statistics	Since the study will be exploratory in nature and the study objectives are descriptive, no clinical endpoints will be developed. LINQ™ derived data will be summarized using descriptive statistics. Their relationship to COPD events (per EAC adjudication) will be evaluated by looking at the data before and after the occurrence of COPD events to identify potential patterns and signals.

4. Introduction

4.1 Background

The Reveal LINQ™ system is an ICM manufactured by Medtronic, Inc. The LINQ™ ICM is designed to automatically record the occurrence of ventricular tachyarrhythmias, bradyarrhythmias, pause, atrial tachyarrhythmias, and atrial fibrillation. While experiencing or immediately after a symptomatic event, the patient can activate the ICM to record their cardiac rhythm.

The current indications are:

US Indications:

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

Chronic Obstructive Pulmonary Disease (COPD) is progressive and currently incurable and refers to a collection of diseases that lead to the key feature of irreversible airflow limitation and breathing related problems. It is characterized by loss of lung elastic recoil, small airway remodeling, a progressive decline in FEV1 (Forced Expiratory Volume), decreased lung emptying, and static and dynamic hyperinflation[1]. Particulate exposure can lead to mucosal and glandular inflammation, increased mucous discharge and epithelial hyperplasia, and altered tissue repair in small conducting airways[1]. COPD is the third leading cause of death worldwide, with an estimated prevalence of 175 million[1]. Of those with COPD, 46% experienced at least one exacerbation within the previous year and 19% needed hospitalization[2]. Approximately 11% of those admitted for exacerbation die within 90 days, with half occurring during the hospitalization[1]. 35% of those admitted for exacerbation are readmitted within 90 days[1]. The financial burden of COPD is also evident, in that over $32 billion was spent for COPD care in the United States in 2010 and it is expected to be close to $50 billion in 2020[3]. More than 70% of the spending is related to hospitalizations in the COPD patients due to acute exacerbations. Most COPD exacerbations are caused by infection, with other major triggers including outdoor and indoor particulate air pollution and weather[2]. Confounding these metrics is the fact that there is much overlap in COPD with other concurrent disease. Approximately 1/3 of COPD patients die of cardiovascular disease and 1/3 of patients with cardiovascular disease have airflow limitation[1].

Reducing healthcare utilization associated with COPD patient management (i.e. short-term readmission and chronic disease management) is a critically important unmet need for patients, caregivers, and hospitals. Early detection, prevention, and treatment of COPD exacerbation would aim to reduce this high morbidity and cost.

4.2 Purpose

The ability to predict which patients will subsequently have an exacerbation for COPD using the traditional evaluation measures such as physical signs and symptoms is limited. Medical interventional methods currently may not identify patients early enough to prevent an exacerbation. To help reduce these exacerbations and improve disease management, sensors in a minimally invasive device can be used to identify factors that are associated with exacerbations. Thus, a solution to continuously monitor COPD patients at risk for acute exacerbations (GOLD stage C/D) in an ambulatory fashion to predict symptom worsening and provide timely remote intervention to prevent hospitalizations is an unmet clinical and economic need. Using sensors in a minimally invasive device like LINQ™ to sense, predict and prevent COPD hospitalizations is the overarching objective of this project. As a first step, the LINQ-COPD study aims to collect sensor data to characterize the changes in these sensor data prior to COPD hospitalizations with the aim to develop a prediction algorithm that can identify when patients are risk and may benefit from a remote intervention.

Prior studies have shown implantable device-measured diagnostics like intra-thoracic impedance,[4] AF burden, heart rate metrics,[5] respiration,[6] and patient activity metrics[7] can be used individually or in a

combined fashion to identify when patients are at risk for certain events. We hypothesize that these measurements made in the subcutaneous thoracic space may be sensitive enough to detect physiological changes associated with COPD.

The use of implantable device features such as the OptiVol™ impedance algorithm is clinically useful in monitoring thoracic fluid status for pacemaker or ICDs and may be measured in the subcutaneous space.[8] 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.[9]

Respiratory distress is the primary driver for HF hospitalization and detection of respiratory distress provides an early indicator of ADHF. Respiratory symptoms such as breathlessness and orthopnea are significantly related to increased mortality and associated with worse clinical outcomes.[10,11] The NOTICE-HF study, patient ambulatory respiration rate (RR) was monitored using an ICD or CRT defibrillator.[7] Maximum, median, and minimum RR was significantly elevated prior to ADHF when compared to baseline. We hypothesize RR may be measured through subcutaneous thoracic space through the use of impedance or R-wave amplitude variations.

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

5. Objectives and/or Endpoints

5.1 Objectives

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

The study objective will be characterized, and a final study report will be completed after the final study exit.

5.1.1 Primary Objective(s)

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

COPD event is defined as an adverse event where the underlying COPD condition exacerbates beyond normal day-to-day variations, where an increase in dyspnea, cough, and/or sputum

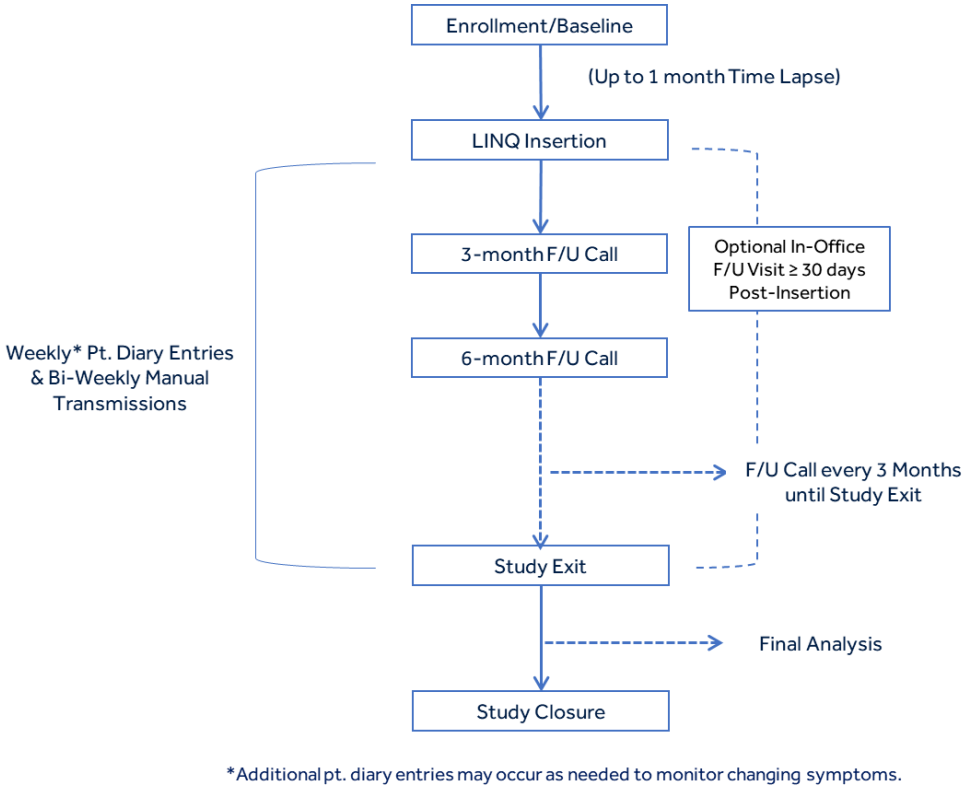
production presents with acute onset and necessitates supplementing regular COPD medications with antibiotics for respiratory pathogens and/or steroids.

6. Study Design

The LINQ™ for COPD is a prospective, non-randomized, multi-center, observational, pre-market clinical study. The study may enroll up to 100 COPD subjects at up to 10 sites in the US, with no more than 20 subjects enrolled per site. Study subjects will be followed until the last enrolled subject reaches their 6-month visit or until official study closure defined as when Medtronic and/or regulatory requirements have been satisfied per the Clinical Investigation Plan and/or by a decision by Medtronic or regulatory authority, whichever occurs first. . Accordingly, the expected total study duration is approximately 33 months, representing approximately 26 months of patient enrollment, at least 6 months of follow-up with 1 month between enrollment and insertion. All Reveal LINQ™ system and procedure-related adverse events will be collected and reported per the study protocol. In addition, all SAEs, all Respiratory related AEs (regardless of seriousness) and all Cardiovascular related AEs (regardless of seriousness) will be collected and reported per study protocol.

Following consent, subjects will undergo a baseline assessment followed by the LINQ™ ICM device insertion procedure. Following insertion, subjects will complete a weekly diary entry, which includes answering the BCSS Questionnaire and recording any PRN medications. Additionally, subjects will complete telephone follow-up visits every three months post device insertion (visits may also be conducted in-person if desired). The optional in-office follow-up visit however can be conducted at any time during study participation, except within 30 days post insertion of the device. All enrolled subjects will be followed until study closure. A study flowchart is shown in Figure 1.

Figure 1: Study Flowchart



6.1 Duration

Subjects will be followed until the last enrolled subject reaches their 6-month visit or until official study closure defined as when Medtronic and/or regulatory requirements have been satisfied per the Clinical Investigation Plan (CIP) and/or by a decision by Medtronic or the applicable external parties (i.e. Ethics Committee (EC) Regulatory Authority) whichever occurs first. The estimated total study duration is approximately 33 months, representing a 26-month enrollment period, at least 6 months of follow-up per subject and up to 1 month between enrollment and insertion.

6.2 Rationale

As discussed in the Background section, reducing healthcare utilization associated with COPD patient management is a critically important unmet need for patients, caregivers, and hospitals. Early detection, prevention, and treatment of COPD exacerbation would aim to reduce this high morbidity and cost. The ability to predict which patients will subsequently have an exacerbation for COPD using the traditional evaluation measures such as physical signs and symptoms is limited, and there are few means for long-term monitoring of these signs and symptoms. Therefore, the purpose of this study is to collect long-term physiological recordings of heart rate, respiratory rate, temperature, and impedance in

relation to COPD exacerbations in a population with high likelihood to suffer exacerbations. The Reveal LINQ™ is suitably positioned to collect such data in relation to COPD exacerbations in a non-obtrusive manner. The data collected will be used to develop methods for predicting and preventing COPD exacerbations, and ultimately to take aim at the unmet need of reducing healthcare utilization in COPD patient management.

Safety will not be a primary focus of this study as 1) the study is only collecting observational data, 2) data collected will not be used to manage the treatment of subjects in the study, 3) data collection procedures other than those related to the LINQ™ are not outside standard of care for COPD patients and 4) the safety profile of LINQ™ is already well known.[12]

6.3 Study Oversight

Overall study Principal Investigator and Steering Committee member contact information is provided below.

Table 2: Overall Study Principal Investigator Contact Information

Name	Contact Information
[redacted]	[redacted]

7. Product Description

7.1 General

The Medtronic LINQ™ ICM is an approved, programmable device that continuously monitors a patient's electrocardiogram (ECG) and other physiological parameters. The device records cardiac information in response to automatically detected arrhythmias and patient activation. The LINQ™ device is indicated in the following:

US Indications:

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

The study will be conducted using the components described in Table below. All components of the LINQ™ system are manufactured by Medtronic, Inc. Instructions for use of the devices used in this study are provided within their respective manuals.

Table 3: Study 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	LINQ HF RAMware, Version 1.1 and subsequent versions as they are released**	Medtronic	Investigational
Not Applicable	LINQ HF Software, Rev 1.1 and subsequent versions as they are released	Medtronic	Investigational
Not Applicable	ALLEVIATE-HF RAMware, Version 1.32 and subsequent versions as they are released**	Medtronic	Investigational
ALVT22	ALLEVIATE-HF Software, Rev 1.1 and subsequent versions as they are released	Medtronic	Investigational
PA96000	Patient Assistant	Medtronic	Market-Released
24950	MyCareLink® Home Monitor	Medtronic	Market-Released
DR220	Holter	NorthEast Monitoring, Inc.	Market-Released
IP-9260	QS+CARE™ Bed Monitor	EMFIT	Market-Released

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

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

Descriptions of each component of the system are provided in the sections below.

7.1.1 Reveal LINQ™ Insertable Cardiac Monitor (ICM)

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

Figure 2: Reveal LINQ™ ICM

7.1.2 Incision Tool

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

Figure 3: Incision Tool

7.1.3 Insertion Tool

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

The Reveal LINQ™ device will be loaded in the Insertion Tool and sterilely 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

7.1.4 2090 Programmer

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

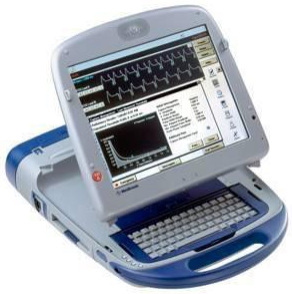


Figure 5: Medtronic 2090 Programmer

The Medtronic 2090 Programmer with the investigational software will be used to download the LINQ HF or ALLEVIATE-HF investigational RAMware onto the LINQ™ device. The investigational RAMware is required to activate additional sensors in the Reveal LINQ™ ICM. The software will be loaded onto the 2090 programmers designated for clinical use only. The 2090 programmer with the investigational software will allow the ability to download and remove the RAMware onto and from the device. In addition, the 2090 programmer will be used during the study activities as well.

7.1.5 Medtronic Investigational RAMware

7.1.5.1 LINQ HF Investigational RAMware

The LINQ HF investigational RAMware is required to activate additional sensors in the Reveal LINQ ICM (pre-TruRhythm) to allow for collection of device data needed for potential detection of early COPD events. In addition to the existing diagnostic data normally stored in the device, the LINQ HF investigational RAMware enables the Reveal LINQ™ hardware to collect and store additional sensor data, including impedance, temperature, activity, R-R interval, R-wave amplitude, posture change count (based on z-axis accelerometer values) and x, y, and z-axis accelerometer measurements. The device

will collect and store this data every 60 minutes for impedance, temperature, activity, R-wave amplitude and every 5 minutes for R-R intervals, posture change count, and x, y, and z-axis accelerometer values. In addition, impedance measurements are collected when the Patient Assistant is used.

7.1.5.2 ALLEVIATE-HF Investigational RAMware

The ALLEVIATE-HF investigational RAMware is required to activate sensors in the Reveal LINQ ICM with TruRhythm to allow for collection of device data needed for potential detection of early COPD events. In addition to the existing diagnostic data normally stored in the device, the ALLEVIATE-HF investigational RAMware enables the Reveal LINQ™ to record and store impedance, temperature, R-R interval, R-wave amplitude, x, y, and z-axis accelerometer measurements and posture change count periodically. The RAMware will calculate the respiration rate and will store daily impedance and respiration rate values.

7.1.6 Patient Assistant

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

The Reveal Patient Assistant is intended for unsupervised patient use away from a hospital or clinic. The Patient Assistant activates the data management feature in the Reveal LINQ™ ICM to initiate recording of cardiac event data in the implanted device memory. Additionally, the investigational RAMware enables the storage of a short segment of impedance signal when the Reveal Patient Assistant device is used.

The subjects will be asked to press the Patient Assistant whenever they experience increased difficulty of breathing not related to an activity. In addition, the subjects may be asked to press the Patient Assistant device during the Optional In-Office F/U study visit.

Figure 6: Patient Assistant

7.1.7 MyCareLink ® Home Monitor

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

Figure 7: MyCareLink Patient Monitor

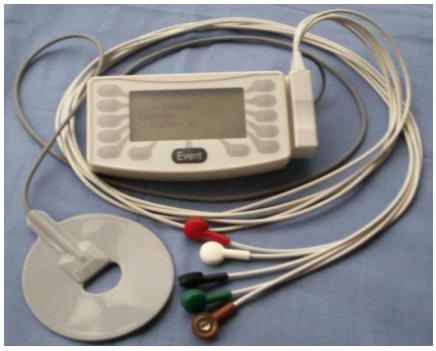
7.1.8 DR 220 Holter Monitor

The NorthEast Monitoring, Inc. DR220 Digital Recorder is a Holter monitor that is commercially available and designed to facilitate the ambulatory cardiac monitoring of those subjects who may benefit from such monitoring on the 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, 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 investigational 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



7.1.9 EMFIT QS + CARE™ Bed Monitor

The commercially available EMFIT QS+CARE™ bed monitor is a real-time occupancy and movement activity monitor with health data tracking that is placed under the mattress. The monitor can track and record heart and breathing rate, heart rate variability, sleep time, movement activity, bed exits, sleep score and sleep stages. The data collected will be transmitted back to Medtronic through a cellular mobile data connection. Medtronic is requesting up to 20 subjects in the study to place the monitor under their mattress for the duration of their study participation, with no more than 10 subjects per site. The bed monitor will be used in accordance with its labeling.

Figure 9: EMFIT QS+CARE™ Bed Monitor

7.2 Manufacturer

All products used in this study are manufactured by Medtronic, Inc., with the exception of the DR220 Holter Monitor and the EMFIT QS + CARE™ Bed Monitor

7.3 Packaging

Labelling for the LINQ HF and ALLEVIATE-HF investigational RAMware will be provided under separate cover. Labelling for all other market approved system components can be found with each package insert and/or are available on http://manuals.medtronic.com.

The LINQ HF and ALLEVIATE-HF investigational programmer software will be distributed electronically through the Software Distribution Network (SDN), therefore physical media labeling is not required.

Once the LINQ HF and ALLEVIATE-HF investigational software is installed on a CareLink 2090 programmer, the programmer will be considered investigational and will be labeled accordingly.

7.4 Intended Population

The intended population for inclusion in the LINQ™ for COPD study is COPD patients who are known to have frequent exacerbations (one requiring hospitalization, ED visit, or urgent care visit, or at least two others in the past year). The Reveal LINQ™ device with investigational LINQ HF or ALLEVIATE-HF RAMware download will be used in study subjects to collect and characterize Reveal LINQ™ derived data from patients with COPD by assessing the relationship between changes in LINQ™ derived data with COPD exacerbation events.

7.5 Product Use

The market released Reveal LINQ™ and investigational LINQ HF/ALLEVIATE-HF software and RAMware will be used in accordance with their respective product manuals, which are available under separate cover.

7.6 Product Training Materials

Clinicians implanting the market released Reveal LINQ ICM device in study subjects must have received prior training on the ICM insertion procedure, which may be documented via prior ICM insertion experience or documentation that training was provided.
Prior to site activation or subsequent involvement in study activities, Medtronic will provide study specific training relevant and pertinent to the involvement of site personnel.

7.7 Shipment of Study Components

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

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

7.8 Product Receipt and Tracking

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

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

The following products will be tracked on an accountability log:

- Reveal LINQ™ device
- 2090 Programmer with the Investigational Software
- Patient Assistants provided to sites for use during in-office visits
- Holter DR220
- EMFIT QS+CARE™ bed monitor

The MyCareLink Patient Monitors and Patient Assistant devices provided to subjects as part of their Reveal LINQ ICM system will not be considered investigational in the study and will not be tracked on a product accountability eCRF.

7.9 Product Storage

It is the responsibility of the investigator to store the study specific components and study specific equipment in a secured and temperature-controlled area. The method of storage shall prevent the use of the study device and components for other applications. Opening sealed cases is forbidden for other than study use and must be reported to the Investigator and Sponsor upon detection. It is the responsibility of the investigator to correctly handle, store, and track the investigational products maintained at the study site. Investigational products will be used only in the clinical study according to the CIP.

The 2090 programmers containing the LINQ HF or ALLEVIATE-HF investigational software will be labeled as investigational.

7.10 Product Return

All explanted product should be returned to Medtronic for analysis according to local laws and regulations. If the products are explanted but not returned, a justification is required to be reported on the appropriate eCRF(s) and/or disposition log(s). The Product Distribution Logs must be updated for explanted devices. To receive a Returned Product Mailer Kit, please contact your local Medtronic personnel or Study Manager. All unused product must be returned to Medtronic upon study closure at the center.

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

Table 4: Study Product Disposition

Model Number	Component	Return to MDT at Center Closure	Disposal after Each Use	Investigational RAMware Removal	Investigational Software Removal
LNQ11	Reveal LINQ™	X (Explant Only)		X (Study Exit)	
24950	MyCareLink® Monitor	X			
96000	Patient Assistant*	X			
2090	2090 Programmer with Investigational Software	X[1]			X
DR220	Holter	X			
IP-9260	EMFIT QS+CARE™ Bed Monitor	X			

[1] *If the 2090 programmer was supplied to the site for purposes of the study, the 2090 programmer should be returned to Medtronic.*

All product returns will be contingent on local laws and regulations.

All Investigational Product will be labeled Investigational.

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

7.11 Product Accountability

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

7.11.1 CareLink Programmer

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

7.11.2 Reveal LINQ ICM

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

7.11.3 Patient Assistant

The Patient Assistant device(s) provided to sites for use during in-office study visits will be tracked on the Patient Assistant device accountability eCRF. Use of the Patient Assistant in the study is not considered investigational. Patient Assistant devices provided to subjects as part of their LINQ ICM system will not be tracked.

7.11.4 Holter DR220

The Holter DR220 will be tracked on the DR220 Holter accountability eCRF.

7.11.5 EMFIT QS+CARE™ bed monitor

The EMFIT QS+CARE™ bed monitor will be tracked on the EMFIT QS+CARE™ bed monitor accountability eCRF.

8. Study Site Requirements

8.1 Investigator/Investigation Site Selection

All investigators or co-investigators managing the subject's COPD must be qualified practitioners and experienced in the diagnosis and treatment of subjects with COPD. All implanting physicians must be experienced and/or trained in the handling of Reveal LINQ™ ICM devices.

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

The principal investigator shall:

- Be qualified by education, training, and experience to assume responsibility for the proper conduct of the clinical investigation

- Be experienced in the field of application and training in the use of Reveal LINQ™ ICM devices
- Disclose potential conflicts of interest, including financial, that interfere with the conduct of the clinical investigation or interpretation of results
- Be able to demonstrate that the proposed investigational study site:
  - Has the required number of eligible subjects needed within the recruitment period.
  - Has one or more qualified investigators, a qualified investigational study site team and adequate facilities for the foreseen duration of the clinical investigation.

Study site personnel training will be completed and documented prior to participation in this study.

8.2 Study Site Activation

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

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

- EC approval (and voting list, as required by local law) of the current version of the CIP and IC.
- RA approval or notification (as required per local law)
- Fully executed CTA
- Financial disclosure (if applicable)
- CV of investigators and key members of the investigation study site team (as required). The signature on the CV must be dated within 3 years prior to the date of activation of the study site.
- Documentation of delegated tasks
- Documentation of study training.
- Additional requirements imposed by local regulations, the EC and RA shall be followed, if appropriate.

In addition, all participating study site staff must be trained on the current version of the CIP as well as on the applicable study requirements depending on their role and must be delegated by the principal investigator to perform study related activities.

Medtronic will provide each study site with documentation of study site/investigator readiness; this letter must be received prior to performing study related activities.

8.3 Role of the Sponsor Representatives

Sponsor representatives will provide support as required for the study under supervision of the Principle Investigator, including:

- Provide study training, including but not limited to training on the: CIP, Informed Consent process, data collection tools, and regulations
- Technical support in installing/uninstalling the programmer software into/from the Programmer manually or via the SDN
- Technical support at all in-office study visits under the supervision of the Principle Investigator, including device programming, but no data entry on eCRFs shall be performed by Medtronic personnel or their representatives at sites
- A trained Medtronic representative may support a study investigator at the Insertion Visit by proactively providing support and feedback during the insertion procedure
- Sponsor representatives may conduct monitoring and auditing activities for this study

9. Selection of Subjects

9.1 Study Population

The subject population for the LINQ™ for COPD study is COPD patients who are known to have frequent exacerbations (one requiring hospitalization, ED visit, or urgent care visit, or at least two others in the past year). Inclusion and Exclusion criteria are listed below.

9.2 Subject Enrollment

Ethics Board/IRB and Medtronic approval of this Clinical Investigation Plan, the informed consent form and any other applicable documents must be obtained prior to enrolling subjects in the study. Medtronic will provide each study center with documentation of study center/investigator readiness; this letter must be received prior to subject enrollment.

When a patient and the principal investigator or authorized designee, as required, have personally signed and dated the informed consent form, the patient is considered a subject enrolled in the study. Subjects must provide informed consent before any study related procedures occur. The date the subject signed the informed consent form and data protection authorization as required by local law must be documented in the subject's medical records.

9.3 Inclusion Criteria

- Patient is ≥ 45 years old
- Patient (or patient's legally authorized representative) is willing and able to provide written informed consent
- Patient is willing and able to comply with the protocol, including follow-up visits, diary submissions and CareLink transmissions
- FEV_1 (post bronchodilator) ≤ 70% of predicted
- Current or former smoker with lifetime cigarette consumption of ≥ 10 pack-years

- One COPD exacerbation in the previous 12 months requiring hospitalization, urgent care or emergency department visit for respiratory illness OR Two COPD exacerbations within the previous 12 months requiring antibiotics and/or corticosteroids for respiratory symptoms
- The patient's medical records must be accessible by the enrolling site over the follow-up period

9.4 Exclusion Criteria

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

* This exclusion criterion has been removed as documented in the Intended CIP deviation dated 13-OCT-2021

This exclusion criterion has been updated to "Patient has an active non-Medtronic insertable cardiac monitor" in the Intended CIP deviation dated 13-OCT-2021

10. Study Procedures

10.1 Schedule of Events

A patient will be considered enrolled in the study once they sign and date the Informed Consent. The subjects will be followed via trimonthly phone calls and potentially at one in-office visit at some point during study participation. In addition, the subjects will be completing their weekly diary submissions and bi-weekly manual device transmissions.

10.2 Data Collection

The requirements for data collection and study procedures by visit are summarized in Table 5 below.

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

STUDY PROCEDURE	Baseline	LINQ™ Insertion	Weekly Subject	F/U Phone Call (every 3 months)	In Office F/U (optional)	Study Exit
Patient Informed Consent	X					
Inclusion/Exclusion Assessment	X					
Medical History	X					
Demographics	X					
SGRQ (St. George's Respiratory Questionnaire)	X					X
BCSS (Breathlessness, Coughing and Sputum Scale)			X			
Baseline Measurements	X				X	
Medication Assessment	X			X	X	X
PRN Medication Assessment			X			
Patient Assistant Activity					X	
Laboratory results	X					X
Final system configuration		X				
Insertion procedure information		X				
LINQ HF or ALLEVIATE-HF RAMware download onto LINQ™ device		X				
Device Data Interrogation (Save to media via USB)		X			X	X
Standard Forced Spirometry Test (pre and post bronchodilator)	X					
Standard Forced Spirometry Test (pre and post bronchodilator) while wearing Holter					X	
Spirometry Test for Tidal Volume while wearing Holter					X	
Chest X-ray					X	
LINQ HF or ALLEVIATE-HF RAMware removal from LINQ™ device and optional explant						X
Adverse Events (including AEs with a fatal outcome)	As they occur					
Device Deficiency						
System Modification						
Study Deviations						

10.3 Scheduled Follow-up Visit Windows

Because the study is estimated to be completed in approximately 33 months (includes approximately 26 months of enrollment and 6 months of follow-up from the last enrolled subject and up to 1 month between enrollment and insertion), window dates are provided for 33 months. If follow-up phone calls need to continue beyond 33 months, the windows will continue at 90-day intervals with ±14-day windows. 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.

Table 6: Scheduled Visit Windows

Study Follow-up Visit	Window (Calculated days post LINQ™ device insertion)		
	Window Start (# of days)	Target (# of days)	Window End (# of days)
3-Month	76	90	104
6-Month	166	180	194
9-Month	256	270	284
12-Month	346	360	374
15-Month	436	450	464
18-Month	526	540	554
21-Month	616	630	644
24-Month	706	720	734
27-Month	796	810	824
31-Month	886	900	924

10.4 Subject Screening

Subjects will be screened to ensure they meet all the inclusion criteria and none of the exclusion criteria prior to study enrollment. The subject will be considered enrolled after both the subject and the investigator (or authorized designee as required by the informed consent form [ICF]) have each personally signed and dated the ICF.

10.5 Subject Consent

The ICF 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 an ICF and an Authorization to Use and Disclose Personal Health Information/Research Authorization/other privacy language as required by law that has been approved by the study site's Institutional Review Board/Ethics Committee (IRB/EC) and signed and dated by the subject.

Investigators shall consider all subjects who meet eligibility requirements for study participation to avoid any bias in the subject population. Prior to enrolling subjects, approval of the CIP, ICF, and any other written study information to be provided to the subjects must have been obtained from each site's IRB/EC. The document(s) must be controlled (i.e. versioned and dated) to ensure it is clear which version(s) were approved by the IRB/EC. Any adaptation of the sample ICF must be reviewed and approved by Medtronic and the IRB/EC reviewing the application prior to enrolling the subject.

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

Refer to Section 18.1 for the informed consent form template.

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

The subject must have ample time and opportunity to read and understand the ICF, to inquire about details of the study, and to decide whether to participate in the clinical study. All questions about the study should be answered to the satisfaction of the subject.

When the subject decides to participate in the clinical study, the ICF must be signed and personally dated by the subject acknowledging that their participation is voluntary and signed and personally dated by the investigator or authorized designee as required by the ICF. If applicable, the witness shall also

sign and personally date the ICF to attest that the information in the ICF was accurately explained and clearly understood by the subject, and that informed consent was freely given.

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

If 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, a witnessed (impartial third party) informed consent will be allowed. In this situation, an independent witness must be present throughout the informed consent process. The written informed consent form and any other information shall be read aloud and explained to the prospective subject. The subject should "make his/her mark" (sign or otherwise physically mark the document so as to indicate consent) on the ICF as well. The witness must also sign and personally date the ICF attesting that the information was accurately explained, and that informed consent was freely given. Detailed documentation of the consent process must be recorded in the subject's case history. The ICF should document a supervised oral process was used for communication with the prospective subject and the specific means by which the prospective subject communicated agreement to participate in the study.

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

10.6 Enrollment

A subject is considered enrolled when the consent process has been finalized. The date the subject (or the subject's authorized/designated representative or guardian) signed the IC and Data Protection Authorization, as required by law, must be documented in the subject's medical records. Enrollment can be a stand-alone visit or can occur on the same day as the baseline visit. Once consent is obtained, report adverse events/deaths, study deviations and subject exits as they occur.

10.7 Baseline

Following subject enrollment, a baseline assessment will be performed. The baseline visit can be a standalone visit or can be performed on the same day as the LINQ™ ICM insertion but prior to the insertion procedure.

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

- Inclusion/exclusion criteria assessment (including pregnancy test if the subject is of childbearing potential)
- Medical history
- Medication assessment
- Demographics
- St. George's Respiratory Questionnaire
- Baseline Measurements
- Standard Forced Spirometry assessment (pre and post bronchodilator) (if it hasn't been done in the past 6 months)
- Lab Results: Creatinine, Brain natriuretic peptide (BNP) OR N-terminal brain natriuretic peptide (NT-proBNP), White Blood Cells, and Eosinophils
- Study deviations
- Adverse events

10.8 Implant

The LINQ™ insertion procedure must occur within 30 days of enrollment or baseline assessment and will be performed in accordance with the Medtronic Reveal LINQ™ implant instructions. The recommended implant locations are located in Figure 10 below. Physicians should follow the implant manuals when performing the Reveal LINQ™ implant.

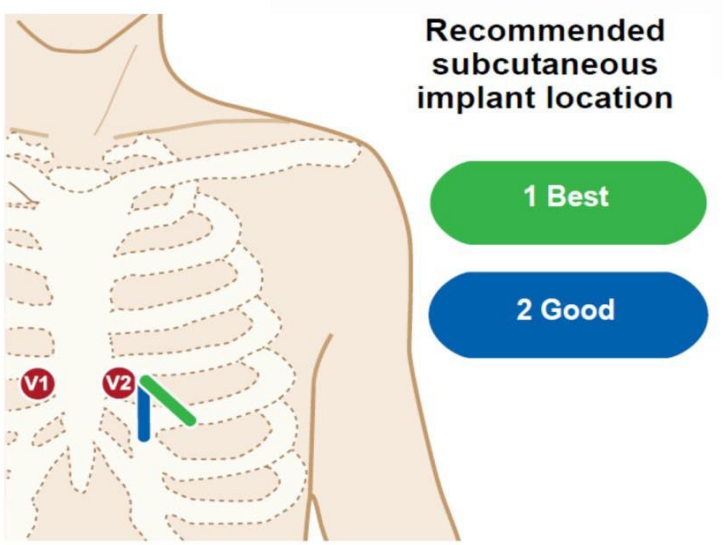


Figure 10: Recommended Insertion Locations

After the Reveal LINQ™ device is inserted, the LINQ HF or ALLEVIATE-HF investigational RAMware will be downloaded to the device via the 2090 programmer depending on the type of the Reveal LINQ device (see Table 7 below).

Table 7. Investigational RAMware compatibility

Reveal LINQ (pre-TruRhythm)	Reveal LINQ with TruRhythm
LINQ HF RAMware	ALLEVIATE-HF RAMware

The following procedures and data collection are required at the insertion visit:

- LINQ™ insertion procedure
- LINQ™ system and procedure information
- LINQ HF or ALLEVIATE-HF Investigational RAMware download
- Device Interrogation (save to media via USB)
- Adverse events (if applicable)
- Device deficiencies (if applicable)
- Study deviations (if applicable)

10.8.1 Device Programming Requirements

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

10.9 EMFIT-QS+CARE™ Bed Monitor

Up to 20 subjects will be asked to place the EMFIT bed monitor under their mattress at home during their participation in the study, with no more than 10 subjects per site. This sensor is a contact-free health monitor using ballistocardiography to measure heart beats and breaths to provide a detailed description of sleep quality. Data collected by the monitor will be transmitted with the built-in cellular connection to Medtronic. Please refer to Section 18.3 for more details on the product.

10.10 Weekly Subject Diary

Subjects will complete diary submissions at least once a week or when their COPD symptoms change, which can be more often than once per week. The diary comprises of the Breathlessness, Coughing and Sputum Scale Questionnaire (BCSS) and PRN medication tracking. The subject will receive instructions on how to complete the weekly diary, refer to Section 18.3 for more details.

The diary data will be reviewed alongside the CRF and LINQ™ device data to track potential COPD events. The subject diary data will not be reviewed for any reportable AEs since all pertinent AEs will be formally collected at the scheduled follow up visits.

10.11 Bi-Weekly CareLink Transmissions

Subjects will be provided with a MyCareLink Patient Monitor and enrolled in the Medtronic CareLink network, and will be instructed on how to set up their monitor to support automatic nightly transmission of their device data. In addition, subjects are required to perform a manual device transmission bi-weekly (every 14 days) from the time they are enrolled in the study until they are exited from the study. This transmission is critical as data collected by the investigational RAMware will be overwritten if not manually transmitted within 32 days.

As described above, the subjects are required to complete a bi-weekly transmission. A report will be made available to the site identifying subjects who have missed their manual transmission.

A monthly study deviation will be required if 2 straight bi-weekly transmissions are missed, unless a device interrogation file for an interrogation occurring within the required timeframe is provided to Medtronic.

10.12 Scheduled Follow-up Visits

10.12.1 Phone Follow-up Visit (every 3 months)

Subjects will complete telephone follow-up visits every three months post device insertion. These visits may also be conducted in-person if desired, e.g. in the case the subject is already in-office for another reason. The following information is required to be collected at these visits:

- Manual data transmission reminder
- Medications Assessment
- Adverse Events
- Device deficiencies
- Study deviations
- System modification

10.12.2 In-Office Follow-up Visit (optional)

The optional in-office follow-up visit can be conducted at any time during study participation, except within 30 days post insertion of the device to collect baseline measurement information and complete a variety of tests as outlined below. Although, this in-office visit is optional, it is requested that at least 30 subjects complete this visit.

The following information is required to be collected at the **In-Office** scheduled follow-up visit:

- Baseline measurements
- Medications Assessment
- Initial device interrogation (pre visit procedures) (save to media via USB)
- Spirometry test for Tidal Volume with breathing maneuvers
    - *DR220 Holter recommended to be used during test*

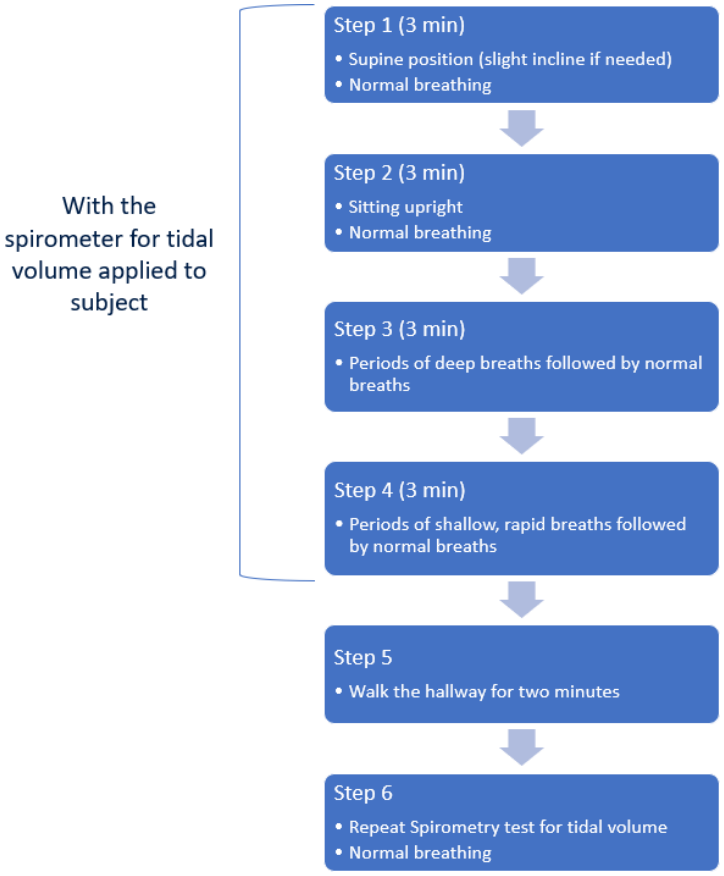
- Standard Forced Spirometry test (pre and post bronchodilator)
    - *DR220 Holter recommended to be used during test*
- Final device interrogation (post visit procedures) (save to media via USB)
- Chest X-ray (if no previous PA or AP and Lateral chest x-ray with LINQ device in image)
- Adverse events (if applicable)
- Device Deficiencies (if applicable)
- Study Deviations (if applicable)
- System Modifications (if applicable)

10.13 Spirometry Test

10.13.1 Assessment of Tidal Volume

A spirometry test for tidal volume will be completed twice at the optional in-office visit accompanied with breathing maneuvers and with the Holter applied. Oftentimes, one of these tests is referred to as the Maximum Voluntary Ventilation (MVV) Test, however in this study, it will be performed with specified breathing maneuvers outlined in Figure 11 below. In addition, a Holter will be recommended

Figure 11. Tidal Volume Spirometry Assessment Workflow



to be worn during the test. The subjects may also be asked to press the Patient Assistant device during the assessment. Refer to section 18.3 for more details.

10.13.2 Standard Forced Spirometry Test

A standard forced spirometry test will be completed at the baseline and the optional in-office visit. If the subject has had the test completed in the past 6 months prior to Baseline, then the test does not need to be repeated (data from the prior spirometry test can be input in Baseline CRF). The forced spirometry assessment will consist of a test pre bronchodilator and post bronchodilator. It is requested of the site to record at most the first eight tries of each test (pre and post bronchodilator).

At the optional in-office visit, a Holter will be recommended to be worn during the test. In addition, the subjects may be asked to press the Patient Assistant device during the assessment. Refer to section 18.3 for more details.

10.14 Chest X-ray

A chest X-ray (i.e. PA or AP and Lateral) displaying the location of the LINQ device must be collected. If the subject has not had a prior chest X-ray with the LINQ device in image, then a chest X-ray will be completed (can occur any time after LINQ insertion but must occur before study exit).

10.15 Holter

Subjects may be asked to have a Holter placed to collect some additional information from the LINQ™ device. The DR220 Holter Recorder used in this study is a portable ECG device able to collect continuously telemetered signals from any Medtronic device for up to 48 hours. The Holter Recorder has application for any subject with a Medtronic ICM. For the purposes of this study, the intended use of the Holter Recorder is to acutely uplink continuous impedance and ECG signals that will be collected by the investigational RAMware in the Holter mode. The intended use of Holter mode is for a short duration of 30 minutes at each spirometry test at the optional in-office visit, or else the Holter does not store any data.

Since only the device data uplink feature of the Holter will be used in this study, the device antenna will only be used, and no ECG electrodes will be used. Please refer to Section 18.3 for more details.

10.16 Device Interrogation

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

10.17 System Modification

A system modification will be reported in the event the device requires invasive modification (e.g., device explant (other than at study exit), device reposition). In the event of a system modification, the

follow-up schedule for the subject will remain unchanged. For a system modification the following activities are required:

- Complete the System Modification eCRF
- Device interrogation (media/USB)
- Adverse events (if applicable)
- Device Deficiencies (if applicable)
- Study Deviations (if applicable)

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

All explanted product (device) should be returned to Medtronic for analysis when permissible by local laws and regulations. See Section 7.6 for final product disposition details.

10.18 Medications Assessment

The name, dose, frequency and route of all medications will be collected at all visits. Changes to medications will be captured on the Medication Log eCRF.

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

10.19 Assessment of Safety

All LINQ™ system and procedure related adverse events (AEs), all serious adverse events (SAEs), all Pulmonary related AEs and all Cardiovascular related AEs will be collected throughout the duration of a subject's participation in the study, beginning at the time of informed consent. Additionally, any device deficiencies related to the LINQ™ system will be collected. Adverse events and device deficiencies will be reported to Medtronic via completion of eCRFs. See section 12.0 for additional details.

LINQ™ system and procedure related AEs reported in the study will be summarized as an ancillary objective. Additionally, reported device deficiencies will be summarized.

10.20 Review of Data Recorded by the Reveal LINQ™Device

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

10.21 Recording Data

Subject data will be collected on electronic case report forms (eCRFs) via a web-based remote data capture (RDC) system. The investigator must ensure accuracy, completeness and timeliness of the data

reported in the eCRFs. Only authorized persons can complete and sign e-CRFs, as specified on the Delegated Tasks List included in the Investigator Site File.

Procedures in the CIP require source documentation. Source documents, which may include worksheets and subject medical records, must be created and maintained by the investigational site team. Subject records must be clearly marked to indicate that subject participates in the study. When copies or printouts of source documents are made, these must be signed and dated by a member of the investigational site team with a statement that it is a true reproduction of the original source document.

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

Refer to section 16.2 for additional detail regarding data management for the study.

10.22 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. If an infringement remains unresolved, multiple deviations need not be completed.

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, right or well-being of a subject in an emergency or in unforeseen situations beyond the investigator's control (e.g. subject failure to attend scheduled follow-up visits, inadvertent loss of data due to computer malfunction, inability to perform required procedures due to subject illness).

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

All study deviations must be reported on the study deviation e-CRF regardless of whether medically justifiable, pre-approved by Medtronic, an inadvertent occurrence, or taken to protect the subject in an emergency. The deviation description and reason for deviation must be recorded. Multiple deviations of the same type at the same visit may be reported on one e-CRF.

In the event the deviation involves a failure to obtain a subject's consent or is made to protect the life or physical well-being of a subject in an emergency, the deviation must be reported to the IRB/EC as well as Medtronic within five (5) working days. Reporting of all other study deviations must comply with IRB/EC policies and/or local laws and/or regulatory agency requirements and must be reported to Medtronic as soon as possible upon the center becoming aware of the deviation. Refer to Table 12 for geography

specific deviation reporting requirements and timeframes for reporting to Medtronic and/or regulatory bodies.

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

10.23 Subject Exit, Withdrawal or Discontinuation

10.23.1 Study Exit

Study exit is defined as the moment when a subject officially stops participating in the study. Subjects will be considered exited upon completion of the study exit e-CRF. Prior to exiting a subject from the study, it is recommended to follow the subject until any ongoing AEs related to the Reveal LINQ™ system or procedure are classified by the investigator, as resolved. The date and reason for subject exit must be reported to Medtronic at the earliest opportunity via eCRF. Exited subjects will not be replaced. Upon exiting from the study, no further study data will be collected, or study visits will occur for the subject. All data available through the time of the subject's exit will be used for analysis. Subjects are urged to remain in the study as long as possible but may be exited from the study for any of the following situations:

- Subject did not meet inclusion/exclusion criteria and was not inserted with a LINQ™ device
- LINQ™ ICM explanted and not replaced with a new LINQ™ ICM (e.g. diagnosis determined, suspected infection, subject request, physician determination)
- Subject chooses to withdraw (e.g., consent withdrawal, relocation to another geographic location)
- Investigator chooses to withdraw a subject (e.g., medically justified, inclusion/exclusion criteria not met, failure of subject to maintain adequate study compliance)
- Implant attempted, however no Reveal LINQ™ was implanted
- Subject lost to follow-up
- Death
- Study completion or termination

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

- Date of exit
- Reason for exit
- Medications Assessment
- St. George's Respiratory Questionnaire

- Laboratory results: Creatinine, Brain natriuretic peptide (BNP) OR N- terminal brain natriuretic peptide (NT-proBNP), White blood cells, Eosinophils
- Initial Device Interrogation (save to media via USB) (prior to removal)
- Removal of the investigational RAMware from the LINQ™ device
- Opting out of the subject diary
- Post Device interrogation (save to media via USB) (post removal)
- Adverse events
- Device deficiencies
- Study deviations

10.23.2 Study Completed

All subjects will be exited from the study when the last subject's 6-month follow-up visit is completed or until official study closure, defined as when Medtronic and/or regulatory requirements have been satisfied per the Clinical Investigation Plan and/or by a decision by Medtronic or regulatory authority, whichever occurs first. Subjects will be provided standard medical care by their physician after their study participation ends.

10.23.3 Lost to Follow-up

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/EC.

10.23.4 Subject Chooses to Exit (i.e. Revokes Consent)

A subject can withdraw from the study at any time. If the subject wishes to exit from the study (i.e. the subject revokes consent), the study site is required to document the reason for exit on the Exit CRF. In addition, study sites shall follow the regulations set forth by the governing EC. If possible, the following data should be collected prior to subject withdrawal:

- Reason for exit

10.23.5 Investigator Withdraws Subject

No subjects should be withdrawn by investigators unless compelling medical justification is present. It is recommended investigators discuss any withdrawals with the study team prior to withdrawing subjects. If an Investigator Withdrawal is necessary, the following data should be collected prior to subject withdrawal if possible:

- Reason for subject withdrawal

10.23.6 Conditional Disengagement

After a subject is enrolled/randomized every effort should be made to keep the subject in the study. However, it is recognized that there are circumstances where limited data may be collected, or study exit will need to occur. In these cases we will consider either modified data collection requirements where subjects may conditionally disengage in study procedures but data from the subject can still be

collected because the subject has not revoked consent, or exit when study participation is completely ended. In randomized subjects, modified data collection is always preferred over exit.

Subjects may be conditionally disengaged from study procedures for any of the following reasons:

- Subject chooses to disengage (e.g., follow-up schedule cannot be adhered to, study burden too large, relocation to another geographic location but telephone follow-up still acceptable)
- Investigator deems conditional disengagement necessary (e.g. medically justified)

If the subject wishes to disengage from the study, or the investigator deems it necessary, the study site is required to document the reason. Prior approval from the study team is required and a Limited Data Collection CRF needs to be completed. Data collection requirements no longer apply, but study sites are encouraged to collect as much data as possible on the regular CRFs.

11. Risks and Benefits

11.1 Potential Risks

Medtronic follows rigorous Quality Assurance and Control procedures throughout the lifecycle of a product, from the business analysis phase through development, market release, and post-market surveillance. The risk analysis process for the LINQ™ for COPD study is being performed in accordance with ISO 14971, and ensures that the level of residual risk is reduced to as low as possible prior to starting the clinical study.

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

- Allergic 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 investigational 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 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 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 investigational RAMware, potentially resulting in loss of or inaccurate Reveal LINQ™ data, and/or premature explant. Once the investigational RAMware feature set is executed, periodic data integrity checks are in place to ensure correct functionality.
- The Reveal LINQ™ device with the investigational RAMware download may present data that are different than anticipated due to unknown circumstances or medical conditions.
- There may be other discomforts and risks related to the Reveal LINQ™ device with investigational RAMware download and/or this study that are not foreseen at this time.

11.2 Risk Minimization

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

In addition, investigators will be actively involved in the implantation and regular follow-up of the subjects implanted with the Reveal LINQ™ with investigational RAMware systems. At each office follow-up visit required per protocol (Table 3: Data collection and study procedure requirements at subject visits), the Reveal LINQ™ device will be interrogated, device data collected to verify appropriate device function and patient's health assessed for any adverse events.

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

Table 8: Potential Risks and Risk Minimization

Potential Risk	Minimization
ICM Pocket Infection from implant/ explant procedure or over duration of implant	• Adherence to international standards for sterility of implanted products • The product packaging designed to protect device sterility • The insertion procedure and tools are designed to be minimally invasive • Wound check following implant, per site's practice

Potential Risk	Minimization
Allergic reaction or 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 biocompatible materials in the Incision/ Insertion Tools and Reveal LINQ™ ICM exterior patient-contacting surfaces
Excessive ICM Migration following implant procedure (internal device movement and externalization)	• Training and Information for User on the Reveal LINQ™ implant technique and incision closure techniques • Use of the implant tools to create small incision and tight pocket • Wound check following implant, per site's practice • Investigator discretion to remove if deemed medically necessary • IFUs (Instructions for Use) provide information regarding medical procedures and activities which may interact with the ICM. • Reveal LINQ™ ICM design includes anti-migration features on the header
Blunt Tissue Injury/Tissue or Vascular Trauma, bleeding from implant/ explant procedure	• The ICM and implant procedure are designed to be minimally invasive. • Insertion Tool has a stop position that prevents insertion of the probe beyond the distance required for implant. • Training on the correct use of implant tools • Selection of experienced investigators
Pain, Scarring from implant/explant procedure or implanted device	• The shape and small device size minimize the invasiveness of the implant and explant procedures, and the discomfort patients may experience from having an ICM. • Use of incision tool will produce the smallest incision possible for implant
Toxicity risks due to ICM battery	• Battery and device and hermeticity and reliability requirements prevent leakage of toxic substances.

Potential Risk	Minimization
Premature/Unexpected ICM explant /revision	• The projected longevity of a Reveal LINQ™ device with investigational 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.
Electromagnetic interference	• Design consideration and precautions in place for the Reveal LINQ™ system remain effective to address EMI risks • Information regarding EMI (possible sources and ways to reduce interference) is provided to the user • The system adheres to international standards for the production of RF energy, reducing the probability of interference with other equipment.
Pain or stimulation due to electrical currents or ICM heating	• Design controls in place to protect against leakage currents in normal and fault conditions • Design controls are in place to protect against device heating in normal and fault conditions. • The amount of current injected as part of the impedance measurements has been minimized to prevent subject harm
Missing/Misleading information causing inappropriate medical intervention	• The system uses data integrity checks to detect data corruption and notify the clinician • The system ensures components are compatible with the system components; the instructions for use provide guidance on maintenance of the system (e.g., software/app updates) • The system provides notifications to the clinician regarding system status (e.g., patient transmissions, battery status)
Injury due to mechanical device failure	• Mechanical device integrity requirements were implemented and verified. They have been validated against the expected use conditions.
Security vulnerability impacting device settings, data integrity, communications, or longevity	• The system uses encrypted communication to transfer data • The system detects unauthorized messages and takes actions to protect itself.
Denial of access to medical therapy or diagnostic	• The ICM is MRI conditional • The system provides information about the compatibility of the ICM with common medical procedures • The system provides means to non-invasively identify the ICM, so its compatibility can be verified prior to the procedure.
Failure to seek necessary medical attention	• Instructions for use warns users against use of the ICM system as a real-time / emergency monitoring system.

Potential Risk	Minimization
Removal and disposal of system components (biohazards, environmental/property damage hazards)	• The insertion tools are designed to be easily disposed of • The IFU provides guidance on disposal of the ICM at the end of service
Undesired device interactions with the investigational RAMware	• Device interactions analysis to ensure there are no undesired interactions between the investigational RAMware and the Reveal LINQ™ device firmware. • The investigational RAMware is designed to be automatically removed by the ROM code during POR processing

There may be a concern for electrical or electromagnetic interference between the LINQ™ device and the other associated study equipment. Among the systems that have the potential for electromagnetic interference, here are the associated frequencies and characteristics:

- LINQ™ – transmits and receives Telemetry B signal frequencies for communication with programmer
- DR220 Holter – receives Telemetry B signal frequencies for recording
- MyCareLink Home Monitor – receives Telemetry B signal frequencies from LINQ and transmits data to the CareLink Network using 3G cellular frequencies
- Emfit bed monitor – the sensor component uses passive electrical signals to collect motion from the ribbon. No electrical signal is transmitted to take a measurement. The data is then transmitted from the communication hub using 3G cellular frequencies

It appears that there should not be any electromagnetic interference from transmission by any of the planned study equipment. However, should it occur, electromagnetic interference can be mitigated by user intervention, such as positioning devices to minimize interference.

There may be additional discomforts and risks associated with the Reveal LINQ™ device or participation in this study that are not foreseen at this time.

11.3 Potential Benefits

The Reveal LINQ™ for COPD study may offer no direct personal benefit to individual subjects.

Subjects may benefit from continuous arrhythmia monitoring with the Reveal ICM, as this monitoring could result in diagnosis of Atrial Fibrillation (or other arrhythmias) and comprehensive evaluation of symptoms on an earlier and more conclusive basis than what would be possible without an implantable cardiac monitor. Subjects may also benefit from being evaluated more frequently in the office according to the study visit schedule.

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

11.4 Risk-Benefit Rationale

Since the differences between the Reveal LINQ™ market-released device and the Reveal LINQ™ device with the 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 investigational RAMware are being evaluated and risk control measures being implemented to reduce the risk to as low as possible to minimize patient harm.

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

12. Adverse Events and Device Deficiencies

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

12.1 Adverse Events

To ensure that all AEs that are potentially relevant are collected, the following subset of AEs will be collected throughout a subject's participation, starting at the time the informed consent form is signed:

- All Reveal LINQ™ Procedure related AEs
- All Reveal LINQ™ System related AEs
- All Serious AEs
- All Pulmonary related AEs
- All Cardiovascular related AEs

Reporting of AEs to Medtronic will occur on an Adverse Event e-CRF, including a description of the event, the diagnosis, the date of event onset, the date the site became aware of the event, the relatedness and seriousness of the event, diagnostic tests and procedures performed, actions taken as a

result of the event, and outcome of the event. Each AE must be recorded on a separate AE eCRF. Subject deaths are also required to be reported and should be collected on an AE CRF with a Fatal outcome. Refer to section 12.6 for subject death collection and reporting requirements.

Documented pre-existing conditions are not considered AEs unless the nature or severity of the condition has worsened post implant. In all geographies, unavoidable adverse events, listed in Table 9, need not be reported unless the adverse event worsens or is present outside the stated timeframe.

12.2 Device Deficiency

Device deficiency (DD) information will be collected throughout the study and reported to Medtronic. Reporting of DDs to Medtronic will occur on a device deficiency e-CRF. Note that DDs that result in an adverse device effect (ADE) to the subject should be captured on an AE CRF only. Device deficiencies that did not lead to an AE but could have led to a serious adverse device effect (SADE) (i.e., if suitable action had not been taken, if intervention had not been made, or if the circumstances had been less fortunate) require immediate reporting.

12.3 Processing 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), an update to the original AE must be provided. All reported adverse events must be followed until the adverse event has been resolved, the subject exits the study or until study closure, whichever occurs first. At the time of study exit, all collected AEs with an outcome of "not recovered/not resolved", "recovering/resolving" or "unknown" must be reviewed and updates provided as applicable.

12.4 Definitions/Classifications

Adverse event (AE) and device deficiency (DD) ISO 14155:2020 definitions are provided in Table below. Where the definition indicates "device", it refers to any device used in the study. This might be the device under investigation, or any market released component of the system.

Table 9: Adverse Event and Device Deficiency Definitions

General	
Adverse Event (AE) (ISO 14155:2020 section 3.2)	Any untoward medical occurrence, unintended disease or injury, or untoward clinical signs (including abnormal laboratory findings) in subjects, users or other persons, whether or not related to the investigational medical device and whether anticipated or unanticipated. NOTE: This definition includes events related to the investigational medical device or the comparator. NOTE: This definition includes events related to the procedures involved. NOTE: for users or other

	persons, this definition is restricted to events related to investigational medical devices. (ISO 14155:2020 section 3.2)
Adverse Device Effect (ADE) (ISO 14155:2020 section 3.1)	Adverse event related to the use of an investigational medical device. NOTE: 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: This definition includes any event resulting from use error or from intentional misuse of the investigational medical device. NOTE: This includes 'comparator' if the comparator is a medical device.
Device Deficiency (DD) (ISO 14155:2020 section 3.19)	Inadequacy of a medical device with respect to its identity, quality, durability, reliability, safety or performance. Note: Device deficiencies include malfunctions, use errors, and inadequate labelling.
Relatedness	
Procedure Related	An adverse event that occurs that is directly related to the insertion or modification of the Reveal LINQ™ system.
System Related	An adverse event that results from the presence or performance of any component of the Reveal LINQ™ system (including the LINQ™ device, incision/insertion tools, patient assistant and programmer).
Pulmonary Related	An adverse event associated with the lungs in which signs and symptoms are experienced in either the upper or lower Respiratory systems (i.e. COPD, Pneumonia, Asthma, Bronchitis, etc.).
COPD Event	An adverse event where the underlying COPD condition exacerbates beyond normal day-to-day variations, where an increase in dyspnea, cough, and/or sputum production presents with acute onset and necessitates supplementing regular COPD medications with antibiotics for respiratory pathogens and/or steroids
Cardiovascular Related	An adverse event related to the heart and blood vessels or the circulation.
Heart Failure Event	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 or HF/Cardiology Clinic Note: Only the Sponsor will be classifying Heart Failure Event relatedness.
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); • Harm 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 be 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) (ISO 14155:2020 section 3.45)	An AE that: • Led to death • Led to a serious deterioration in the health of the subject, resultingin: ○ A life-threatening illness or injury, or ○ A permanent impairment of a body structure or a body function, or ○ In-patient or prolonged hospitalization, or ○ Medical or surgical intervention to prevent life-threateningillness or injury or permanent impairment to a body structure or a body function, • Led to fetal distress, fetal death or a congenital abnormality orbirth defect. Note: Planned hospitalization for a pre-existing condition, or a procedure required by the CIP, without serious deterioration in health, is not considered a SAE.
Serious Adverse Device Effect (SADE) (ISO 14155:2020 section 3.44)	Adverse device effect that has resulted in any of the consequences characteristic of a serious adverse event. .
Complication	An adverse event that includes the following is considered a complication: • Results in death, • Involves any termination of significant device function, or • Requires an invasive intervention Non-invasive (21 CFR 812): when applied to a diagnostic device or procedure, means one that does not by design or intention: • Penetrate or pierce the skin or mucous membranes of the body, the ocular cavity, or the urethra, or

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Penetrate: to pass, extend, pierce, or diffuse into or through something; to enter by overcoming resistance; to gain entrance to
Pierce: to force a way into or through something

Enter the ear beyond the external auditory canal, the nose beyond the nares, the mouth beyond the pharynx, the anal canal beyond the rectum, or the vagina beyond the cervical os

Note (FDA): Blood sampling that involves simple venipuncture is considered noninvasive, and the use of surplus samples of body fluids or tissues that are left over from samples taken for non- investigational purposes is also considered noninvasive.
</td></tr>
<tr><td>Observation</td><td>Any Adverse Event that is not a complication.

Note 1: Pulmonary related AEs will be the only AEs requiring classification of either Complication or Observation by Sponsor and EAC.</td></tr>
<tr><td>Unanticipated Adverse Device Effect (UADE)
(21 CFR 812.3(s))</td><td>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.</td></tr>
<tr><td colspan="2">Other</td></tr>
<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>

12.5 Reporting of Adverse Events

To ensure that all AEs that are potentially relevant are collected, the following subset of AEs will be collected throughout a subject's participation, starting at the time the informed consent form is signed:

- All Reveal LINQ™ Procedure related AEs
- All Reveal LINQ™ System related AEs
- All Serious AEs
- All Pulmonary related AEs
- All Cardiovascular related AEs

Reporting of AEs to Medtronic will occur on an Adverse Event e-CRF, including a description of the event, the diagnosis, the date of event onset, the date the site became aware of the event, the relatedness and seriousness of the event, diagnostic tests and procedures performed, actions taken as a result of the event, and outcome of the event. Each AE must be recorded on a separate AE eCRF. Subject deaths are also required to be reported and should be collected on an AE CRF with a Fatal outcome. Refer to section 12.6 for subject death collection and reporting requirements.

Documented pre-existing conditions are not considered AEs unless the nature or severity of the condition has worsened post implant. In all geographies, unavoidable adverse events, listed in Table 10, need not be reported unless the adverse event worsens or is present outside the stated timeframe.

12.5.1 Adverse Event and Device Deficiency Classification

All reported AEs and DDs will be reviewed by a Medtronic representative. Adverse events will be classified according to the standard definitions as outlined in Table 9.

Upon receipt of AEs and DDs 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.

Regulatory reporting of AEs and DDs that could have led to a SADE will be completed according to local regulatory requirements. Refer to Table 11 for a list of required investigator and Medtronic reporting requirements and timeframes. It is the responsibility of the investigator to abide by any additional AE reporting requirements stipulated by the IRB/EC responsible for oversight of the study at their site.

For emergency contact regarding a SAE and/or SADE, contact a Medtronic 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).

An Event Adjudication Committee (EAC) will review the Pulmonary related AEs and will provide a COPD event relatedness adjudication and a Complication or Observation classification for each Pulmonary

related event. The EAC will additionally be providing a death classification for all reported AEs with an outcome of fatal.

Table 10: Adverse Event Classification Responsibilities

What is classified?	Who classifies?	Classification Parameters
Relatedness	Investigator	Reveal LINQ™ system related, Reveal LINQ™ procedure related, Pulmonary Related, Cardiovascular related
	Sponsor	Reveal LINQ™ system related, Reveal LINQ™ procedure related, Pulmonary Related, Cardiovascular related, Heart Failure Event, COPD event
Seriousness	Investigator	SAE, Device Deficiency with SADE potential
	Sponsor	SAE, Device Deficiency with SADE potential, UADE, Complication/Observation
AE Term (Diagnosis)	Investigator	Based on presenting signs and symptoms and other supporting data
	Sponsor	MedDRA term assigned based on the term provided by Investigator
Death Classification	Investigator	Sudden Cardiac, Non-sudden Cardiac, Non-Cardiac, Unknown

12.5.2 Adverse Event and Device Deficiency Reporting Requirements

Regulatory reporting of AEs and DDs will be completed according to local regulatory requirements. Investigator and sponsor reporting requirements are outlined in Table 11. It is the responsibility of the investigator to abide by the adverse event and device deficiency reporting requirements stipulated by local law and the site's IRB/EC.

For adverse events and device deficiencies that require immediate reporting, initial reporting may be completed by contacting the study sponsor (refer to the study contact list provided in the site's study documents binder/investigator site file or refer to the contact information provided in Table 1).

Table 11: Reporting Requirements

Serious Adverse Device Effects (SADEs)	
Investigator submit to:	
Medtronic	Submit as soon as possible as per local reporting requirement, but not later than within 10 working days after the investigator first learns of the event.
IRB/Ethics Committee	Submit per local reporting requirement.
Regulatory Authorities	Submit per local reporting requirement.

Sponsor submit to:	
Regulatory Authorities	Submit as soon as possible as per local reporting requirement, but not later than within 10 working days after the investigator first learns of the event.
IRB/Ethics Committee	Submit per local reporting requirement.
Serious Adverse Events (SAE)/ Adverse Device Effects (ADE)	
Investigator submit to:	
Medtronic	Submit as soon as possible as per local reporting requirement, but not later than within 10 working days after the investigator first learns of the event.
Regulatory Authorities	Submit per local reporting requirement.
IRB/Ethics Committee	Submit per local reporting requirement.
Sponsor submit to:	
Regulatory Authorities	Submit per local reporting requirement.
IRB/Ethics Committee	Submit per local reporting requirement.
All other AEs	
Investigator submit to:	
Medtronic	Submit as soon as possible as per local reporting requirement after the investigator first learns of the event.
Regulatory Authorities	Submit per local reporting requirement.
IRB/Ethics Committee	Submit per local reporting requirement.
Sponsor submit to:	
Regulatory Authorities	Submit per local reporting requirement.
IRB/Ethics Committee	Submit per local reporting requirement.
Device Deficiency with SADE potential	
Investigator submit to:	
Medtronic	Submit as soon as possible as per local reporting requirement, but not later than within 48 hours after the investigator first learns of the event.
Regulatory Authorities	Submit per local reporting requirement.
IRB/Ethics Committee	Submit per local reporting requirement.
Sponsor submit to:	
Regulatory Authorities	Submit per local reporting requirement.
IRB/Ethics Committee	Submit per local reporting requirement.
All other Device Deficiencies	
Investigator submit to:	
Medtronic	Submit as soon as possible as per local reporting requirement, but not later than within 48 hours after the investigator first learns of the event.
Regulatory Authorities	Submit per local reporting requirement.
IRB/Ethics Committee	Submit per local reporting requirement.

12.6 Subject Death

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

In the event of a subject's death, the inserted system should be explanted and returned to Medtronic for analysis whenever possible. Local laws and procedures must be followed where applicable. If any device or system component is returned to Medtronic, internal returned product reporting systems may be used to gather additional information about the returned device/component.

A copy of the death certificate, if available and allowed by state/local law, should be sent to the Medtronic clinical study team. When a death occurs in a hospital, a copy of the death summary report and all relevant hospital records should be sent to the Medtronic clinical study team, if available. If an autopsy is conducted, the autopsy report should also be sent to the Medtronic clinical study team if available and allowed by state/local law. When the death occurs at a remote site, it is the investigative 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 (if available, postmortem preferred)
- Death summary/hospital records (if available and allowed by state/local law)
- Autopsy report (if available and allowed by state/local law)
- Death certificate (if available and/or allowed by state/local law)

12.6.1 Death Classification and Reporting

Sufficient information will be required in order to properly classify the subject's death.

The Investigator shall classify each subject death per the following definitions:

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

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

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

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

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

The EAC will review all AEs with a fatal outcome and provide a final adjudication of both COPD event and death classification. Regulatory reporting of subject deaths will be completed according to local regulatory requirements. Refer to Table 11 for investigator and sponsor reporting requirements and timeframes.

12.7 Product Complaint Reporting

In geographies where devices are market-released, product complaint reporting is applicable. This includes when an AE is related to a market-released device during the study. The reporting of product complaints is not part of the clinical study and should be done in addition to the Adverse Event reporting requirements. Refer to local regulations for reporting requirements.

Product Complaint: Any written, electronic or oral communication that alleges deficiencies related to the identity, quality, durability, reliability, safety, effectiveness or performance of a medical device that has been placed on the market.

It is the responsibility of the investigator to report all product complaint(s) associated with a medical device distributed by Medtronic, regardless whether they are related to intended use, misuse or abuse of the product. Reporting must be done immediately and via the regular channels for market-released products.

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

- Any malfunction or deterioration in the characteristics and/or performance of a device, as well as any inadequacy in the labeling or instructions for use which led or might have led to the death or serious deterioration in the state of health of a patient, user, or other person.
- Any technical or medical reason resulting in withdrawal of a device from the market by the manufacturer.

13. Data Review Committees

13.1 Event Adjudication Committee

At regular intervals, an Event Adjudication Committee (EAC) will review and adjudicate at a minimum, all events classified by the investigator or Medtronic as Pulmonary related and all AEs with a fatal outcome. The EAC will provide an adjudication for COPD event and a Complication or Observation classification for all AEs that are reviewed. The EAC will additionally provide a death classification for all AEs with an outcome of fatal. The EAC will consist of a non-Medtronic employed physicians that are not participating investigators for the study.

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

For all adverse events reviewed by the EAC, Medtronic will provide the EAC with the investigator's description and classification. The EAC is responsible for reviewing the investigator's assessment and supportive documentation (when available), reviewing applicable definitions, and determining final classifications for all adjudication parameters.

13.2 CRO

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

Table 12: CRO Information

Contact Information	Duties performed
Cognizant Technology Solutions [redacted]	• Development of study electronic case report forms, edit checks, and study management reports. • Review of electronic case report forms, management of discrepancies, and coding of deviations.

14. Statistical Design and Methods

The LINQ™ for COPD is a prospective, non-randomized, multi-center, observational, pre-market clinical study. The purpose of the study is to characterize the Reveal LINQ™ derived data from patients with COPD.

This is a feasibility study that is exploratory in nature and with no hypothesis. Therefore, justification on sample size is not required. The study plans to enroll up to 100 subjects from up to 10 centers in the United States, with no more than 20 subjects enrolled per site. Enrolled subjects are expected to be followed up for at least 12 months after the insertion of Reveal LINQ™ device and download of either the LINQ HF or ALLEVIATE-HF investigational RAMware. The expected total study duration is approximately 33 months, representing approximately 26 months of patient enrollment and 6 months of subject follow-up with up to 1 month between enrollment and insertion.

14.1 General Aspects of Analysis

Medtronic statisticians or designees will perform all statistical analyses.

The study is exploratory in nature with no formal statistical hypothesis planned. A separate Statistical Analysis Plan (SAP) will be developed and include a comprehensive description of the statistical methods and analyses to be included in the final study report. Any change to the data analysis methods described in the protocol will require an amendment only if it changes a principal feature of the protocol. Any other change to the data analysis methods described in the protocol, and the justification for making the change, will be described in the clinical study report.

14.2 Analysis Execution

The study objective will be analyzed after the last subject exits the study.

14.3 Primary Objective

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

14.3.1 Hypothesis

There is no statistical hypothesis for this objective.

14.3.2 Endpoint Definition

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

According to section 5.1, COPD event is defined as an adverse event where the underlying COPD condition exacerbates beyond normal day-to-day variations, where an increase in dyspnea, cough, and/or sputum production presents with acute onset and necessitates supplementing regular COPD medications with antibiotics for respiratory pathogens and/or steroids.

14.3.3 Analysis Methods

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

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

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

14.3.4 Determination of Subjects/Data for Analysis

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

14.4 Sample Size Determination

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

According to a review by Seemungal et al., the annual rates of COPD exacerbations were estimated to be as low as 0.5 to a high of 3.5 exacerbations per patient from several studies, and hospitalization rates ranged from as low as 0.09 to 2.4 per patient per year.[13] This study requires that a subject should have 2 COPD exacerbations within the previous 12 months as one of the inclusion criteria. Assuming the COPD exacerbation rate remains as 2 COPD exacerbations per patient year after subjects are enrolled, a group of 60 enrolled subjects being followed up for 12 months after successful insertion of Reveal LINQ™ device and download of the investigational RAMware would expect to have 120 COPD exacerbations. Assuming 50% of the COPD exacerbations would meet the study definition of "COPD event", a total of 60 COPD events would be expected.

14.5 Minimization of Bias

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

- Subjects will undergo screening to confirm eligibility with defined inclusion/exclusion criteria prior to enrollment.
- All sites will use the same version of the Clinical Investigation Plan and electronic case report forms (eCRFs).
- All investigational site personnel and Medtronic personnel will be trained using standardized training materials.
- Monitoring visits will be conducted for adherence to the CIP and verification of source data.
- An independent Event Adjudication Committee (EAC) will be used to review and adjudicate at a minimum, all Pulmonary related AEs and all AEs with a fatal outcome.
- A statistical analysis plan will be developed prior to analyzing data. The plan will document all pre-specified analyses and analysis methods.

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

14.6 Missing data

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

14.7 Additional Considerations Due to COVID-19

- Subject follow-up visits.
  Follow-up visits every three months post device insertion will be done by telephone or in-person if desired. The flexibility in the way to complete these visits will allow subjects to continue to be followed in the study as well as to follow local COVID-19 guidelines.

- COPD exacerbation rate.
  A patient with COVID-19 may be at higher risk of a COPD exacerbation event. At the same time there could be underreporting of COPD exacerbation events compared to literature. Therefore, the impact of COVID-19 on the COPD exacerbation rate is unknown.

- COPD event outcome.
  Under potentially limited care resources of sites due to COVID-19, subjects with COPD may experience delayed treatment that could also increase the subject's risk of worse outcomes. In addition, subjects with COPD may experience worse/poorer event outcomes if also infected by COVID-19.

15. Ethics

15.1 Statement(s) of Compliance

The LINQ™ for COPD Study will be conducted according to the Declaration of Helsinki, Version 2013, Clinical Investigation Plan, Good Clinical Practice (GCP) and in accordance to the national and local laws, regulations, standards, and requirements of the countries/geographies in which the study is conducted. The principles of the Declaration of Helsinki are implemented in this study by means of the informed consent process, Ethics Board approval, study training, clinical trial registration, and risk benefit assessment. The sponsor shall avoid improper influence on, or inducement to, the subject, monitor, any investigator(s) or other parties participating in, or contributing to, the LINQ™ for COPD Study.

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

Ultimately, all sites in all geographies will follow and comply with:

- Principles of Declaration of Helsinki
- 21 CFR Part 11: Electronic Records, Electronic Signatures
- 21 CFR Part 54: Financial Disclosure by Clinical Investigators
- The Clinical Trial Agreement
- The procedures described within this CIP
- Local Ethics Board Requirements

In addition to the regulatory requirements outlined above, 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. These include but are not limited to the following:

In the US, the study will be conducted in compliance with:

- 21 CFR Part 50: Protection of Human Subjects
- 21 CFR Part 56: Institutional Review Boards
- 21 CFR Part 803: Medical Device Reporting
- 21 CFR Part 54: Financial Disclosure
- 21 CFR Part 812 Investigational Device Exemptions

The study will not begin until IRB/EC and regulatory authority approvals/notification, as appropriate, are received.

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) and Declaration of Helsinki on (PL 110-85, Section 810(a)).

16. Study Administration

16.1 Monitoring

It is the responsibility of Medtronic to ensure proper monitoring of the LINQ™ for COPD 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 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, Data Protection Authorization (where applicable) and clinical trial agreement. The principal investigator should also be available during monitoring visits.

16.1.1 Monitoring Visits

Monitoring for the study, including site initiation visits, interim monitoring visits, and closeout visits, 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, and 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 to site personnel. Monitors may work with study personnel to determine recommendations for preventative/corrective/effectiveness action(s) recommendations and to identify trends within the study or at a particular 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. Regulatory documents may be reviewed at each study center.

16.2 Data Management

Electronic case report form (e-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 sites for resolution. Study management reports may be generated to monitor data quality and study progress.

Device data from CareLink transmissions will be uploaded to secure servers. Upon receipt, device data will be maintained within databases and retrieved for analysis and reporting.

Changes to the data elements in the electronic system will retain the original data and an audit trail (date, time, and originator of the change and reason). It is possible that AE and device data files may be provided to Medtronic before the PI has reviewed and released the e-CRF. At the end of the study, the data will be frozen and will be retained indefinitely by Medtronic.

16.3 Direct Access to Source Data/Documents

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

16.4 Confidentiality

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

16.5 Liability

Warranty information will be provided in the product packing and will be available upon request. Insurance information for participating geographies is provided below.

Medtronic maintains appropriate clinical study liability insurance coverage as required under applicable laws and regulations and will comply with applicable local law and custom concerning specific insurance coverage. If required, a clinical study insurance statement/certificate will be provided to the IRB/EC.

16.6 CIP Amendments

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

- Medtronic
- An independent Institutional Review Board / Ethics Committee

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

16.7 Record Retention

16.7.1 Investigator Records

The investigator is responsible for the preparation and retention of the records including, but not limited to those cited below. All of the below records, with the exception of case history records and case report forms (CRFs), should be kept in the Investigator Site File (i.e., the study binder provided to the investigator) or Subject Study Binder. CRFs must be maintained and signed electronically within the electronic data capture system during the study. The following records are subject to inspection and must be retained for a period of two years (or longer as local law or hospital administration requires) after the date on which the investigation is terminated. Measures shall be taken to avoid loss or premature destruction.

- All correspondence between the IRB, sponsor, monitor, regulatory authority and/or the investigator that pertains to the investigation, including required reports
- Subject's case history records, including:
  - Signed and dated informed consent form
  - Observations of adverse events/adverse device effects/device deficiencies
  - Medical history
  - Baseline, LINQ™ Insertion and follow-up data (if applicable)
  - Documentation of the dates and rationale for any deviation from the protocol
- List of investigation sites
- Insurance certificates (if applicable)
- All approved versions of the CIP and Informed Consent Form
- Fully executed Clinical Trial Agreement
- Curriculum Vitae of principal investigator and all co-investigators/sub-investigators
- Documentation of delegated tasks
- Study training records for site personnel involved in the study
- IRB approval documentation, including the IRB composition where required by law, and written information that the investigator or other study staff, when member of the IRB, did not participate in the approval process

- Regulatory authority correspondence, notification and approval, where required by national legislation
- Any other records that local regulatory agencies require to be maintained
- Final Study Report including the statistical analysis

16.7.2 Sponsor Records

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

- All correspondence which pertains to the investigation
- Executed Clinical Trial Agreement for all participating sites
- Curriculum vitae (signed and dated as required by local law) of principal investigator and all co-investigators/sub-investigators at participating sites
- Documentation of delegated tasks for all participating sites
- Study training records for site personnel and Medtronic personnel involved in the study
- All approved informed consent versions, and other information provided to the subjects and advertisements, including translations
- Copies of all IRB approval letters and relevant IRB correspondence and IRB voting list/roster/letter of assurance, if applicable
- Electronically signed and dated eCRFs
- List of names, addresses, telephone numbers and professional position of the clinical investigators and coordinating clinical investigator(s), if appointed
- Names and addresses of the institutions in which the clinical study will be conducted
- Regulatory authority correspondence, notification and approval as required by national legislation
- Names/contact addresses of monitors
- Monitoring reports
- Site qualification visit reports
- Statistical analyses and underlying supporting data
- Final report of the clinical study
- The Clinical Investigation Plan and study related reports, and revisions
- Sample of CRFs
- Any other records that local regulatory agencies require to be maintained

16.8 Reporting Requirements

16.8.1 Investigator Reports

The investigator is responsible for the preparation (review and signature) and submission to the sponsor of all case report forms, adverse events and adverse device effects (reported per the

country-specific collection requirements), device deficiencies, deaths, and any deviations from the Clinical Investigation Plan. If any action is taken by an IRB/EC with respect to this clinical study, copies of all pertinent documentation must be forwarded to Medtronic in a timely manner. Reports are subject to inspection and to the retention requirements as described above for investigator records. Safety data investigator reporting requirements are listed in section 12.5.2. The investigator shall prepare and submit in a complete, accurate and timely manner the reports listed in this section.

Table 13: Investigator Reports

Report	Submit to	Description/Constraints
Withdrawal of IRB Approval (either suspension or termination)	Sponsor and Relevant Authorities, if applicable	The investigator must report a withdrawal of approval by the reviewing IRB of the investigator's part of the investigation within 5 working days.
Study Deviations	Sponsor and IRB/EC	Notice of deviations from the CIP to protect the life or physical wellbeing of a subject in an emergency shall be given as soon as possible, but no later than 5 working days after the emergency occurred. Reporting of all other study deviations must comply with IRB/EC policies and/or local laws and/or regulatory agency requirements and must be reported to Medtronic as soon as possible upon the center becoming aware of the deviation.
Progress Report	Sponsor and IRB/EC and relevant authorities if applicable	The investigator must submit this report to the sponsor and IRB at regular intervals, but in no event less than yearly.
Final Report	Sponsor and IRB/EC and relevant authorities if applicable	This report must be submitted within 3 months of study completion or termination of the investigation or the investigator's part of the investigation.

16.8.2 Sponsor Reports

Required sponsor reports are listed in Table 14 below.

Table 14: Sponsor Reports

Report	Submit to	Description/Constraints
Premature Termination or Suspension of the Clinical Investigation	Investigators, IRBs/ECs, regulatory authorities (if required per local regulations)	Provide prompt notification of termination or suspension and reason(s).
Progress Reports	IRB	Progress reports will be submitted at least annually. *(21 CFR 812.150(b)(5), 812.36(f)*
Recall and device disposition	Investigators, IRB	Notification within 30 working days and will include the reasons for any request that an investigator return, repair, or otherwise dispose of any devices. *(21 CFR 812.150(b)(6))*
Study Deviations	Investigators	Ensure that all deviations from the Clinical Investigation Plan are reported on the case report forms and the final report of the clinical investigation. Site specific study deviations will be submitted to investigators annually.
Final Report	Investigators, IRB/EC, regulatory authorities (if required per local regulations)	Sponsor final report including study analyses will be provided.
Significant risk device determination	FDA	If an IRB determines that the device is a significant risk device, the sponsor shall submit to FDA a report of the IRB's determination within 5 working days after sponsor learns of the determination. *(21CFR 812.150(b)(9))*

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

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

16.9 Publication and Use of Information

Publications from the LINQ™ for COPD Study will be handled according to Medtronic's Policies and Standard Operating Procedures and as indicated in the Clinical Trial Agreement.

16.9.1 Publication Committee

The LINQ™ for COPD Study will utilize a Publication Committee which will include the study Oversight Committee member as well as Medtronic personnel. This committee will manage study publications with the goal of publishing findings from the data.

The Publication Committee's role is to:

- Manage elements addressed in the publication plan as outlined in this section
- Develop the final Publication Plan under a separate cover
- Execute the Publication Plan
- Oversee the publication of primary, secondary and ancillary study results
- Review and prioritize publication proposals
- Provide input on publication content, and
- Apply and reinforce the authorship guidelines set forth in the Publication Plan.

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

16.9.2 Management of Primary, and Ancillary Publications

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

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

16.9.3 Criteria for Determining Authorship

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

Decisions regarding authorship and contributor ship will be made by the Publication Committee. The selected authors will be responsible for drafting the publication. All selected authors must fulfill ICMJE authorship conditions to be listed as authors.

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

16.9.4 Transparency

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

- A final report describing the results of all objectives and analysis will be distributed to all investigators and IRBs/ECs and Competent Authorities of participating countries when required by local law
- Registering and posting the study results on ClinicalTrials.gov based on the posting rules stipulated
- Submitting for publication the primary study results after the study ends
- Disclosing conflicts of interest (e.g., financial) of the co-authors of publications according to the policies set forth by the corresponding journals and conferences
- Making an individual site's study data accessible to the corresponding investigator after the completion of the study, if requested

16.10 Suspension or Early Termination

16.10.1 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 CIP 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/EC oversight is required until the overall study closure process is complete. Upon study closure, subjects should be managed and followed per physician discretion.

16.10.2 Early Termination or Suspension

Early Termination is the closure of a clinical study that occurs prior to meeting defined endpoints. This is possible for the whole study or a single site. 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 site. In the event the whole study or a single site is terminated, subjects will be exited.

16.10.2.1 Study-wide termination or suspension

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

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

16.10.2.2 Investigator/study site termination or suspension

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

- Failure to obtain initial IRB/EC 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 CTA (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.)
- Institutional Review Board/Ethics Committee suspension of the site
- Fraud or fraudulent misconduct is discovered (as defined by local law and regulations)
- Investigator request (e.g. no longer able to support the study)

16.10.3 Procedures for Termination or Suspension

16.10.3.1 Medtronic-initiated and regulatory authority-initiated

- Medtronic will promptly inform the clinical investigators of the (early) termination or suspension and the reasons and inform the regulatory authority(s) where required
- In the case of study termination or suspension for reasons other than a temporary IRB/EC approval lapse, the investigator will promptly inform the IRB/EC
- 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

16.10.3.2 Investigator-initiated

- The investigator will inform Medtronic and provide a detailed written explanation of the termination or suspension
- The investigator will promptly inform the institution (where required per regulatory requirements)
- The investigator will promptly inform the IRB/EC
- The investigator will promptly inform the regulatory authorities (if required)
- 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

16.10.3.3 Ethics Committee-initiated

- The investigator will inform Medtronic and provide a detailed written explanation of the termination or suspension within 5 business days
- The investigator will promptly inform the regulatory authorities (if required)
- Subject enrollment must stop until the suspension is lifted

- Subjects already enrolled should continue to be followed in accordance with IRB/EC 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, and/or the personal physician of the subjects, with the rationale for the study termination or suspension

17. References

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18. Appendices

18.1 Informed Consent Template(s)

Patient informed consent form templates will be provided under separate cover.

18.2 Data Collection Elements (Electronic Case Report Forms)

Electronic Case Report Forms for the LINQ™ for COPD study will be provided under separate cover. Final eCRFs will be provided to sites via the electronic data management system after the site has fulfilled all requirements for database access.

18.3 LINQ™ for COPD Study Procedure Handbook

A LINQ™ for COPD Study Procedure handbook that will provide instructions on the following: how to apply and utilize the DR220 Holter during the Spirometry tests, EMFIT Bed Monitor instructions, and Subject diary instructions will be provided under a separate cover.

18.4 Participating Investigators and Institutions

A complete list of participating investigators and institutions (including names, titles/professional positions, address(es), and telephone numbers) where study activities will be conducted will be distributed under a separate cover when available. Approval of the LINQ™ for COPD Study CIP will be documented by signing the Clinical Trial Agreement or a separate investigator agreement.

18.5 IRB Committee List

A complete list of participating IRBs and the Chairperson(s) will be provided under separate cover. This information will be updated throughout the course of the study. The updated list will be maintained at Medtronic and will be available upon request.

18.6 Committees

The Reveal LINQ™ for COPD study will utilize an Event Adjudication Committee (EAC) for the assessment of Pulmonary related AEs and AEs with a fatal outcome.

The Reveal LINQ™ for COPD study may utilize a Publication Committee aiming to manage study publications.

A Data Monitoring Committee (DMC) is not needed for this study. This decision was made based on the following criteria: it is felt there are no additional benefits of a DMC reviewing the data in addition to the Event Adjudication Committee (EAC)

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

18.7 Labeling

Labeling for the investigational RAMware will be provided under separate cover. Labeling for all system components used in this study can be found with each package insert and/or will be available on http://manuals.medtronic.com.

19. Version History

Version	Summary of Changes	Author(s)/Title
1.0	• Not Applicable, New Document	[redacted], Clinical Research Specialist [redacted], Sr. Principal Statistician
2.0	• Updated exclusion criteria • Inserted a max number of subjects per site that can utilize the EMFIT bed monitor • Clarified manual transmission requirements • Made minor formatting and grammar changes • Updated CIP title to Reveal LINQ™ for COPD Study	[redacted], Clinical Research Specialist
3.0	• Removed "electronic" when referencing to the subject diary • Added clarification regarding potential risks in section 10.1 • Adjusted required manual transmissions to a bi-weekly basis	[redacted], Clinical Research Specialist
4.0	• Updated I/E criteria • Added option of investigational ALLEVIATE-HF Software and RAMware • 6-month in office visit changes: Made the visit to be optional and allowed it to be done in-office at any time during study participation, except within 30 days post insertion of the device. Removed the BioPac system, 6-minute walk test and lab requirement. Added the tidal volume spirometry assessment accompanied with breathing maneuvers and Chest X-ray procedure • Allowed for prior spirometry results to be used at baseline visit if done in the past 6 months • Changed diary requirement to be weekly and when symptoms change • Changed laboratory collection requirement to either Brain natriuretic peptide (BNP) OR N-terminal brain natriuretic peptide (NT-proBNP) instead of requiring both	[redacted] Clinical Research Specialist [redacted], Principal Statistician
5.0	• The CIP was transitioned to CIP template version E from version 3.	[redacted], Clinical Research Specialist

	• Updated the follow-up period to 6 months for the last patient enrolled and the expected total study duration to 33 months in section 4 (synopsis), section 7 (study design) and section 7.1 (duration). • Updated figure 1 (study flowchart) to correspond to the follow-up period of 6 months. • Footer was added in section 3. Synopsis and section 9.4 Exclusion criteria to correspond to the Intended Study deviation dated 13-OCT-2021. • Sections (7.2 Manufacturer, 7.3 Packaging, 7.4 Intended Population, 7.5 Product Use, 7.6 Product Training Materials, 7.7 Shipment of Study Components, 7.8 Product Receipt and Tracking, 7.9 Product Storage, 7.10 Product Return, 7.11 Product Accountability, 8.1 Investigator/ Investigation Site Selection, 8.2 Study Site Activation, 8.3 Role of the Sponsor Representatives, 10.23.2 Study completed, 10.23.4 Subject chooses to Exit, 10.23.5 Investigator Withdraws Subject and 10.23.6 Conditional Disengagement) were updated. • Scheduled follow up visits was updated in section 10.12 • Definition for Serious Health Threat (Section 12.4 Definitions/Classifications (table 9)) was removed as this definition was incorrectly included in the CIP and it is not necessary as this study is not ISO compliant.	