Medtronic Clinical Investigation Plan	
Clinical Investigation Plan/Study Title	DEFINE AFib Study
Clinical Investigation Plan Identifier	MDT20024
Study Product Name	Any market-released LINQ device Medtronic research application
Sponsor	Medtronic, Inc. 8200 Coral Sea Street NE Mounds View, MN U.S.A. 55112 Phone: 1-800-328-2518
Document Version	4.0, dated 29JUL2022
Lead Principal Investigator(s)	Dr. Jonathan Piccini Associate Professor of Medicine Duke University
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1. Contact Information and Glossary

1.1 Sponsor Contact Information

Medtronic contact information is provided below. The information is subject to change during the course of the clinical study. Periodic updates to study contact information will be sent to the sites as needed. Other sponsor contact information, such as name and address of local monitor, etc. will be provided under a separate cover as needed.

Table 1: Study Sponsor Contact Information

Research Director	Program Manager	Clinical Study Manager	Monitoring Manager
[redacted]	Cody Johnson Direct Phone: [redacted] cody.c.johnson@medtronic.com	[redacted]	Taryn Randall Direct Phone: [redacted] taryn.randall@medtronic.com

1.2 Glossary

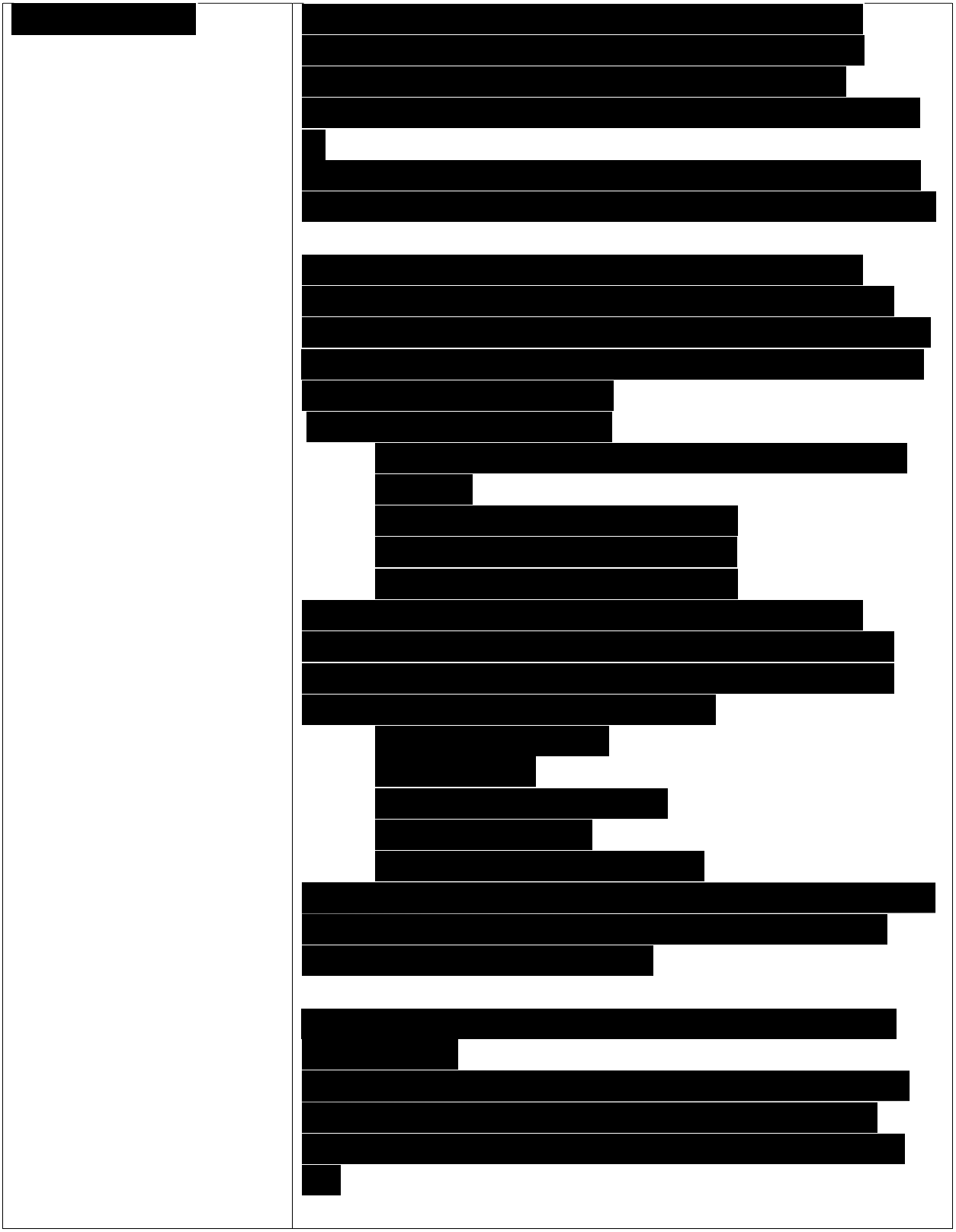
Term	Definition
AE	Adverse Event
AF/AFib	Atrial Fibrillation
AHF	Acute Heart Failure
API	Application Programming Interface
App	A computer program or software application designed to run on mobile devices
CIP	Clinical Investigational Plan
CFR	Code of Federal Regulation
eCRF	Electronic Case Report Form
CTA	Clinical Trial Agreement
CV	Cardiovascular
DTL	Delegated Task List
EC	Ethics Committee
ECG	Electrocardiogram
EHR	Electronic Health Record
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HCU	Healthcare Utilization
HF	Heart Failure
HIPAA	Health Insurance Portability and Accountability Act
ICF	Informed Consent Form
ICM	Insertable Cardiac Monitor
iOS	an operating system used for mobile devices manufactured by Apple Inc.
IRB	Institutional Review Board

Term	Definition
LINQ	May refer to Reveal LINQ, LINQ II, or future LINQ ICM, unless otherwise specified
MDT	Medtronic
NSR	Non-Significant Risk
PHI	Protected Health Information
IC	Informed Consent
QoL	Quality of Life
RAMware	Software downloaded onto LINQ™ device
RDC	Remote data capture
SpO2	Oxygen Saturation

2. Synopsis

Title	DEFINE AFib
Clinical Study Type	Prospective, observational, post-market study
Product Name	Reveal LINQ Insertable Cardiac Monitor or newer commercial model Medtronic research application
Sponsor	Medtronic Cardiovascular Diagnostics & Services
Local Sponsor	Medtronic, Inc. 8200 Coral Sea Street NE Mounds View, MN U.S.A. 55112 1-800-328-2518
Indication under investigation	Patients will be eligible to participate if they 1) have an existing market-released LINQ ICM; **and** 2) have received their LINQ ICM for the identification of AF (includes cryptogenic stroke, AF management, AF ablation, palpitations, or suspected AF; **and** 3) a self-reported history of AF. These conditions will be confirmed prior to study enrollment.
Investigation Purpose	The purpose of this study is to evaluate the association between complex patterns of device-detected AF and other summary and episodic measurements collected by the market-released LINQ ICM device and AF-related healthcare utilization, quality of life, AF-related symptoms, and specific clinical outcomes in patients with a market-released LINQ ICM. The Medtronic Discovery app will be used to collect data both (1) via the iPhone® through patient-reported health surveys and Bluetooth-enabled devices connected through the Apple Health app and (2) data accessed through or stored on the phone pertaining to health records, activity, and other lifestyle data. Secondarily, this study will examine associations between clinical

	procedures, medications and lifestyle actions taken and their impact on device-detected AF. Additionally, this study will help Medtronic evaluate patients' interaction with reports generated from health data collected by the market-released LINQ ICM. This study will improve our understanding of how data from the LINQ family of devices can be used to guide the management of AF patients.
• **Product Status**	The study will be conducted using the components of the Medtronic Reveal LINQ or LINQ II system which are currently market-released in the participating geography (United States). Future LINQ devices may also be used, should a new iteration be released during the study. This study will also use an iPhone® app built using Apple ResearchKit to collect data both (1) via the iPhone® through patient-reported health surveys and Bluetooth-enabled devices connected through the Apple Health app and (2) data accessed through or stored on the phone pertaining to health records, activity, and other lifestyle data. This will require an iOS of 13.X or higher. EHR and claims data will be collected if the patient has connected their DEFINE AFib profile to their EHR or claims data through the Apple Health app. The app will also be used to provide patients visibility to select data collected by their market-released LINQ (and other future models), and to characterize patient preferences for viewing and interacting with device data. The iPhone® app will not directly communicate with any component of the Reveal LINQ or LINQ II system.
Primary Objective	To evaluate whether summary and episodic measurements collected by market-released LINQ ICMs are able to predict increased AF-related healthcare utilization (HCU) **Endpoint:** Confirmed healthcare visit in the inpatient hospital, outpatient hospital, clinic/office, emergency department, or other care location (including remote visits) where AF was a reason or suspected reason for healthcare interaction



	
Study Design	DEFINE AFib is a prospective, observational post-market clinical study. This study will enroll approximately 5,000 patients in the United States who have a Reveal LINQ or LINQ II ICM (or future market-released LINQ devices) and using an Apple iPhone® with iOS version 13.X or higher. Health and activity data will be collected from the iPhone® directly. A study application will be used to administer health-focused and QoL surveys to patients at variable time points. Additionally, patients will be provided a summary of their device-related data with subsequent patient experience surveys to understand how patients respond to and interact with their device data. Patients will be followed to either the end of their ICM service life or for up to five years.
Randomization	As this is an observational study, patients will not be randomized
Sample Size	Approximately 5,000 patients (see section 13.1)
Inclusion/Exclusion Criteria	Specific Inclusion/Exclusion criteria can be found in the applicable Addendum

Study Procedures and Assessments	Interested patients will complete a screening questionnaire to determine eligibility. Eligible patients will be invited to undergo an DEFINE AFib app-based electronic informed consent. Following consent, the app will guide patients through the completion of their research profile, including the enabling of data collection and will complete baseline medical history and quality of life surveys. Consent documents will be stored in the DEFINE AFib app on the iPhone®. A copy of the consent will also be stored on secure Medtronic servers for compliance purposes. Following consent, patients will be asked to review what data they are willing to share with the study sponsor. For approved data sources, data will be collected through the iPhone® applications on an ongoing basis (including but not limited to physical activity and electronic medical record information). Health, medication, symptom, and QoL surveys will be administered at variable timepoints based on LINQ ICM summary and episodic measurements, and the time interval since the last completed survey. Lastly, patients will be provided select data from their LINQ ICM device, with subsequent patient experience surveys to understand how patients respond to and interact with their device data. Patients will have the ability to terminate their participation at any time.
Safety Assessments	The collection of adverse events and device deficiencies are not required to meet the objective(s) of this study.

3. Introduction

3.1 Background

Atrial fibrillation (AF) is the most frequent clinically significant cardiac arrhythmia.[1] When diagnosed clinically, AF is associated with increased risk for stroke, heart failure (HF), cardiovascular (CV) morbidity and mortality.[2] It is also a major contributor to the costs of health care.[3, 4] The prevalence of AF is predicted to rise significantly in the coming years due to the aging of the population and growing frequency of other AF risk factors.[5, 6] Considering the rising burden and clinical sequalae of AF, strategies that enable early detection and appropriate clinical management are needed.

Insertable cardiac monitors (ICMs) now allow for continuous arrhythmia monitoring for up to four years.[7] These devices have enabled early detection of AF that can be asymptomatic, infrequent, and/or of short duration.[8-12] Accordingly, AF detected by ICMs may not be diagnosed through traditional clinical assessment. Studies have demonstrated significantly higher rates of AF detection with ICM versus conventional monitoring in patients with a recent cryptogenic stroke[11] and in patients undergoing catheter ablation for AF.[13] Moreover, four recent trials have observed high rates of AF detection (21%-40% over 12-30 months of follow-up) with ICM monitoring in patients who have risk factors for AF and stroke, but no clinical history of AF.[8-10, 14] Two of these studies required conventional cardiac monitoring at baseline.[9, 10] Together these studies demonstrate that continuous monitoring with an ICM can identify AF that would not be readily detected through standard clinical assessment.

Prior studies have demonstrated that device-detected AF is associated with the same clinical outcomes as AF diagnosed through standard clinical practice, including stroke, mortality, and heart failure.[15-17] However, AF detected on implantable cardiac devices including ICMs can be transient and short in duration. The amount of device-detected AF required to increase the risk of cardiovascular morbidity and mortality is unclear. Prior studies have observed device-detected AF of different thresholds ranging from 6 minutes to 24 hours is associated with an increased risk of stroke.[18-22] While stroke risk seems to increase with longer durations of device-detected AF, this relationship is not linear,[17] and is impacted by the presence of other stroke risk factors.[23, 24] Even less evidence is available for other adverse consequences of AF such as mortality, healthcare utilization and quality of life. Accordingly, physicians are not clear when or how to intervene when AF is detected by ICM monitoring.[25, 26] A key requirement to advance the management of AF patients is the development of tools that can assess important variables such as AF burden or patterns of AF that, alone or in combination with other clinically important variables, improve the risk prediction for AF-associated clinical outcomes with greater efficacy than current risk stratification modalities. Therefore, the goal of this study is to characterize the association between summary and episodic measurements collected by LINQ ICMs and AF-related healthcare utilization (HCU) in patients with device-detected AF.

This information will inform how LINQ may be used to guide the appropriate care of patients with device-detected AF.

3.2 Purpose

The purpose of this study is to evaluate the association between complex patterns of device-detected AF and elevated healthcare utilization, reduced QoL and specific clinical outcomes in patients with a market released LINQ ICM. These data will improve our understanding of how data from the LINQ ICM Family can be used to guide the management of patients with AF.

4. Objectives and/or Endpoints

4.1 Objectives

4.1.1 Primary Objective(s)

To evaluate whether summary and episodic measurements collected by market-released LINQ ICMs are able to predict increased AF-related healthcare utilization (HCU)

Endpoint: Confirmed healthcare visit in the inpatient hospital, outpatient hospital, clinic/office, emergency department, or other care location (including remote visits) where AF was a reason or suspected reason for healthcare interaction

[redacted]

[redacted]

5. Study Design

DEFINE AFib is a prospective, observational, post-market clinical study. This study will enroll approximately 5,000 patients (see section 13.1) in the United States who have a Reveal LINQ or LINQ II (or any other market-released LINQ device) and using an Apple iPhone®.

This study will utilize the Reveal LINQ and LINQ II ICM or newer commercial ICM models and a Medtronic, Inc. developed research application for the Apple, Inc. iPhone®. The research application will allow for the remote enrollment and follow-up of patients by first administering electronic consent, providing patients the option to share their data from the Apple Health app, Electronic Health Records through the Apple Health app or location data, and deploying scheduled and triggered surveys to collect patient reported outcome measures. The market-released LINQ device will collect and report standard cardiac parameters through the CareLink network. The purpose of this study is to evaluate whether summary and episodic measurements collected by the market-released LINQ ICM are able to predict increased AF-related healthcare utilization (HCU) in patients with device-detected AF.

Interested patients will download Medtronic's research app (the "study app" or "research app") and complete a brief in-app screening questionnaire to determine eligibility. Eligible patients will be invited to proceed through the app to review and sign an electronic consent document. Should the patient have any questions regarding the study, the patient will have access to a phone number that connects them with a study help desk. The help desk has been qualified through Medtronic's Global Security Office and Global Privacy Office to handle patient calls and is trained and overseen by Medtronic. Following consent, patients will create a profile, opt in to sharing location, EHR data and other optional components of the study, and complete a baseline medical history survey and medication log.

Following consent, data will be collected directly from the iPhone® on an ongoing basis (see section 9.9). Health, medication, and QoL surveys will be administered at baseline and at regularly scheduled intervals, while healthcare utilization and symptom surveys will be administered at variable timepoints based on market released LINQ ICM summary and episodic measurements and a patient, with anonymized location services (if enabled), crossing a predetermined healthcare location geofence. Lastly, patients will be provided select data from their LINQ ICM device, with subsequent patient impact surveys to understand how patients respond to and interact with their device data. To limit survey fatigue in patients with frequent health care utilization or qualifying AF episodes, no triggered survey will be deployed within 7 days of a previously deployed survey of the same kind. To limit the opportunity for duplicate surveys, each survey will have an expiration that is dependent upon how frequently it is issued (Table 4). Patients will have the ability to terminate their participation at any time through the study app.

5.1 Duration

All patients will be followed for up to 5 years, until study closure, or until their ICM either completes its service life or is explanted, upon which time they will no longer be followed. Study closure may occur

when Medtronic requirements have been satisfied per the Clinical Investigation Plan (CIP) and/or following a decision by Medtronic or applicable external parties (i.e. institutional review board (IRB) or regulatory authority) to discontinue the study. The estimated total study duration is up to 9 years, representing a four-year enrollment period and up to 5 years of follow-up for patients. Follow-up may be shortened based upon the interim analysis as outlined in section 13.

5.2 Rationale

The DEFINE AFib study is a prospective, observational, post market study to allow for the association between device-detected AF and healthcare utilization, physician-guided treatment, and QoL. A up to 5-year follow-up duration was chosen to accommodate the low event rates expected in this patient population.

A retrospective analysis using existing datasets including Optum electronic health records (EHR) and Claims data was considered. Because these data sources are not specifically intended for research, they have numerous limitations including: inaccuracies, upcoding, absence of data provenance, insufficient granularity, and incomplete information (e.g. missing information due to receipt of care at different locations, changes in coverage, absence of data on medication compliance and QoL, etc.). Considering these limitations, we have chosen to conduct a prospective study. However, existing data sources have been leveraged in a preliminary analysis to inform the present investigation.

5.3 Study Oversight

The study will utilize a Steering Committee. The Steering Committee advises on the scientific content of the study and provides input for the execution. Members may be study site investigators. The purpose of the Steering Committee is to provide unbiased opinions and expertise to the clinical study design and process. The Steering Committee will support the execution of the DEFINE AFib study and provide guidance, feedback and direction to the study. The Steering Committee is comprised of the members as indicated in the DEFINE AF Steering Committee Charter. As membership may change, the current list of members can be made available upon request.

6. Product Description

6.1 General

The study will be conducted using market released products/components as described below. Instructions for use of the devices used in this study are provided in their respective manuals.

6.1.1 Reveal LINQ™ and LINQ II™ ICM System

The Reveal LINQ™ ICM is a 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. Patients with an existing Reveal

LINQ™ ICM for approved indications will be enrolled. Instructions for use of this device is available in the Reveal LINQ clinician manual.

The Medtronic LINQ II™ ICM is a 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. Patients with an existing LINQ II™ ICM for approved indications will be enrolled. Instructions for use of this device is available in the LINQ II™ clinician manual.

Indications for both devices are identical.

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 Reveal LINQ and LINQ II system components are illustrated in Table 2 below.

Table 2: Reveal LINQ and LINQ II System Component Information

Model Number	Component	Manufacturer	Investigational or Market-released
Reveal LINQ			
LNQ11 or other commercial model	Reveal LINQ™ Insertable Cardiac Monitor	Medtronic	Market-released
PA97000	Patient Assistant	Medtronic	Market-released
MSW002 IOS (Apple)	LINQ™ Mobile Manager (LMM)	Medtronic	Market-released
2090	Medtronic Programmer	Medtronic	Market-released
24967	Patient Connector head for LMM	Medtronic	Market-released
24950 or other commercially approved model	MyCareLink Patient Monitor	Medtronic	Market-released
LINQ II			
LNQ22	LINQ II™ Insertable Cardiac Monitor	Medtronic	Market-released
MSW003 Android MSW004 IOS	MyCareLink Heart™ App	Medtronic	Market-released
24960	MyCareLink Relay™ Home Communicator	Medtronic	Market-released
PA97000	Patient Assistant	Medtronic	Market-released
MSW002 IOS (Apple)	LINQ™ Mobile Manager (LMM)	Medtronic	Market-released
24967	Patient Connector head for LMM	Medtronic	Market-released

Reveal LINQ Description

Reveal LINQ ICM: is a small, leadless device that is inserted under the skin, in the chest. The device uses 2 electrodes on the body of the device to monitor the patient's subcutaneous ECG continuously. The device is designed to record the occurrence of an arrhythmia in a patient automatically. Arrhythmias may be classified as tachyarrhythmia, brady arrhythmia, pause, atrial tachyarrhythmia, or atrial fibrillation. In addition, while experiencing or immediately after a symptomatic event, the patient can activate the device to record their cardiac rhythm.

The device memory can store up to 27 min of ECG recordings from automatically detected arrhythmias and up to 30 min of ECG recordings from patient-activated episodes. The system provides 3 options for segmenting the patient-activated episode storage: up to four 7.5 min recordings, up to three 10 min recordings, or up to two 15 min recordings. Arrhythmia detection parameters are set to pending automatically, based on patient information entered on the programmer during pre-insertion device setup: the patient's date of birth and the clinician's reason for monitoring the patient. Arrhythmia detection parameters can also be programmed manually by the clinician.

The Medtronic Programmer and LINQ Mobile Manager (LMM) are used to set up the device to detect arrhythmias and allow the user to view, save, or print the information stored by the device.

The Patient Assistant is a hand-held, battery-operated telemetry device that enables the patient to activate the recording of cardiac information in the Reveal LINQ ICM while experiencing or immediately after a symptomatic event. The clinician uses the recorded information to determine if the symptoms were associated with a cardiac event.

The MyCareLink Patient Monitor is used by patients to gather information automatically from their inserted device and communicate the information to their physician. The inserted device communicates wirelessly with this monitor which then transmits the information over a cellular telephone connection to the Medtronic CareLink Network. This daily wireless audit transmission is scheduled by the clinic and is usually set for a time when the patient is asleep. At other times, if requested to do so by their physician or clinic, the patient can use their monitor to perform a manual device interrogation to gather information from their inserted device and communicate it to their physician.

Additional information related to the Reveal LINQ ICM, including indications, contraindications, warnings, and precautions can be found in the respective clinician manual.

LINQ II Description

LINQ II ICM: The LINQ II™ ICM is a small, leadless device that is inserted under the skin, in the chest. The device uses two electrodes on the body of the device to monitor the patient's subcutaneous ECG

continuously. The device memory can retain ECG details for up to 30 min of symptom marked episodes per day. The system provides three options for segmenting the patient activated episode storage: a 10 min recording (9 min before and 1 min after a symptom mark), a 15 min recording (14 min before and 1 min after a symptom mark) or no symptom activated episode storage.

MyCareLink Heart App: The MyCareLink Heart™ mobile app is an application downloaded onto the patient's smartphone. The patient app paired with a mobile device transfers encrypted medical device data between the inserted device and the CareLink Network. The patient interacts with the patient app for initial setup, viewing status information, and recording symptoms. The patient app can be enabled to record cardiac information in the LINQ II™ ICM while the patient is experiencing symptoms or immediately after a symptomatic event. The clinician uses the recorded information to determine if the symptoms were associated with a cardiac event.

MyCareLink Relay Home Communicator: The MyCareLink Relay™ Home Communicator is a stationary device that transfers encrypted data from/to the patient's inserted device and the CareLink Network for patients unwilling or unable to use a smartphone/tablet. Data communication is via Bluetooth Low Energy (BLE) to the LINQ II™ device and wireless internet to the CareLink Network.

Patient Assistant: The Patient Assistant is a hand-held, battery-operated device that communicates with the LINQ II™ ICM via Bluetooth Low Energy. The Patient Assistant enables the patient to record cardiac information in the LINQ II™ ICM while experiencing symptoms or immediately after a symptomatic event. The clinician uses the recorded information to determine if the symptoms were associated with a cardiac event.

LINQ Mobile Manger (LMM) and Patient Connector Head: The Reveal LINQ Mobile Manager (LMM) clinician app is an application downloaded onto the clinic's tablet that communicates with the LINQ II™ device using BLE (the tablet downloaded with the clinician app is also referred to as the "LMM" within this document). The LMM provides the operator an interface to change device settings (programming), interrogate the collected data, and display real-time data such as ECG, telemetered EGM and Marker Channel information. The LMM can also be used to assess the system. The LMM uses the 24967 Patient Connector head for communication.

6.1.2 Medtronic Research App

Medtronic's research app (or "study app") will be used for Define AFib to collect iPhone® data (including the iPhone® Health App data, anonymized location services, and EHR/claims data if available), to electronically consent the subject in the app, administer patient questionnaires and to display select data from their LINQ ICM device directly to the patient. This app is not intended as a substitute for medical diagnosis or treatment. This app was developed by Medtronic using the Apple ResearchKit and will be used for other studies in the future. The research app will be available for download in Apple's App Store. The name for this app is the Medtronic Discovery App however, may be renamed through the course of the study. All data collected from Medtronic's research app will be stored in a Medtronic

secure, 21 CFR Part 11 compliant databases with controlled access. The databases have been reviewed and approved by Medtronic's Global Security and Privacy Office.

6.1.3 Data Collection from LINQ Devices

The following (but not limited to) data will be collected passively through the CareLink database. All device parameters and alerts will be programmed by the physician per standard care, and no changes will be mandated for the patient to participate in the study. Data will be collected on an ongoing basis following documented patient consent, and until study termination or patient withdrawal. Select variables will be collected.

- AF Episode
- AF Episode Duration
- Number of AF Episodes
- Episodes History
- AF events reported
- Daily AF Burden
- Baseline Heart Rate
- Daily Activity Level
- History of EGMs
- Counters
- HR Variability
- HR in AT/AF
- HR Day
- HR Night

Data collection schedule is outlined in section 9.

6.2 Manufacturer

The Reveal LINQ and LINQ II ICM systems are manufactured by Medtronic, Inc.

The Medtronic research app was developed by Medtronic, Inc.

The Apple iPhone® is manufactured by Apple, Inc.

6.3 Packaging

Instructions for use of the devices used in this study are provided within their respective manuals. None of the devices used in this study are investigational and therefore are not labeled with study-specific information.

6.4 Intended Population

The Reveal LINQ and LINQ II ICMs are indicated for the following:

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

See Section 8 for a description in inclusion and criteria.
Medtronic's research app is intended for all participants in the DEFINE AFib study.

6.5 Product Use

The Reveal LINQ and LINQ II ICMs will be used in accordance with approved indications and site-specific standard of care. No investigational products are being used in this study.

The Medtronic's research app will be available for download in Apple's App Store. All data collected from the DEFINE AFib Study research app will be stored in a Medtronic secure, 21 CFR Part 11 compliant databases with controlled access. The databases have been reviewed and approved by Medtronic's Global Security and Privacy Office.

7. Study Site Requirements

Study Site requirements, including site selection and activation, can be found in each specific DEFINE AFib study addendum.

8. Selection of Subjects

Selection of subjects, including study population, subject enrollment and inclusion/exclusion criteria can be found in each specific DEFINE AFib study addendum.

9. Study Procedures

9.1 Schedule of Events

Clinical data are collected at designated time points throughout the study. The requirements for data collection and study procedures by visit are summarized in Table 3 below.

Table 3: Study Procedures Organized by Study Events

STUDY PROCEDURE/ DATA COLLECTION	Enrollment	Daily Data Collection	Patient Surveys	Study Exit
Informed Consent	X			
Inclusion/Exclusion Assessment	X			
Medical History, Demographics	X			
AF-Associated Symptoms			X	
HCU			X	
System Modification			X	
Change in Medical Management for AF			X	
Quality of Life Questionnaires	X		X	
Study App Use Metrics		X		
HealthKit Data Including EHR,if available		X		
Patient Impact			X	

Table 4: Survey Type and Deployment Logic

• Survey Category	• Survey	• Survey Type	• Deployment Prerequisites	• Rules	• Expiration
• Medical History	• Patient history	• Static	• eConsent completed	• Only completed once at joining of study, necessary for enrollment	• No expiration
	• Medication history (MDT developed tool)	• Static	• eConsent completed	• Completed at beginning of study, available to update/modify over study timeline	• No expiration
• Quality of Life	• EQ-5D-5L	• Static	• eConsent completed	• Starting at enrollment and then every 3 months (every 90 days +/-2 days**)	• 30 days post issuance
	• AFEQT	• Static	• eConsent completed	• Starting at enrollment and then monthly (every 30 days +/- 2 days**)	• 14 days post issuance
• Healthcare Utilization	• HCU	• Dynamic	• Starting 30 days after enrollment	• Starting 30 days after enrollment and then monthly (30 days +/-5	• 7 days post-issuance

			or first triggered event	days*) (+/-2days**) (For triggered surveys, including healthcare facility geofence and daily AF burden from CareLink see section 9.9.2) • HCU survey should always be deployed with Symptom and Symptom Severity Survey	
• Symptom and Symptom Severity	• MAFSI and modified EHRA symptom severity	• Dynamic	• Starting 30 days after enrollment or first triggered event	• Starting 30 days after enrollment and then monthly (30 days +/- 5 day*)(+/-2days**) (For triggered surveys, including healthcare facility geofence and daily AF burden from CareLink see section 9.9.2) • Symptom and Symptom Severity survey should always be deployed with HCU survey	• 7 days post issuance
• Medication	• SMAQ	• Static	• Starting 90 days after enrollment (+/-2 days**)	• Starting 90 days after enrollment and then every 3 months (every 90 days +/-2days**)	• 30 days post-issuance
• Patient App	• Patient impact	• Static	• Starting 6 months after enrollment (180 days +/-2 days**),	• Starting 6 months after enrollment and then every 6 months (every 180 days +/-2 days**)	• 90 days post-issuance

*+/-5 days survey administered randomly within each deployment window
**+/-2 days is to correct for survey transmission issues

9.2 Subject Screening

Interested patients will be required to download Medtronic's research application. Upon first accessing the application after downloading, potential subjects will undergo authentication. Potential participants will complete the eligibility survey available in the app. Patients who meet the inclusion criteria based on self-report and a device serial number check via the app will be invited to participate in the study and directed to a digital consent form within the app for their review and electronic signature. A phone number for the Help Desk will be provided prior to consenting of the subject if the subject has any questions regarding their participation in the clinical study.

9.3 Prior and Concomitant Medications/Therapies

There are no requirements or restrictions with respect to prior or concomitant medications. Patients will be asked to record the medications they are taking and will be routinely asked to recall medication compliance through regularly deployed surveys throughout the study.

9.4 Subject Consent and Enrollment

The informed consent is defined as a legally effective documented confirmation of a patient's voluntary agreement to participate in a particular clinical study after information has been given to the patient through the study app on all aspects of the clinical study that are relevant to the patient's decision to participate. This process includes obtaining an ICF and an Authorization to Use and Disclose Personal Health Information that has been approved by an Institutional Review Board and electronically signed and dated by the patient.

Prior to enrolling patients, approval of the CIP, ICF, and all other written study information to be provided to the patients must have been approved by a registered IRB. The document(s) must be controlled (i.e. versioned and dated) to ensure it is clear which version(s) were approved.

The investigator must notify patients 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 patient, as this could impact a patient's willingness to participate in the study. If relevant, approval may be requested from patients to confirm their continued participation.

Electronic consent will be obtained prior to subject enrollment and before any study-specific procedures are initiated. Consent will be self-administered by the patient via the informed consent process. The process of obtaining informed consent must be conducted without using coercion or undue improper influence on or inducement of the patient to participate by the study or affiliated personnel. The informed consent process shall not waive or appear to waive patient's legal rights. The language used shall be as non-technical as possible and must be understandable to the patient.

The patient must have ample time and opportunity to read and understand the ICF, to inquire about details of the study via the study help desk, and to decide whether to participate in the clinical study. All questions about the study should be answered to the satisfaction of the patient. To facilitate patient access for questions, patients will have access to the study help desk, which will be equipped to answer study-related questions. A phone number for the Help Desk will be provided prior to consenting of the subject to allow the subject the ability to answer any questions regarding their participation in the clinical study.

When the patient decides to participate in the clinical study, the ICF must be electronically signed and dated by the subject acknowledging that their participation is voluntary.

The ICF and Authorization to Use and Disclose Personal Health Information will be electronic. A copy of the signed and dated ICF and Authorization documents will be available within Medtronic's research app for patient reference. An additional copy of the signed and dated ICF and Authorization will be stored in a secure part 11 compliant system, access-controlled Medtronic database and shared with the primary investigator upon request.

The informed consent will be obtained the same day the subject is eligible to begin participating in study-related procedures, and therefore consent date and time will be documented in the meta-data collected with consent. The study app will allow for the patient to access their consent at any time.

9.5 Randomization and Treatment Assignment

There will be no randomization or treatment assignments as this is an observational study.

9.6 Medication Use and Compliance

Patients will be asked to log medications at baseline and asked at regular intervals to update their medication list if there are any changes throughout the duration of their participation in the DEFINE AFib study (Table 4). Patients will store current medications in their research profile and update every 6 months; medication use and compliance assessed via the SMAQ survey deployed every 3 months. For patients with health record access, statistical models will be developed to estimate the proportion of days covered by leveraging EHR or claims data and/or patient surveys regarding prescription fills and/or refills. All changes in medication use will be marked with time and date via meta-data tracked in Medtronic's research application. All medication changes will be confirmed.

9.7 Survey and Device Data Non-Compliance

Monthly reports will be generated to assess response rates on surveys. Patients with missing survey responses or other incomplete tasks will be sent reminders through the app, via email, and via text depending on which communication methods are available and the patient has enabled. A schedule of these reminders can be found in Table 5. In the instance that a patient has undergone a prolonged period of time without transmitting device data, they will be notified via the app. At 90 days, mortality, HCUs, and specific clinical outcome status will be assessed via EHR or confirmed via study site personnel. After 90 days, if confirmed to be alive, they will continue to be monitored but may be excluded from statistical analysis.

Subjects will be reimbursed $25 every 6 months if they complete >75% of surveys. Subjects will receive an electronic gift card to their email.

Table 5: Notification and Reminder Schedule

Expiration Schedule	Reminder Schedule
7 Day Expiration Schedule	4 Days post issuance
14 Day Expiration Schedule	7 Days post issuance

1 Month Expiration Schedule	10 Days post issuance, then 20 days post issuance if action not completed
3 Month Expiration Schedule	10 Days post issuance, then 20 days post issuance if action not completed
6 Month Expiration Schedule	10 Days post issuance, then 20 days post issuance if action not completed

9.8 Assessment of Safety

Because 1) this is an observational study using market approved devices for approved indications and 2) there are no study aims evaluating device safety, adverse events will not be collected. Should any new risks associated with the study be identified including patient data security, patients will be notified via push notifications, in-app messaging, email, and SMS text message, depending on what form of communications the patient has opted into. Physicians will be notified of any new risks associated with the study. Continuous monitoring of study risks will be performed using Medtronic's Global Security Office-required security controls which include monitoring procedures/platforms that are capable of logging, monitoring, detecting data breaches and app problems. These procedures are governed by Medtronic' Global Security Office and Cloud Governance teams. Monitoring of study risks will be performed using standard monitoring procedures.

9.9 Recording Data

The following data will be collected passively through Medtronic's research app. Data will be collected on an ongoing basis following documented patient consent, and until study termination or patient withdrawal. Following consent, patients will create a profile, opt in to sharing location, EHR data and other optional components of the study and the patient will have the opportunity to change data permissions that determine collectable data throughout the study. If patients consent to sharing their EHR data, that patient's EHR data will be pulled via the Apple Health app. If EHR access is available, it will be used to confirm patient-reported events as described in section 12. EHR data may also be used to compile and analyze variables as outlined in section 13.

- Electronic Health Records
    - Clinical Vitals
    - Diagnoses/Conditions
    - Lab results
    - Medications
    - Medical procedures/clinical actions
    - Patient mortality

- Health app data (when available, including but not limited to)
    - Step counts to assess activity
    - Nutrition
    - Sleep
    - Vitals
        - Glucose
        - Blood pressure
        - SPO_2
    - Body measurements:
        - Weight
        - Height
        - Body mass index
- Location services (when available)
    - Anonymized geofencing triggers

9.9.1 Geofencing and Location Services

Use of geofences will only be permissible in patients who have consented and enabled to the use of their phone's location services feature. Geofenced facilities will include 12,000+ hospitals and urgent care healthcare facilities in which a patient is likely to seek care. Only anonymized geofence data will be collected which cannot be connected back to the patient it originated from. After Consent, Medtronic servers will deploy the appropriate surveys under the logic provided in Table 4.

9.9.2 Patient Surveys

Patient surveys will be administered to assess medical history, QoL, HCU, changes in medical management, AF-associated symptoms, and medication use. Surveys will also be administered to evaluate patient preferences for viewing and interacting with device data. Exact content of the surveys may change throughout the study, but any significant content changes will be submitted to IRBs for approval.

Survey deployment logic is outlined in Table 4.

- QoL Questionnaires
    - The EQ-5D-5L general QoL survey will be distributed via the app at enrollment and then every 3 months(90 days +/-2 days) to assess general quality of life metrics
    - AFEQT, an AF specific QoL survey will be deployed via the app at enrollment and then every month (30 days +/-2 days) to characterize and assess the impact of AF on each patient
- Symptom Survey:
    - A symptom survey will be administered to characterize the presence and severity of AF-related symptoms when a patient crosses a predefined healthcare facility geofence, reaches the threshold for a single AF episode or daily AF burden or AF pattern, or;
    - On a routine monthly (30 days +/-5 days) schedule unless a symptom survey has been deployed for any reason within the previous 7 days.
- Healthcare Survey
    - A healthcare survey will be deployed to characterize healthcare utilization and modifications to patient care (administration of medical interventions/procedures) when a patient crosses a predefined healthcare facility geofence, reaches the threshold for a single AF episode or daily AF burden or AF pattern, or;
    - On a routine monthly (30 days +/-5 days) schedule unless a symptom survey has been deployed for any reason within the previous 7 days.
- Medication compliance
    - Patients will answer the Simplified Medication Adherence Questionnaire (SMAQ) every 3 months (90 days +/- 2 days) following initial enrollment.
- Medication list
    - Patients will be prompted to input/update their medications upon enrolling in the study and every 6 months (180 days +/-2 days) following initial enrollment.

Surveys will also be administered to evaluate patient preferences for viewing and interacting with device data. Data around app-use will also be collected (time in app, app feature use, number of clicks, etc.).

In the event that the patient has lost connectivity (no signal or phone powered off) for an extended period of time, all non-expired surveys will be received upon first opportunity of connectivity. Expiration windows will remain consistent as noted in table 4 regardless of connectivity.

9.9.2.1 Dynamic Surveys

The HCU and Symptom survey are dynamic in nature. Patients will be prompted to complete surveys through Medtronic's research app. Surveys will be triggered at variable times based on the following factors:

- Time from enrollment
- Time since last survey – (HCU and Symptom and Symptom Severity surveys)
- ICM device data (triggers HCU and Symptom and Symptom Severity surveys)
    - A single AF episode lasting longer than 1-hour
    - Cumulative daily AF burden of 5% or greater
    - A patient meets the running average/AF pattern threshold as developed by a prior internal analysis
- Geofence (triggers HCU and symptom surveys)
    - Patient crosses a geofence threshold and remains within the geofenced area for ≥45 minutes

Each patient will receive surveys via one of three methods: 1) Regularly scheduled surveys at specified cadences, 2) AF burden or pattern trigger detected via the Reveal LINQ or LINQ II device (or future market-released LINQ devices) and transmitted through CareLink, 3) a patient crossing and staying within a geofence. Each regularly scheduled deployment window will be +/- 5 days around 30 days from previous survey deployment, with the survey administered randomly within each deployment window. This method reduces the likelihood that a patient will suspect a survey has been given in response to an AF episode they experienced, and helps to avoid any bias associated with the expectation of a survey at a particular cadence. Additionally, patients may receive a HCU and symptom survey at pre-specified trigger points based on Reveal LINQ or LINQ II (or future market-released LINQ devices) detected AF burden or AF patterns, or via the patient being present in a geofenced healthcare facility, within 24-48 hours of the trigger being activated in order to best associate AF patterns with patient health and environmental factors. Patients who trigger any of the AF burden thresholds for HCU or symptom survey deployment will, at the first instance, all receive the assigned surveys. Patients will not be notified which method triggered a survey. Thereafter, any AF burden trigger will be administered at a rate of 50%,

allowing for the testing of bias introduced by triggered survey deployment and reduce patient survey burden.

9.9.3 Healthcare Utilization

Healthcare utilization (HCU) information data will be collected and classified according to the below definitions.

Details on how HCU will be confirmed can be found in each specific DEFINE AFib study addendum.

Table 6: Healthcare Utilization Definitions

Healthcare Utilizations (HCU)	All inpatient hospitalizations, outpatient hospital encounters, emergency department visits, clinic visits, urgent care visits, rehab center or other care location interactions (including remote visits)
CV-related HCU	A healthcare utilization relating to the heart and the blood vessels or the circulation (e.g., atrial fibrillation, myocardial infarction, stroke, peripheral vascular disease, heart failure).
AF-related HCU	HCU related to AF, suspected AF, AF treatment, or complications related to AF (including bleeding and drug toxicity as determined by treating clinician.
HF-related HCU	A healthcare utilization related to worsening heart failure signs and symptoms (as determined by treating clinicians) such as (but not limited to) hypervolemic and hypovolemic status requiring the administration, alteration, adjustment, or augmentation of HF therapy (diuretics, inotropes and/or vasodilators etc.) or the utilization of ultrafiltration devices.
Hospitalization	A therapeutic inpatient hospitalization (excludes outpatient and emergency room visits) lasting greater than or equal to 24 hours.
Non-hemorrhagic stroke	Rapid onset of a focal or global neurological deficit or other neurological signs/symptoms consistent with stroke; whereas focal, global cerebral or spinal dysfunction was NOT caused by a non-traumatic intraparenchymal, intraventricular, or subarachnoid hemorrhage, as determined by the treating clinician.
Systemic embolism	An embolus resulting in clinical and objective evidence of sudden loss of end organ perfusion.
TIA	New focal neurological deficit with rapid symptom resolution (usually 1 – 2 hours), always within 24 hours without tissue injury (based on neuroimaging) as determined by the treating clinician.

9.10 Patient Access to Device Data

Select data collected by the market-released LINQ devices will be accessible to patients through Medtronic's research app. Through the app, patients will be able to see and interact with infographic screens and charts that show their average daily, weekly or monthly Atrial fibrillation burden.

Patients will be notified through the app that they should not make any changes in behavior, modifications to treatment, or any other actions related to their health without first speaking with their physician. Patients will be notified that the Medtronic research app does not communicate with other

Medtronic apps and that data shared through the research app is not shared with their physician and will not be sent back through the CareLink network. Patients will also be notified how the data they are viewing is generated and any reason for delays in their data updates.

9.11 Deviation Handling

A study deviation is defined as an event within a study that did not occur according to the Clinical Investigation Plan. Due to the nature of this study, deviations will not be collected via the patient or site. Patients who do not meet inclusion/exclusion criteria will be excluded from analysis. Study level deviations will be collected as appropriate and submitted to IRBs.

9.12 Subject Exit, Withdrawal or Discontinuation

A subject may choose to discontinue participation at any point, and can do so by selecting the appropriate option through the study app. Subjects may also be notified and exited by the sponsor (via the study app) if they are inactive, have either stopped responding to surveys or stopped transmitting LINQ data for 90 days or greater, or determined to be deceased. Upon study exit, subject data collection will discontinue and data collected up until the time of withdrawal will be utilized for statistical analysis unless otherwise specified by the patient and in accordance with data privacy laws. Patients who withdraw from the study prior to a minimum 12 month follow up will be replaced to ensure appropriate statistical power can be achieved. As this is an observational study in a patient population that received their ICM device per standard of care and independently of their participation in this study, patients will continue routine care with their physician.

See specific Addendum for additional details.

10. Risks and Benefits

10.1 Potential Risks

There are no additional risks of having the LINQ device since all patients are indicated to have the LINQ device as part of standard of care.

Medtronic's research app does not present a potential for serious risk to the health, safety, or welfare of a participant, as the app only serves as a method to collect non-invasive study data and present the patient's own device data back to them.

As there is the potential for a patient to have more than one Medtronic app for their LINQ device, any screens that could be confused with another Medtronic app for clinical management of patients (i.e. the MyCareLink Heart app), plain language disclaimers with acknowledgement prompts will be present to inform the patient that any information reported through Medtronic's research app will not reach their physician, unless otherwise specified. There is no interaction between any other Medtronic app for this study.

The patient data view does have the potential to share device data that may include false positive AF episodes. To minimize this risk, the only AF specific device data patients will have the ability to view is their daily AF burden in intervals, and will include notification that the data has not been adjudicated by their physician. There is the possibility of app dysfunction that could delay participants' ability to enter information into the study. Any modifications to the study, including the cessation/re-starting of study data collection, or newly detected risks of participating in the study will be communicated to the patient via several outreach methods including in app notification and text message, and email, if the patient has opted into those notification methods.

Continuous monitoring of study risks will be performed using Medtronic's Global Security Office-required security controls which include monitoring procedures/platforms that are capable of logging, monitoring, detecting data breaches and app problems. These procedures are governed by Medtronic' Global Security Office and Cloud Governance teams.

10.2 Potential Benefits

The DEFINE AFib study may not provide direct benefit to the patient, although the patient will have a platform to view certain data about their health. Patients will be able to view certain summary views of their LINQ or LINQ II (or other approved LINQ family of products) device data, including AF burden (in summarized graphs), patient activity, and average heart rates. This may lead to a better understanding of their condition. The information gained from the study could result in improved management of AF and help better understand outcomes in different patient populations in the future.

10.3 Risk-Benefit Rationale

Medtronic has minimized the possibility of applicable risks and potential sources of bias by providing guidelines for subject selection and evaluation. In addition, a documented protocol and standardized data collection within the app will be used. Privacy risks have been minimized by the use of Part 11 compliant systems.

10.4 Risk Determination

No investigational devices are being used in this study. This study is a prospective, observational, post-market study.

11. Adverse Events and Device Deficiencies

11.1 Adverse Events

The collection of adverse events/device deficiencies are not required to meet the objective(s) of this study. The LINQ devices used in the study are market-approved and used within the current indications for use as indicated in the product labeling; however, it is the responsibility of the Investigator to abide by any adverse event and/or device deficiency reporting requirements stipulated by the site's IRB. User

(Investigator) reporting of events to regulatory authorities related to market approved product may be required. Refer to local regulations for reporting requirements.

11.2 Product Complaint Reporting

For devices that are market-released, product complaint reporting is applicable. The reporting of product complaints is not part of the clinical study. 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.

12. Data Review Committees

This is a prospective, observational, post-market clinical study. There are no objectives for this study related to safety or efficacy. The collection of adverse events is not required to meet the objective(s) of this study. Therefore, data review committees will not be used for this study, however, there are reviews and confirmation of certain variables as detailed below.

Individual AF episodes will be batched and adjudicated throughout the study by an independent reviewer that will classify the event as a true-positive or false positive AF episode.

Healthcare utilization and modification to treatment or management of AF will be reviewed and confirmed in subjects with available health records to compare to patient completed surveys. Specifics on how each utilization is confirmed can be found in each DEFINE AFib Study addendum.

Data from Apple Health App will not be independently adjudicated as there are no reliable means to do so within the scope of this study. Patient geofence trigger counts will be reviewed to screen for patients who may have reasons for triggering this survey deployment tool due to reasons other than seeking medical care (i.e. a patient works in or directly near a hospital, a mislabeled hospital, etc.).

13. Statistical Design and Methods

Data analysis will be performed by a Medtronic statistician or designee.

The cohort will include all enrolled subjects, but non-confirmed events will not contribute to the study's endpoints.

A Statistical Analysis Plan will be developed and kept under separate cover and will include a comprehensive description of the statistical methods and reports to be included in the final study report, as well as a description of how missing, unused, and spurious data will be accounted. Any change to the data analysis methods described in the CIP will require an amendment only if it changes a principal feature of the CIP. Any other change to the data analysis methods described in the CIP, and the justification for making the change, will be described in the clinical study report.

13.1 Statistical Study Design Considerations

The DEFINE AFib study is a prospective, observational post-market clinical study intended to leverage machine learning to evaluate the association between complex patterns of device-detected AF and elevated healthcare utilization, reduced QoL and specific clinical outcomes in patients with a LINQ ICM. These data will improve our understanding of how data from the LINQ ICM can be used to guide the management of AF patients. The DEFINE AFib study is not designed to be powered and no specific hypotheses will be tested. However, the sample size was determined with the goal of having an adequate number of endpoint events to develop risk prediction models that can have incremental clinical benefit beyond what is available as standard of care.

A retrospective analysis of the Optum EHR deidentified database (2007-2019), linked to the Medtronic CareLink database of insertable cardiac monitoring (ICM) devices, suggests that in a cohort of 5,000 patients from the intended population of ICM patients, 600 (12%) will have at least one ischemic stroke event and 2,350 (47%) will have at least one healthcare utilization in a five-year follow-up period. Of the healthcare utilization events, 1,050 (21%) will be AF-related. It is expected there will be approximately 5.2 million follow-up days. Given the large number of follow-ups, the ratio of events to follow-up days is extremely rare. Traditional classification approaches (CART, random forest) require under/over-sampling methods and control parameters for adequate convergence. In our retrospective analysis, we defined the target window as the five days prior to an event (thereby over-sampling events by a factor of five) and then under-sampled controls to a 1:1 ratio with over-sampled cases to create a balanced data set. Setting a minimum node size of 80 patients and requiring the minimum node size to range between 2% and 5% of balanced data, adequately converged to results. The under-sampling and model fitting exercise was repeated 100 times to bootstrap an estimate of variable importance for each variable in the model. Using this methodology for convergence and estimation, we expect a minimum of 160 (80/0.05/10) to 400 (80/0.02/10) events are needed for analyzing predictor variable influence and 320 to 800 events for creating a prediction algorithm that requires development, test, and validation partitions as part of its methodology. This latter range is sufficient for deep learning approaches (e.g., LSTM autoencoder, CNN classification network) for predicting extremely rare events.

A minimum of 320 to 800 events implies a 5,000 patient cohort is minimally sufficient for algorithm development. This, however, assumes patients enroll immediately after implant and does not consider attrition. Moreover, this retrospective analysis showed that 30% of patients will miss at least 50% of their daily CareLink transmissions. Considering these challenges, it is reasonable to expect as little as

50% of our cohort to provide complete data. In such a scenario, a 5,000 patient cohort would be sufficient for modeling health care utilization (1,175 events, 525 AF-related) but would be insufficient for modeling ischemic stroke or for modeling outcome events by smaller subgroups.

A planned interim analysis will be performed in which we will re-assess these assumptions to determine if the sample size or follow-up duration of the study needs to be adjusted.

13.2 General Aspects of Analysis

Data from all enrolled patients will be summarized, but analysis of each objective will account for the completeness of the data in the context of addressing the objective. In particular, patients contributing to objectives that are modeling HCU-based outcomes should have provided a minimal amount of information to ensure that HCU data has been made available. This can be accomplished through the completion of monthly and triggered surveys or by sharing EHR information through the study app or via sites. Complete device data should be available for all patients. Patients should have regularly transmitted CareLink data throughout follow-up. If no device data or limited device data is available from a patient, that patient will need to be either excluded from analysis or follow-up will need to be limited to the period of time up until device data is not available.

For patients that enroll at the time of ICM implant, all follow-up data will be analyzed from the time of implant if the patient completes all baseline enrollment tasks within 7 days of the ICM implant. Baseline enrollment tasks include enrollment, signing their consent, and completing all baseline survey questionnaires (patient profile, medical history, medication history, EQ-5D-5L, AFEQT). For patients that are enrolled more than 7 days after the ICM implant or that complete enrollment tasks more than 7 days post-implant, follow-up will begin when the patient has completed electronic consent.

13.3 Primary Objective

To evaluate whether summary and episodic measurements collected by the market-released LINQ ICMs are able to predict increased AF-related healthcare utilization (HCU)

13.3.1 Hypothesis

No formal statistical hypotheses will be tested for this objective. Rather, the goal will be to determine whether a risk prediction model can be developed from device-collected measurements that can has adequate sensitivity and specificity to be of use in a clinical setting.

Analysis Methods

Various risk prediction models will be developed and compared to each other. The model(s) with best predictive power will be selected. The input data of these models might be composed of values (original or derived) collected by LINQ ICMs, and the output of the model will be the risk of patient having a AF-related HCU in the future. The model may also account for attributes of patients' medical histories, including CHA2DS2-VASc scores, individual components of CHA2DS2-VASc scores and any other medical

history information provided by the patient at enrollment. The predictive value of the model will generally be assessed against the predictive power of any clinical tools available at the time of model development. If additional predictive tools become available at the time of model development, those tools can be integrated into the development of the model and the value of the model will reflect the incremental benefit provided above and beyond the available clinical tools.

Endpoint: Confirmed healthcare visit in the inpatient hospital, outpatient hospital, clinic/office, emergency department, or other care location (including remote visits) where AF was the reason or suspected reason for healthcare interaction.

13.3.2 Determination of Subjects/Data for Analysis

All subjects enrolled in the study that have successfully installed the app and consented will be included in the primary objective analysis.

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

14. Ethics

14.1 Statement(s) of Compliance

The DEFINE AFib study is classified as an prospective, observational, post market study.

The principles of the Declaration of Helsinki have been implemented in this study by means of the patient informed consent (PIC) consent (also known as the Informed Consent Form), IRB approval, study training and clinical trial registration.

In the United States, the study will be conducted in compliance with: 21 CFR 803, 21 CFR Parts 11, 50, and 56. Local laws and regulations will be applicable in the countries where the study is conducted. This study will be conducted in compliance with international ethical and scientific quality standards, known as good clinical practice (GCP). GCP includes review and approval by an independent IRB before initiating a study, continuing review of an ongoing study by IRBs, and obtaining and documenting the freely given informed consent of a subject before initiating the study.

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

15. Study Administration

15.1 Monitoring

Monitoring requirements can be found in each specific DEFINE AFib study addendum.

15.2 Data Management

Data collected via the study app and will be stored in a secure, part 11 compliant, password-protected database which will be backed up routinely. At the end of the study, the data will be frozen and will be retained by Medtronic in accordance with applicable regulations.

Data will be reviewed using programmed and manual data checks in addition to reports that compile relevant data collected from the study app. Subjects will receive notifications and reminders when their study tasks are due. 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). At the end of the study, the data will be frozen and will be retained indefinitely by Medtronic.

15.3 Direct Access to Source Data/Documents

The sponsor or a regulatory authority may audit or inspect the study site to evaluate the conduct of the study. The clinical investigator(s)/institution(s) shall allow study related monitoring, audits, IRB review, and regulatory inspection(s) by providing direct access to source data/documents. If study site's documents are electronic, these must be made available in their original form (or printouts signed and dated with the statement that this is complete and true reproduction of the original source document) if requested by the sponsor and/or regulatory authority. Study sites should inform Medtronic upon notification of an audit by a regulatory body immediately.

15.4 Confidentiality

All records and other information about subjects participating in this study will be treated as confidential. This means information about subjects participating in the study will be secured and protected from unauthorized access. Data will be key coded prior to use by Medtronic or any designated third-parties to reduce any risk of reidentification unless it's impossible to make it anonymous.

15.5 Liability

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.

15.6 CIP Amendments

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

- Medtronic
- An independent institutional review board

Similarly, approval of subsequent revisions to the CIP from the above mentioned groups is required prior to implementation of the revised CIP.

15.7 Record Retention

15.7.1 Investigator Records

Investigator record requirements can be found in each DEFINE AFib Study Addendum.

15.7.2 Sponsor Records

Sponsor record requirements can be found in each DEFINE AFib Study Addendum.

15.8 Reporting Requirements

15.8.1 Investigator Reports

Investigator report requirements can be found in each DEFINE AFib Study Addendum.

15.8.2 Sponsor Reports

Required sponsor reports are listed in Table 7 below.

Table 7: 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).
Final Report	Investigators, IRB/EC, regulatory authorities (if required per local regulations)	Sponsor final report including study analyses will be provided.

15.9 Publication and Use of Information

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

15.9.1 Publication Committee

The Define AFib study will utilize a Publication Committee which will include the Steering Committee members 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.

15.9.2 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.

15.9.3 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 "Define AFib 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.

15.9.4 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

15.10 Suspension or Early Termination

Early Suspension or Early termination, including study-wide or Investigator/Site suspension or early termination, requirements can be found in each DEFINE AFib Study Addendum.

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17. Version History

Version	Summary of Changes	Author(s)/Title
1.0 (not released to sites)	Not Applicable, New Document	Cody Johnson, Clinical Research Program Manager Katy Muckala, Clinical Study Manager, Sr. Clinical Research Specialist
2.0	Minor formatting/grammatical/syntax changes Clarified "electronic" signature Updated patient notification cadence Added "but not limited to" in LINQ data collection list Clarified Geofencing procedure Changed "Define Afib research app" to Medtronic's research app; updated section 6.1.2 with the planned app name	Cody Johnson, Clinical Research Program Manager Katy Muckala, Clinical Study Manager, Sr. Clinical Research Specialist
3.0	Updated to new template Minor formatting/grammatical/syntax changes Updated Study Sponsor Contact information	Cody Johnson, Clinical Research Program Manager

	Updated Clinical Study Type to be consistent and match regulatory determination Created DEFINE AFib Core CIP that is generic to all phases Clarified the electronic Consenting process Added in subject payments Clarified Study Level Deviations will be collected. All specifics to the Site Assisted Model moved to an Addendum Extended enrollment from 2 years to 3 years Updated EHR and Claims Data Source Updated 9.10 to reflect what device data patients have access to Updated Ancillary Objective #6 and #7 Removed reference to a run in phase since that did not occur due to slower than anticipated enrollments Updated Analysis Methods for clarification Updated Determination of Subjects/Data for Analysis as specifics will be provided in the Statistical Analysis Plan Updated Analysis methods for Ancillary Objective #1	Nancy McClelland, Clinical Study Manager, Principal Clinical Research Specialist
4.0	Administrative changes to clarify survey timing Combined Table 4 and 6 Added section 9.9.2.1 to separate out Dynamic Scheduled Surveys Removed the requirement to have completed all enrollment surveys to be included in the primary analysis – Section 13.3.2	Cody Johnson, Senior Clinical Research Program Manager Nancy McClelland, Clinical Study Manager, Principal Clinical Research Specialist

Medtronic

Clinical Investigation Plan Addendum
Site Assisted Phase

Clinical Investigation Plan/Study Title	DEFINE AFib Site Assisted Phase A part of the DEFINE AFib Study Platform
Clinical Investigation Plan Identifier	MDT20024
Study Product Name	Any market-released LINQ device Medtronic research application
Sponsor/Local Sponsor	Medtronic, Inc. 8200 Coral Sea Street NE Mounds View, MN U.S.A. 55112 Phone: 1-800-328-2518
Version	2.0, 29JUL2022 Comprised of: DEFINE AFib v4, 29JUL2022 DEFINE AFib Site Assisted Phase Addendum2.0, 29JUL2022
Lead Principal Investigator(s)	Dr. Jonathan Piccini Associate Professor of Medicine Duke University

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1. Glossary

Term	Definition
AE	Adverse Event
AF/AFib	Atrial Fibrillation
AHF	Acute Heart Failure
API	Application Programming Interface
App	A computer program or software application designed to run on mobile devices
CIP	Clinical Investigational Plan
CFR	Code of Federal Regulation
eCRF	Electronic Case Report Form
CTA	Clinical Trial Agreement
CV	Cardiovascular
DTL	Delegated Task List
EC	Ethics Committee
ECG	Electrocardiogram
EHR	Electronic Health Record
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HCU	Healthcare Utilization
HF	Heart Failure
HIPAA	Health Insurance Portability and Accountability Act
ICF	Informed Consent Form
ICM	Insertable Cardiac Monitor
iOS	an operating system used for mobile devices manufactured by Apple Inc.
IRB	Institutional Review Board
LINQ	May refer to Reveal LINQ, LINQ II, or future LINQ ICM, unless otherwise specified
MDT	Medtronic
NSR	Non-Significant Risk
PHI	Protected Health Information
IC	Informed Consent
QoL	Quality of Life
RAMware	Software downloaded onto LINQ™ device
RDC	Remote data capture
SpO2	Oxygen Saturation

2. Synopsis

Title	DEFINE AFib Site Assisted Addendum v1.0
Clinical Study Type	Prospective, observational, post-market study

Product Name	Reveal LINQ Insertable Cardiac Monitor or newer commercial model Medtronic research application
Sponsor	Medtronic Cardiovascular Diagnostics & Services
Local Sponsor	Medtronic, Inc. 8200 Coral Sea Street NE Mounds View, MN U.S.A. 55112 1-800-328-2518
Indication under investigation	Patients will be eligible to participate if they 1) have an existing market-released LINQ ICM; **and** 2) have received their LINQ ICM for the identification of AF (includes cryptogenic stroke, AF management, AF ablation, palpitations, or suspected AF; **and** 3) a self-reported history of AF. These conditions will be confirmed prior to study enrollment.
Investigation Purpose	The purpose of this study is to evaluate the association between complex patterns of device-detected AF and other summary and episodic measurements collected by the market-released LINQ ICM device and AF-related healthcare utilization, quality of life, AF-related symptoms, and specific clinical outcomes in patients with a market-released LINQ ICM. The Medtronic Discovery app will be used to collect data both (1) via the iPhone® through patient-reported health surveys and Bluetooth-enabled devices connected through the Apple Health app and (2) data accessed through or stored on the phone pertaining to health records, activity, and other lifestyle data. Secondarily, this study will examine associations between clinical procedures, medications and lifestyle actions taken and their impact on device-detected AF. Additionally, this study will help Medtronic evaluate patients' interaction with reports generated from health data collected by the market-released LINQ ICM. This study will improve our understanding of how data from the LINQ family of devices can be used to guide the management of AF patients.
Product Status	The study will be conducted using the components of the Medtronic Reveal LINQ or LINQ II system which are currently market-released in the participating geography (United States). Future LINQ devices may also be used, should a new iteration be released during the study. This study will also use an iPhone® app built using Apple ResearchKit to collect data both (1) via the iPhone® through patient-reported health surveys and Bluetooth-enabled devices connected through the Apple Health app and (2) data accessed through or stored on the phone pertaining to health records,

	activity, and other lifestyle data. This will require an iOS of 13.X or higher. EHR and claims data will be collected if the patient has connected their DEFINE AFib profile to their EHR or claims data through the Apple Health app. The app will also be used to provide patients visibility to select data collected by their market-released LINQ (and other future models), and to characterize patient preferences for viewing and interacting with device data. The iPhone® app will not directly communicate with any component of the Reveal LINQ or LINQ II system.
Primary Objective	To evaluate whether summary and episodic measurements collected by market-released LINQ ICMs are able to predict increased AF-related healthcare utilization (HCU) **Endpoint:** Confirmed healthcare visit in the inpatient hospital, outpatient hospital, clinic/office, emergency department, or other care location (including remote visits) where AF was a reason or suspected reason for healthcare interaction
[redacted]	[redacted]

	[redacted]
Study Design	DEFINE AFib is a prospective, observational post-market clinical study. This study will enroll approximately 5,000 patients in the United States who have a Reveal LINQ or LINQ II ICM (or future market-released LINQ devices) and an Apple iPhone® with iOS version 13.X or higher. Health and activity data will be collected from the iPhone® directly. A study application will be used to administer health-focused and QoL surveys to patients at variable time points. Additionally, patients will be provided a summary of their device-related data with

	subsequent patient experience surveys to understand how patients respond to and interact with their device data. Patients will be followed to either the end of their ICM service life or for up to five years.
Randomization	As this is an observational study, patients will not be randomized
Sample Size	Approximately 5,000 patients (see section 1 of the DEFINE AFib Core CIP v3.0)

Inclusion/Exclusion Criteria	Inclusion Criteria
	• Patients who have a self reported history of AF
	• Patients with a LINQ ICM who have received an ICM for the following device- logged indications, categorized into the following discreet groups:
	  ○ Stroke: Cryptogenic stroke indications
	  ○ AF management: AF management and post-ablation management indications
	  ○ Suspected AF: Suspected AF and palpitations indications
	• Individual Access and ability to use an Apple iPhone® compatible with Medtronic's research app (iOS v. 13.X or higher)
	• Patient is willing and able to comply with the protocol, including CareLink transmissions (requires adequate connectivity), remotely administered instructions, and remote survey participation
	• Patient is 22 years of age or older
	• Located in the United States, with CareLink managed through servers located in United States (50 states or District of Columbia)
	• Valid email address from self-report at enrollment
	• Patient must be able to read and write in English
	Exclusion Criteria
	Patients with > 24 months elapsed time from recorded LINQ device implant or > 48 months elapsed from recorded LINQ II implant date

Study Procedures and Assessments	Interested patients will complete a screening questionnaire to determine eligibility. Eligible patients will be invited to undergo an DEFINE AFib app-based electronic informed consent. Following consent, the app will guide patients through the completion of their research profile, including the enabling of data collection and will complete baseline medical history and quality of life surveys. Consent documents will be stored in the DEFINE AFib app on the iPhone®. A copy of the consent will also be stored on secure Medtronic servers for compliance purposes.

	Following consent, patients will be asked to review what data they are willing to share with the study sponsor. For approved data sources, data will be collected through the iPhone® applications on an ongoing basis (including but not limited to physical activity and electronic medical record information). Health, medication, symptom, and QoL surveys will be administered at variable timepoints based on LINQ ICM summary and episodic measurements, and the time interval since the last completed survey. Lastly, patients will be provided select data from their LINQ ICM device, with subsequent patient experience surveys to understand how patients respond to and interact with their device data. Patients will have the ability to terminate their participation at any time.
Safety Assessments	The collection of adverse events and device deficiencies are not required to meet the objective(s) of this study.

3. Study Site Requirements

3.1 Investigator/Investigation Site Selection

The role of the principal investigator is to implement and manage the day-to-day conduct of the clinical investigation as well as 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
- Disclose potential conflicts of interest, that interfere with the conduct of the clinical investigation or interpretation of results
- Maintain the Investigational Site File (ISF) at the site or for the entire network, if applicable
- Be able to demonstrate that the proposed investigational study site:
- Has the required number of eligible subjects needed within the recruitment period
- Has site personnel that can confirm patient-reported events via EHR
- Drive enrollment referrals within their network/site

- Ensure study site personnel training is completed and documented prior to participation in this study

3.2 Study Site Activation

During the activation process (prior to subject enrollment), Medtronic will train study site personnel on the clinical investigation plan, study flow, app overview, and relevant standards and regulations. 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. At a minimum, the principal investigator and site personnel responsible for confirming patient-reported events at the site or within the network will be trained.

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

- IRB approval (and voting list, as required by local law) of the current version of the CIP and ICF
- Fully executed CTA
- Documentation of delegated tasks
- Documentation of study training
- Documentation of completed Participating Sites and Clinics Form
- Additional requirements imposed by local regulations and the IRB shall be followed, as 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.

3.3 Role of the Sponsor Representatives

In addition to performing monitoring and auditing, Medtronic personnel may provide support as required for the study under supervision of the Principal Investigator, including:

Study training relevant and pertinent to the involvement of personnel conducting study activities and investigator responsibilities

Patient or physician education, support with app questions/resources, in compliance with IRB approved guidelines.

4. Selection of Subjects

4.1 Study Population

The DEFINE AFib study will enroll approximately 5,000 patients (see section 13.1 of the DEFINE AFib Core CIP v3.0) in the United States who have a Reveal LINQ or LINQ II ICM and an Apple iPhone®. Patients must have a history of AF.

4.2 Subject Enrollment

Institutional Review Board (IRB) and Medtronic approval will be obtained for this Clinical Investigation Plan, the informed consent form (ICF) and all other applicable study documents 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.

Patients will initially be recruited through official study sites and engaged healthcare networks, after the site or network has undergone its initiation. Patients may also be recruited through additional sites that qualify based on the study specifications.

When a patient has completed the eligibility survey (including the components to calculate a virtual CHA2DS2-VASc score) and electronically signed and dated the ICF via the study app, the patient is considered a subject enrolled in the study. Subjects must provide informed consent before any study related procedures occur (data collection). While vulnerable populations will not be targeted, there is no exclusion of vulnerable populations, other than those that do not meet inclusion/exclusion criteria.

The ICF and Authorization to Use and Disclose Personal Health Information will be electronic. A copy of the signed and dated ICF and Authorization documents will be available within the DEFINE AFib Research app for patient reference. An additional copy of the electronically signed and dated ICF and Authorization will be stored in a secure part 11 compliant system, access-controlled Medtronic database and shared with the primary investigator of that site or network.

4.3 Inclusion Criteria

- Patients who have a self-reported history of AF
- Patients with a Reveal LINQ or LINQ II ICM who have received an ICM for the following device logged indications, categorized into the following discreet groups:
    - Stroke: Cryptogenic stroke indication
    - AF management: AF management and post-ablation management indications
    - Suspected AF: Suspected AF and palpitations indications

- Individual access and ability to use an Apple iPhone® compatible with Medtronic's research app (iOS v. 13.X or higher)
- Patient is willing and able to comply with the protocol, including CareLink transmissions (requires adequate connectivity), remotely administered instructions, and remote survey participation
- Patient is 22 years of age or older
- Located in the United States, with CareLink managed through servers located in United States (50 states or District of Columbia)
- Valid email address self-reported at enrollment
- Patient must be able to read and write in English

4.4 Exclusion Criteria

Patients with > 24 months elapsed time from recorded LINQ device implant or > 48 months elapsed from recorded LINQ II implant date.

5. Study Procedures

5.1 Healthcare Utilization Confirmation

Healthcare utilization and modification to treatment or management of AF will be reviewed and confirmed via EHR by healthcare site personnel for subjects with available health records to compare to patient completed surveys. Trained and Delegated personnel will be sent patient reported outcomes via a part 11 compliant system for only the subjects that are part of their care network or clinic and asked to confirm patient HCU reports. There will be a standardized set of questions related to each HCU and/or medication/treatment change that includes whether or not the patient-reported utilization/change truly occurred. The reason and specific details for each visit will be recorded (as determined by the treating clinician in the EHR). If there are errors in the patient report, the designated site personnel will have the opportunity to record a correction stating the true events that happened upon a patient's visit to their affiliated health care facility. This process will also be used for all exits performed by the sponsor, as outlined in section 9 of the DEFINE AFib Core CIP v3.0. Site personnel will be asked to determine patient's mortality status along with any HCUs or medication/treatment changes/certain clinical outcomes since the last reported event. Non-confirmable events will be noted as such and will not contribute to the study's endpoints.

Table 7 Healthcare Utilization Definitions

Healthcare Utilizations (HCU)	All inpatient hospitalizations, outpatient hospital encounters, emergency department visits, clinic visits, urgent care visits, rehab center or other care location interactions (including remote visits)

CV-related HCU	A healthcare utilization relating to the heart and the blood vessels or the circulation (e.g., atrial fibrillation, myocardial infarction, stroke, peripheral vascular disease, heart failure).
AF-related HCU	HCU related to AF, suspected AF, AF treatment, or complications related to AF (including bleeding and drug toxicity as determined by treating clinician.
HF-related HCU	A healthcare utilization related to worsening heart failure signs and symptoms (as determined by treating clinicians) such as (but not limited to) hypervolemic and hypovolemic status requiring the administration, alteration, adjustment, or augmentation of HF therapy (diuretics, inotropes and/or vasodilators etc.) or the utilization of ultrafiltration devices.
Hospitalization	A therapeutic inpatient hospitalization (excludes outpatient and emergency room visits) lasting greater than or equal to 24 hours.
Non-hemorrhagic stroke	Rapid onset of a focal or global neurological deficit or other neurological signs/symptoms consistent with stroke; whereas focal, global cerebral or spinal dysfunction was NOT caused by a non-traumatic intraparenchymal, intraventricular, or subarachnoid hemorrhage, as determined by the treating clinician.
Systemic embolism	An embolus resulting in clinical and objective evidence of sudden loss of end organ perfusion.
TIA	New focal neurological deficit with rapid symptom resolution (usually 1 – 2 hours), always within 24 hours without tissue injury (based on neuroimaging) as determined by the treating clinician.

5.2 Subject Exit, Withdrawal or Discontinuation

Any subject who is exited by the sponsor will be assessed by the site to confirm mortality status and to document any HCUs or certain clinical outcomes observed since the last reported/confirmed HCU. If a death is found via site confirmation or EHR, the patient will be exited from the study.

6. Study Administration

6.1 Monitoring

It is the responsibility of Medtronic to ensure proper monitoring of this clinical study. Trained Medtronic personnel or delegates appointed by Medtronic may perform study monitoring at the study center or via remote monitoring in order to ensure that the study is conducted in accordance with the CIP, the Clinical Trial Agreement, and applicable regulatory requirements. Medtronic, or delegates, must therefore be allowed access to the subject's case histories upon request as per the Informed Consent Form and Clinical Trial Agreement. The Principal Investigator should also be available during onsite monitoring visits.

Frequency of monitoring visits may be based upon subject enrollment, duration of the study, study compliance, findings from previous monitoring visits and any suspected inconsistency in data that

requires investigation. Regulatory documents may be reviewed for each study center. Monitoring for the study, including site qualification and site initiation visits, interim monitoring visits, and closeout visits will be done in accordance with the Define AF monitoring plan.

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

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

Medtronic will request that study centers upload identified subject case history files and regulatory documents to a secure, password-protected website prior to remote monitoring visits.

6.2 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 confirmed patient-specific information, should be kept in the Investigator Site File (i.e., the study binder provided to the investigator) or Subject Study Binder. 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
- All records of patient-specific events' source documentation
- All approved versions of the CIP and informed consent form
- Fully executed Clinical Trial Agreement
- Study training records for site personnel
- Documentation of delegated tasks
- 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

6.3 Investigator Reports

The investigator is responsible for the following reports:

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.
Progress Report	Sponsor and IRB/EC and relevant authorities if applicable	The investigator must submit this report to the IRB per their institutional policies.
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.

6.4 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
- 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
- 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 (or waivers when applicable)
- Statistical analyses and underlying supporting data
- Final report of the clinical study
- The Clinical Investigation Plan and study related reports, and revisions
- Sample of data collection screens
- Any other records that local regulatory agencies require to be maintained

6.5 Suspension or Early Termination

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.

6.5.1 Study-wide Suspension or Early Termination

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

- Observed/suspected performance of study app different from the original intent
- Decision by Medtronic or regulatory body (where the study is operating under regulatory body authority)

6.5.2 Investigator/Site Suspension or Early Termination

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

- Failure to obtain initial IRB approval or annual renewal of the study approval
- Lack of enrollment
- Noncompliance to regulations and the terms of the Clinical Trial Agreement (e.g., failure to submit data in a timely manner)
- IRB 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)

6.5.3 Procedures for Suspension or Early Termination

Below procedures will apply in addition to any other specific requirement per local regulations.

Medtronic-initiated and regulatory authority-initiated

- Medtronic will promptly inform the clinical investigators of the termination or suspension and the reasons and inform the regulatory authority(ies) where required
- In the case of study termination or suspension for reasons other than a temporary EC approval lapse, the investigator will promptly inform the EC. A detailed written explanation of the termination or suspension will be provided, where required per regulatory requirements
- In the case of study termination, Medtronic will inform the subjects via the study app.
- 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

Investigator-initiated

- The investigator will immediately or promptly inform Medtronic and provide a detailed written explanation of the termination or suspension (Medtronic, in turn, will notify affected patients via the study app)
- The investigator will promptly inform the institution (where required per regulatory requirements)
- The investigator will promptly inform the EC, along with a detailed written explanation of the termination or suspension (where required per regulatory requirements)
- In the case of a study suspension, subjects enrolled should continue to be followed out of consideration of their safety, rights, and welfare

IRB-initiated

- The investigator will inform Medtronic and provide a detailed written explanation of the termination or suspension within 5 business days, or sooner if required per local requirements
- Subject enrollment must stop until the suspension is lifted
- Subjects already enrolled should continue to be followed in accordance with 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 Medtronic, who will in turn inform the subjects via the study app with the rationale for the study termination or suspension to ensure appropriate care and follow-up is provided

7. Version History

Version	Summary of changes	Author(s)/Title
1.0	Not Applicable, New Document	Nancy McClelland, Principal Clinical Research Specialist
2.0	• Removal of CHA2DS2-VASc1 score from inclusion criteria • Removed reference to requirement of Financial Disclosures since study is not following 21 CFR part 54 – administrative error it was included	Nancy McClelland, Principal Clinical Research Specialist