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Signed By	Meaning of Signature	Date/Time (UTC)
[redacted]		

Reveal LINQ Registry

Clinical Investigation Plan

Version 2.0

29 JAN 2016

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SPONSOR CONTACT INFORMATION

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

Table 1: Study Sponsor Contact Information

Study sponsors and contacts	
Worldwide clinical study leader Jen Diouf, Clinical Research Specialist [redacted]	*Europe, Central Asia / Middle East, Africa (ECA/MEA))* Silvia Giuli, Sr. Project and Clinical Research Specialist [redacted]
Japan Tomoyuki Tejima, Clinical Research Supervisor [redacted]	*China* Lauren Zhang, Clinical Research Manager [redacted]
Monitoring Contact Information	
Worldwide monitoring leader Taryn Randall, Clinical Monitoring Manager [redacted]	

OVERSIGHT COMMITTEE

An Oversight Committee will be utilized to provide oversight of study execution and evidence generation for the Reveal LINQ Registry. Additional members may be added at a later date. Any changes to the Oversight Committee membership will be provided under separate cover.

Table 2: Oversight Committee Contact Information

Committee Member	Contact information
Suneet Mittal, MD Coordinating Investigator	The Valley Hospital 1111 Amsterdam Ave Fl 3 New York, NY 10025 USA [redacted]
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Scott Kasner, MD, MSCE	Hospital of the University of Pennsylvania 3400 Spruce St. Philadelphia, PA 19104-4283 [redacted]

1. SYNOPSIS

Title

Reveal LINQ Registry

Purpose

The purpose of the Reveal LINQ Registry is to generate reliable long-term “real world” data of product performance, economic valuation, site-of-service procedural information, and will assist with identification of the Reveal LINQ™ Insertable Cardiac Monitor (ICM) in the care pathway.

Design

The study is a prospective, non-randomized, observational, multi-center, post-market, global study. The study will characterize clinical actions initiated by Reveal LINQ arrhythmia detection and estimate procedure-related acute infection rate. Approximately 2,300 subjects will be implanted with a Reveal LINQ ICM and be followed prospectively from insertion through 3 years.

Medical device

The Reveal LINQ Registry study will be conducted using the components of the Medtronic Reveal LINQ system, as described in the below.

Model Number	Component (Manufacturer)	Investigational or Market-released
LNQ11 or currently market released model	Reveal LINQ Insertable Cardiac Monitor	Market- released
2090 or currently market released model	Medtronic Programmer	Market- released
960000 or currently market released model	Patient Assistant	Market- released
24950 or currently market released model	MyCareLink® Patient Monitor	Market- released

Objectives

Primary Objectives:

- Characterize clinical actions initiated by Reveal LINQ arrhythmia detection
- Estimate procedure-related acute infection rate

Ancillary Objectives:

- Characterize healthcare utilization
- Characterize conditions diagnosed and clinical actions taken initiated by Reveal LINQ detection
- Characterize procedure-related acute infections
- Characterize onset and/or progression of diseases
- Summarize reasons for post-insertion modifications to Reveal LINQ

Subject population

The study is expected to be conducted at approximately 100 study sites globally with approximately 2,300 subjects contributing to total enrollment numbers. Participating geographies are expected to include, but are not limited to: the United States, Europe Middle East and Africa (EMEA), China and Japan. Subjects will be followed for 3 years or until study closure which is expected to be in January of 2021.

Inclusion criteria

- Subject or legally authorized representative provides written authorization and/or consent per institution and geographical requirements
- Subject is intended to have a Reveal LINQ ICM inserted in the next 30 days
- Subject consent prior to Reveal LINQ ICM insertion

Exclusion criteria

- Subject who is, or is expected to be inaccessible for follow-up
- Subject with exclusion criteria required by local law
- Subject is enrolled in a concurrent study that may confound the results of this study. Co-enrollment in any concurrent clinical study (including registries) requires approval of the study manager or designee.

Clinical Procedures

Data Collection Item(s)	Enrollment/ Baseline	Procedure	Follow-Up
Consent Form or Data Release Form Completion	X		
Inclusion/Exclusion Assessment	X		
Subject Demographics, Medical History	X		
Subject Arrhythmia/Symptom Status			X
Medications	X		X*
Treatments			X
Procedure Information		X	
Device Information		X	
Device/Monitor Data		X	X
AF Follow-Up			X**
AF Procedure and AF Status	Reported upon occurrence		
Adverse Events			
Device Deficiencies			
System Modification			
Study Deviations			
Subject Exit			
Subject Death			

*If applicable
**Only completed if the subject received an AF Ablation after Reveal LINQ ICM implant

2. INTRODUCTION

2.1 Study purpose

Medtronic, Inc. is sponsoring the Reveal LINQ Registry, a prospective, non-randomized, observational, multi-center, post-market, global clinical study.

The purpose of the Reveal LINQ Registry is to generate reliable long-term “real world” data of product performance, economic valuation, site-of-service procedural information, and will assist with identification of the Reveal LINQ Insertable Cardiac Monitor (ICM) in the care pathway. The primary endpoint will characterize clinical actions initiated by Reveal LINQ arrhythmia detection and estimate procedure-related acute infection rate.

The registry data is intended to benefit and support interests of patients, hospitals, clinicians, regulatory bodies, payers, and industry. Observational data collection in large populations over time provides an effective means of assessing product performance, patient safety and other clinical outcomes.

This post market registry is not required by any regulatory body. However, data collected in this registry may be submitted to a regulatory body for specific purposes when appropriate.

2.2 Study description

The study is expected to be conducted at approximately 100 study sites globally with approximately 2,300 subjects contributing to total enrollment numbers. Participating geographies are expected to include, but are not limited to: the United States, Europe Middle East and Africa (EMEA), China and Japan. Subjects will be followed for 3 years or until study closure which is expected to be in January of 2021.

To ensure a widespread distribution of data and minimize site bias in study results, the maximum number of subjects who may have a Reveal LINQ inserted at a single site is recommended to be fifteen percent (15%) of total projected enrollment in a given geography based on enrollment allocations. Sites that enroll faster than others will be allowed to do so in order to maintain an adequate overall study enrollment rate, but may not exceed the maximum number of insertions per site.

All subjects will be followed in-office in accordance with standard care practices of their respective care provider. Follow-up data collection is required at minimum every 6 months post-insertion and real time reporting is required for arrhythmia events and actions taken as a result of the Reveal LINQ ICM. This data may be collected via in-office subject clinic visit, remote monitor transmissions review, or chart review. Subjects are followed until subject death or exit, the implanted device becomes inactive or explanted, the subject has been followed for 3 years, or study closure which is expected to be in January of 2021.

3. BACKGROUND AND JUSTIFICATION

The Reveal LINQ™ programmable device is a subcutaneously Insertable Cardiac Monitor (ICM) designed to simplify the diagnosis, monitoring, and management of cardiac arrhythmias. The Reveal LINQ ICM is able to record cardiac arrhythmias including pause, bradycardia, and tachycardia episodes, specifically atrial fibrillation, asystole, bradycardia, fast VT and VT. The Reveal LINQ ICM has the capability to identify the detection and termination of all detected episodes. The identification and recording of these arrhythmias are essential in diagnosing and monitoring disease and its progression.

The Reveal LINQ ICM system is equipped with a number of features that enable ease of use. The size of the device has a volume of 1.2 cc which is 87% smaller than its predecessor Reveal XT. This small size facilitates a simple, minimally invasive insertion procedure using local anesthetic and not requiring the device to be internally fixated with sutures. In the Reveal LINQ Usability study, 90% of implantations were rated as easy or very easy.[1] These insertion procedures have a very high success rate on the first attempt with minimal complications. In an analysis of a controlled clinical trial and a real-world registry, the Reveal LINQ infection rate was 1.3 and1.6%, respectively and procedure-related serious adverse events were 0.7 and1.6% of patients.[2]

The Reveal LINQ ICM system has wireless and continuous monitoring capabilities and is able to store up to 59 minutes of ECG recordings. The data from these recordings is automatically transmitted daily via the patient's MyCareLink home monitor to Medtronic's CareLink network. The MyCareLink monitor performs the automatic transmission overnight when the patient is sleeping close to the monitor. If the automatic daily transmission was incomplete or not received, the patient has the option of performing a manual transmission which only lasts approximately 10 minutes. Nearly 97% of patients using the MyCareLink monitor in the LINQ Usability study indicated the monitor was "very easy to use".[3] Clinicians have the option to set up CareAlerts which will notify a clinician via CareLink based on pre-defined thresholds that a received transmission indicates a patient activated or device-detected episode (Pause, brady, tachy), low batter, or electrical reset.

The Reveal LINQ ICM has similar arrhythmia detection features compared to its predicate devices (Reveal DX®, Reveal XT®). However, Reveal LINQ has enhanced AF detection capabilities using the Reveal LINQ™ ICM P-SENSE algorithm. The original AF detection algorithm looked at differences in the pattern of R-R interval. The improved algorithm utilized in the Reveal LINQ ICM works on R-R interval regularity along with P-wave enhancements which improves accuracy by reduction in inappropriate AF detection potentially caused by noise, sinus tachycardia, etc..

Pürerfellner et al compared the original algorithm in the Reveal XT to the improved algorithm implemented in the Reveal LINQ ICM.[4] This study reported an overall performance with similar

1 Pürerfellner, Helmut, et al. "Miniaturized Reveal LINQ insertable cardiac monitoring system: First-in-human experience." *Heart Rhythm* 12.6 (2015): 1113-1119.
2 MITTAL, SUNEET, et al. "Safety Profile of a Miniaturized Insertable Cardiac Monitor: Results from Two Prospective Trials." *Pacing and Clinical Electrophysiology* 38.12 (2015): 1464-1469.
3 Pürerfellner, Helmut, et al. "Miniaturized Reveal LINQ insertable cardiac monitoring system: First-in-human experience." *Heart Rhythm* 12.6 (2015): 1113-1119.
4 Pürerfellner, Helmut, et al. "P-wave evidence as a method for improving algorithm to detect atrial fibrillation in insertable cardiac monitors." *Heart Rhythm* 11.9 (2014): 1575-1583.

device sensitivity and included a reduction in total duration of false positives by 55%, a reduction in total number of false positives by 46%. In addition, the study reported that episodes with ≥ 1 hour in duration have 100% sensitivity and a 95% positive predictive value. With the advancement in AF detection utilizing the P-SENSE algorithm in the Reveal LINQ™ ICM device, detection of AF is more accurate allowing clinicians to better manage patients with all types of AF including that which is symptomatic or asymptomatic.

While indication for use varies across geographies, use of ICM devices has been effectively utilized to monitor various types of arrhythmias to provide data for various conditions. One common use is in patients with suspected cardiac causes of syncope. The actual diagnosis of syncope can be difficult requiring conventional testing (Holter + tilt table) and be resource intensive; however, using ICM with remote monitoring is superior to these methods (52% vs. 20%, p = 0.012).[5] In addition, ICMs have proven to be helpful in guiding diagnosis recurrent syncope events.[6]

Another common use is using ICMs as part of a stroke primary prevention strategy (identification of AF to inform clinical decisions). Worldwide 15 million people suffer a stroke resulting in 5 million deaths and leaving 5 million others with permanent disabilities each year.[7] The presence of AF is a risk factor for stroke increasing the risk of stroke by 5-fold.[8 9 10] Furthermore, device-detected AF burden has been associated with an increase ischemic stroke risk.[11 12 13] Leveraging the Reveal LINQ™ ICM to correctly identify the total AF duration of AF[14] may be effectively used to manage patients at risk for stroke.

Similarly, ICMs have been proven to be beneficial in the management of patients with cryptogenic stroke. Around 20% to 40% of strokes are cryptogenic in nature where the mechanism cannot be identified despite extensive evaluation.[15] The ability to detect AF in cryptogenic stroke is important

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5 Krahn, A. D., et al. "Randomized assessment of syncope trial (RAST): Conventional investigations vs. Implanted loop recorder." *Circulation*. Vol. 102. No. 18. 530 WALNUT ST, PHILADELPHIA, PA 19106-3621 USA: LIPPINCOTT WILLIAMS & WILKINS, 2000.

6 Edvardsson, Nils, et al. "Use of an implantable loop recorder to increase the diagnostic yield in unexplained syncope: results from the PICTURE registry."*Europace* 13.2 (2011): 262-269.

7 World Heart Federation. http://www.world-heart-federation.org/cardiovascular-health/stroke/

8 Wolf PA, Dawber TR, Thomas HE Jr, Kannel WB. Epidemiologic assessment of chronic atrial fibrillation and risk of stroke: The Framingham study. *Neurology.* 1978;28(10):973-977.

9 Wolf PA, Abbott RD, Kannel WB. Atrial fibrillation as an independent risk factor for stroke: the Framingham Study. *Stroke*. 1991;22(8):983-988.

10 Wang TJ, Massaro JM, Levy D, Vasan RS, Wolf PA, D'Agostino RB, Larson MG, Kannel WB, Benjamin EJ. A risk score for predicting stroke or death in individuals with new-onset atrial fibrillation in the community: The Framingham Heart Study. *JAMA*. 2003;290(8):1049-1056.

11 Glotzer, Taya V., et al. "The Relationship between daily atrial tachyarrhythmia burden from implantable device diagnostics and stroke risk the trends study." *Circulation: Arrhythmia and Electrophysiology* 2.5 (2009): 474-480.

12 Kaufman, Elizabeth S., et al. "Positive predictive value of device-detected atrial high-rate episodes at different rates and durations: an analysis from ASSERT." *Heart Rhythm* 9.8 (2012): 1241-1246.

13 Boriani, Giuseppe, et al. "Device-detected atrial fibrillation and risk for stroke: an analysis of> 10 000 patients from the SOS AF project (Stroke preventiOn Strategies based on Atrial Fibrillation information from implanted devices)." *European heart journal* 35.8 (2014): 508-516.

14 Pürerfellner, Helmut, et al. "P-wave evidence as a method for improving algorithm to detect atrial fibrillation in insertable cardiac monitors." *Heart Rhythm* 11.9 (2014): 1575-1583.

15 Guercini F, Acciarresi M, Agnelli G, Paciaroni M. Cryptogenic stroke: time to determine aetiology. *J Thromb Haemost*. 2008;6(4):549-554.

as AF detection may prompt a change from antiplatelet to anticoagulation medication[16 17 18]. ICM's are superior at yielding an AF diagnosis when compared to standard monitoring in patients with a history of cryptogenic stroke and without a history of AT/AF.[19]

A third use of an ICM device is to monitor arrhythmias in patients with a history of AF and ablation. AF ablation efficacy at one year has been reported to be 66% to 89%.[20] Arrhythmia monitoring of AF patients post-ablation has been shown to be of value in both symptomatic and asymptomatic patients to help guide long-term treatment decisions.[21] Using Reveal LINQ ICM may be an optimal strategy for deciding whether to perform a second ablation or to implement drug therapy in patients with recurrences after their first ablation.

The evidence collected during the Reveal LINQ Registry trial will provide information necessary to inform current and future clinical practice for patients implanted with the Reveal LINQ ICM. A better understanding of the incorporation of Reveal LINQ ICM in the current care pathway and understanding the clinical actions to treat patients with arrhythmias will be observed.

16 Adams Jr HP, del Zoppo G, Alberts MJ, et al. Guidelines for the early management of adults with ischemic stroke: a guideline from the American Heart Association/ American Stroke Association Stroke Council, Clinical Cardiology Council, Cardiovascular Radiology and Intervention Council, and the Atherosclerotic Peripheral Vascular Disease and Quality of Care Outcomes in Research Interdisciplinary Working Groups: the American Academy of Neurology affirms the value of this guideline as an educational tool for neurologists. *Circulation.* 2007;115:e478-e534.

17 Sacco R. Guidelines for prevention of stroke in patients with ischemic stroke or transient ischemic attack. A statement for healthcare professionals from the American Heart Association/American Stroke Association Council on Stroke. *Stroke.* 2006;37:577-617.

18 The European Stroke Organisation (ESO) Executive Committee, ESO Writing Committee. Guidelines for management of ischaemic stroke and transient ischaemic attack 2008. *Cerebrovasc Dis*. 2008;25:457-507.

19 Sanna, Tommaso, et al. "Cryptogenic stroke and underlying atrial fibrillation."*New England Journal of Medicine* 370.26 (2014): 2478-2486.

20 Calkins H, Kuck KH, Cappato R, Brugada J, Camm AJ, Chen SA, Crijns HJ, Damiano RJ Jr, Davies DW, DiMarco J, Edgerton J, Ellenbogen K, Ezekowitz MD, Haines DE, Haissaguerre M, Hindricks G, Iesaka Y, Jackman W, Jalife J, Jais P, Kalman J, Keane D, Kim YH, Kirchhof P, Klein G, Kottkamp H, Kumagai K, Lindsay BD, Mansour M, Marchlinski FE, McCarthy PM, Mont JL, Morady F, Nademanee K, Nakagawa H, Natale A, Nattel S, Packer DL, Pappone C, Prystowsky E, Raviele A, Reddy V, Ruskin JN, Shemin RJ, Tsao HM, Wilber D; Heart Rhythm Society Task Force on Catheter and Surgical Ablation of Atrial Fibrillation. 2012 HRS/EHRA/ECAS expert consensus statement on catheter and surgical ablation of atrial fibrillation: recommendations for patient selection, procedural techniques, patient management and follow-up, definitions, endpoints, and research trial design: a report of the Heart Rhythm Society (HRS) Task Force on Catheter and Surgical Ablation of Atrial Fibrillation. *Heart Rhythm*. 2012;9(4):632-696.

21 Calkins H, Kuck KH, Cappato R, Brugada J, Camm AJ, Chen SA, Crijns HJ, Damiano RJ Jr, Davies DW, DiMarco J, Edgerton J, Ellenbogen K, Ezekowitz MD, Haines DE, Haissaguerre M, Hindricks G, Iesaka Y, Jackman W, Jalife J, Jais P, Kalman J, Keane D, Kim YH, Kirchhof P, Klein G, Kottkamp H, Kumagai K, Lindsay BD, Mansour M, Marchlinski FE, McCarthy PM, Mont JL, Morady F, Nademanee K, Nakagawa H, Natale A, Nattel S, Packer DL, Pappone C, Prystowsky E, Raviele A, Reddy V, Ruskin JN, Shemin RJ, Tsao HM, Wilber D; Heart Rhythm Society Task Force on Catheter and Surgical Ablation of Atrial Fibrillation. 2012 HRS/EHRA/ECAS expert consensus statement on catheter and surgical ablation of atrial fibrillation: recommendations for patient selection, procedural techniques, patient management and follow-up, definitions, endpoints, and research trial design: a report of the Heart Rhythm Society (HRS) Task Force on Catheter and Surgical Ablation of Atrial Fibrillation. *Heart Rhythm*. 2012;9(4):632-696.

4. SYSTEM DESCRIPTION AND INTENDED USE

The study will be conducted using the components of the Medtronic Reveal LINQ system which are currently market-released in the participating geography, as described in Table 3 below. The Reveal LINQ system is being used in accordance with the geography indications for the device.

US Indications

The Reveal LINQ Insertable Cardiac Monitor is an implantable patient-activated and automatically-activated monitoring system that records subcutaneous ECG and is indicated in the following cases:

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

OUS Indications (EMEA, China)

The Reveal LINQ Insertable Cardiac Monitor is an implantable patient-activated and automatically-activated monitoring system that records subcutaneous ECG and is indicated in the following cases:

- Patients with clinical syndromes or situations at increased risk of cardiac arrhythmias
- Patients who experience transient symptoms that may suggest a cardiac arrhythmia

Table 3: Reveal LINQ System Component Information

Model Number	Component (Manufacturer)	Investigational or Market-released
LINQ11 or currently market released model	Reveal LINQ Insertable Cardiac Monitor	Market-released
2090 or currently market released model	Medtronic Programmer	Market-released
960000 or currently market released model	Patient Assistant	Market-released
24950 or currently market released model	MyCareLink Patient Monitor	Market-released

4.1 Reveal LINQ System

The Reveal LINQ system consists of 4 main components as illustrated in Table 3.

The Medtronic Reveal LINQ ICM is a programmable device that continuously monitors a patient's ECG and other physiological parameters. The device records cardiac information in response to automatically detected arrhythmias and patient activation.

The 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.

Reveal LINQ ICM: is a small, leadless device that is inserted under the skin, in the chest. Two electrodes on the body of the device monitor the patient's subcutaneous ECG continuously. 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.

Medtronic Programmer: is used to set up the device to detect arrhythmias. It also allows the user to view, save, or print the information stored by the device.

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.

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. Patient interaction with their monitor includes the initial setup procedure, performing physician-requested data gathering, and responding to physician-specified notifications on the monitor screen. Refer to the literature that is included with the MyCareLink Patient Monitor for connection and usage information.

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

5. REGULATORY COMPLIANCE

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

The registry is designed to reflect the GCP and other international clinical requirements outlined below. These include the protection of the rights, safety and well-being of human subjects, controls to ensure the scientific conduct and credibility of the study and the definition of responsibilities of the sponsor and investigators.

The study will be conducted according to federal, national and local laws, regulations, standards, and requirements of the countries/geographies where the study is being conducted and this clinical investigation plan (CIP), and the Clinical Trial Agreement (CTA) at each site. The study will also be conducted in accordance with the Declaration of Helsinki (most current version) outside of the United States. The principles of the Declaration of Helsinki have been implemented through the patient informed consent (IC) process, the subject data release process, Ethics Committee approval or a written statement by the Ethics Board Chairperson stating approval is not required, study training, clinical trial registration, risk benefit assessment and publication policy.

In addition:

- In the US, the study will be conducted in compliance with 21 CFR Parts 11 (Electronic Records; Electronic Signatures), 50 (Protection of Human Subjects), and 56 (Institutional Review Boards (IRBs)).
- In EMEA, local laws and regulations will be followed
- In Japan, Ethical Guidelines for Medical and Health Research Involving Human Subjects will be followed.

For additional countries added at a later time, local laws and regulations will be followed. Geography-specific requirements will be documented under a separate cover.

The study will be publicly registered 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)). The study will be also registered in national databases of participating geographies as required.

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

- Medtronic
- Principal Investigators (where required by local law)
- Geography-specific regulatory authorities (if regulatory approval is required)
- An independent Ethics Committee.

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

For any subject recruitment materials, documented approval of each site's Ethics Committee must have been received prior to use in the study, if applicable.

6. METHODOLOGY

Study objectives

The Reveal LINQ Registry will characterize clinical actions and procedure related data in subjects implanted with Medtronic Reveal LINQ ICM.

The study is observational in nature. Sample size calculations for the study objectives provide information on the reliability of the estimates. At the same time, data analysis may be carried out throughout the study without having all enrolled subjects completing study required follow-ups.

6.1 Primary Objectives

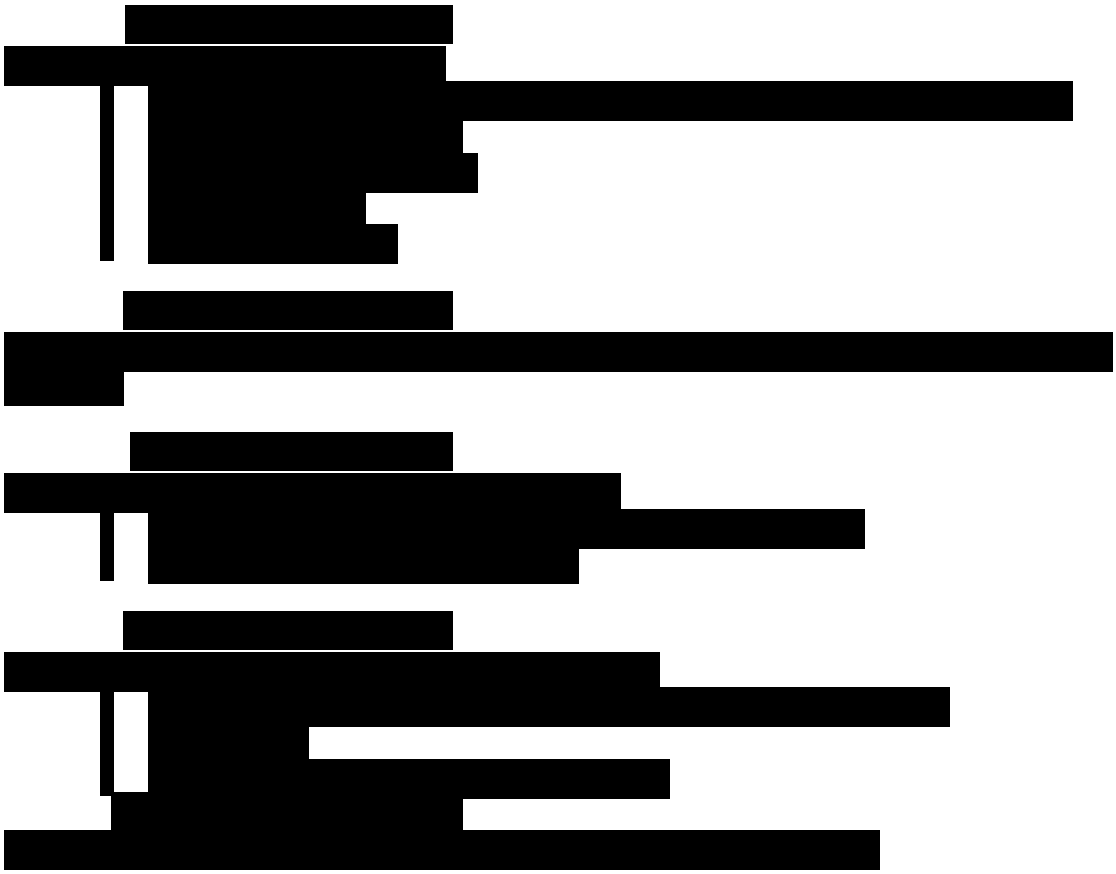
i. Primary objective #1

Characterize clinical actions initiated by Reveal LINQ arrhythmia detection feature.

ii. Primary objective #2

Estimate procedure-related acute infection rate (up to 30 days post insertion procedure).

6.2 [redacted]



6.3 Subject selection criteria

Patients will be screened to ensure they meet all of the inclusion and none of the exclusion criteria prior to study enrollment. Ethics Committee approval of the Reveal LINQ Registry Clinical Investigation Plan and Informed Consent Form (ICF) or Data Release Form (DRF) must be obtained prior to enrolling patients in the study.

Subjects are considered enrolled in the study upon signing the ICF or DRF. Enrollment of the subject must occur before insertion of the Reveal LINQ ICM.

viii. Inclusion criteria

- Subject or legally authorized representative provides written authorization and/or consent per institution and geographical requirements
- Subject is intended to have a Reveal LINQ ICM inserted in the next 30 days
- Subject consent prior to Reveal LINQ ICM insertion

ix. Exclusion criteria

- Subject who is, or is expected to be inaccessible for follow-up
- Subject with exclusion criteria required by local law
- Subject is enrolled in a concurrent study that may confound the results of this study. Co-enrollment in any concurrent clinical study (including registries) requires approval of the study manager or designee.

6.4 Minimization of Bias

The following methods have been incorporated to minimize potential bias:

- Subjects will be confirmed eligible for enrollment with defined Inclusion/Exclusion criteria.
- Demographics and medical history will be collected at baseline in order to later assess possible characteristics that may influence endpoints.
- To ensure a widespread distribution of data from study sites, no more than 15% of total expected insertions may come from a single site in a given geography based on enrollment allocations.
- All study site and Medtronic personnel will be trained using standardized training materials.
- Regular monitoring visits will be conducted to verify source data and adherence to the Clinical Investigation Plan

7. STUDY PROCEDURES

Prior to performing study related procedures, all sites must have Ethics Board/IRB/MEC approval or a written statement by the Principal Investigator/Ethics Board Chairperson stating approval is not required and associated regulatory authority approval if applicable (e.g., Competent Authority approval) as well as documentation from Medtronic of site readiness.

7.1 Role of the sponsor representatives

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

- Provide study training relevant and pertinent to the involvement of personnel conducting study activities and investigator responsibilities
- Technical support during the insertion procedure and follow-up under the supervision of a study investigator as part of standard of care, but no data entry, shall be performed by Medtronic personnel or their representatives at sites

7.2 Investigator / Investigation site selection

Sites participating in the study are located globally. At a minimum, the following criteria will be met before sites are selected for participation:

The principal investigator shall:

- Be qualified by education, training, and experience to assume responsibility for the proper conduct of the clinical investigation
- Be experienced in the diagnoses and treatment of patients receiving Reveal LINQ ICM
- Disclose potential conflicts of interest that interfere with the conduct of the clinical investigation or interpretation of results

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

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

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

7.3 Site activation

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

Prior to enrolling any patients into the study, sites must fulfill all local law and regulatory requirements. The term Ethics Board will be used to define Institutional Review Board (IRB), Medical Ethics Committee (MEC), Research Ethics Board (REB), or Human Research Ethics committee (HREC). Participation readiness includes, but is not limited to:

- Documented Ethics Board and sponsor approval of the current version of the CIP and Patient Informed Consent or Data Release Form (if required) and voting list, as required by local law
- A legally executed Clinical Trial Agreement (CTA)
- Insurance certificates (as required per geography)
- Applicable Regulatory Approval (as required per geography)
- Documentation of study training, including training on the CIP, informed consent process and data collection tools depending on the responsibilities
- Documentation of delegated tasks
- Curriculum Vitae (CV) of investigators and key members of the investigation site team (as required by law)

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

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

Upon site readiness, the site will be provided with the Investigator Site File for filing of the study documentation, and database access will be granted for the investigator and each authorized designee. Medtronic will provide each study site with documentation of study site/investigator readiness; this letter must be received prior to subject enrollment.

7.4 Data collection

Data collection requirements are summarized in Table 4 below.

Table 4: Summary of Data Collection

Data Collection Item(s)	Enrollment/ Baseline	Procedure	Follow-Up
Consent Form or Data Release Form Completion	X		
Inclusion/Exclusion Assessment	X		
Subject Demographics, Medical History	X		
Subject Arrhythmia/Symptom Status			X
Medications	X		X*
Treatments			X
Procedure Information		X	
Device Information		X	
Device/Monitor Data		X	X
AF Follow-Up			X**
AF Procedure and AF Status	Reported upon occurrence		
Adverse Events			
Device Deficiencies			
System Modification			
Study Deviations			
Subject Exit			
Subject Death			

*If applicable
**Only completed if the subject received an AF Ablation after Reveal LINQ ICM implant

7.5 Patient Informed Consent process

Patient Informed Consent is defined as legally effective, documented confirmation of a patient's (or their legally authorized representative or guardian) voluntary agreement to participate in a particular clinical study after information has been given to the patient on all aspects of the clinical study that are relevant to the subject's decision to participate in the clinical study. The Patient Informed Consent Form (PIC) or Data Release Form (DRF) is signed only after all relevant information regarding participation has been provided to the patient.

Patient Informed Consent will be obtained in accordance with local law and regulations. The PIC or DRF and in the US only an Authorization for Access to and use of Health Information

(HIPAA) must be approved by the sponsor and the site's Ethics Board unless an Ethics Board waiver for consent is obtained.

In addition, the documents referenced must be maintained in such a way as to assure control for the document (i.e. version and/or date) such that the version(s) approved by the Ethics Board are clear with a documented change history for all revisions.

The process for obtaining informed consent shall:

- Ensure that the principal investigator or an authorized designee conducts the PIC process.
- Include all aspects of the clinical study that are relevant to the patient's decision to participate throughout the clinical study.
- Avoid any coercion of, or undue improper influence on or inducement of patients to participate
- Not waive or appear to waive patient's legal rights
- Ensure the PIC and Authorization to Use and Disclose Personal Health Information/Research Authorization/HIPAA/other privacy language as required by law are given to the subject (or their legally authorized representative or guardian) in a non-technical language the patient is able to read and understand.
- Provide documents to the patients in a language s/he is able to read and understand
- Provide ample time for the patient to read and understand the patient informed consent form and to consider participation. All questions about the clinical study should be answered to the satisfaction of the patient.
- Include a personally dated signature of the patient or legal representative acknowledging that their participation in the clinical study is voluntary
- Include a personally dated signature by the responsible clinician (if required by local law).
- Include any other locally required signatories, such as witnesses, as indicated by country-specific legislations.
- In addition to the requirement of obtaining written informed consent,
- Ensure the subject (or their legally authorized representative or guardian) are notified of any significant new findings about the study that become available during the course of the study which are pertinent to the safety and well-being of the subject, as this could impact a subject's willingness to participate in the study.

In the event that the patient cannot read or write, a witnessed (impartial third party) PIC or DRF and authorization/data protection will be allowed (as determined by local law), provided detailed documentation of the process is recorded in the patient's case history and the witness signs and dates the appropriate PIC or DRF and the authorization.

The PIC shall be obtained through a supervised oral process. An independent witness must be present throughout the process. The PIC and any other information must be read aloud and explained to the prospective subject or his/her legally authorized representative. The witness signs and personally dates the PIC attesting that the information was accurately explained and that informed consent was freely given. The subject should "make his mark" (sign or otherwise physically mark the document so as to indicate consent) on the PIC as well. The PIC should document the method used for communication with the prospective subject and the specific means by which the prospective subject communicated agreement

to participate in the study. The original of the signed and dated PIC must be filed in the hospital/clinical chart or with the subject's study documents.

The PIC and Authorization to Use and Disclose Personal Health Information/Research Authorization/other privacy language as required by law must be available for monitoring and auditing.

Any designated Medtronic personnel who support the procedure must be able to review the subject's signed and dated PIC and verify its completeness prior to proceeding with the procedure. In the event the designated Medtronic personnel identify PIC as being incomplete, the procedure will not be allowed to occur until the consent of the subject can be adequately and appropriately obtained.

Unless waived by the Ethics Board (geography specific) the signed PIC or DRF and the authorization (US only) must be filed at the center. A copy of the signed and dated PIC must be provided to the patient. The original signed PIC or DRF and the authorization (US only) or other privacy language where required by law must be retained and made available for review by site monitors, auditors, or inspectors. All important new information should be provided in written form to new and existing subjects throughout the study. If relevant, all affected subjects must be asked to confirm their continuing informed consent in writing.

The consent process should be documented at each site with a progress note in the patient's case history.

Prior to initiation of any study-specific procedures, patient informed consent must be obtained from the subject (or their legally authorized representative). If the PIC is obtained the same day the subject begins participating in study-related procedures, it must be documented in the subject's case history that consent was obtained prior to participation in any study-related procedures.

DRF and PIC templates will not be automatically updated with a protocol amendment unless the protocol changes impact the elements of the PIC or DRF. Medtronic must approve any adaptation of the templates prior to use in consenting patients. For all sites requiring a Patient Informed Consent the Ethics Board and Medtronic must approve the final PIC prior to use in consenting prospective patients.

7.6 Enrollment

Enrollment of a patient is complete once consent (DRF or PIC) and an Authorization (geography specific) have been obtained. Additionally, the signature date will be collected at consent on the DRF or PIC. The subject must consent prior to insertion and be intended to have a Reveal LINQ ICM inserted within the next 30 days.

A subject ID log must be maintained and the hospital patient file must be marked to indicate that subject's enrollment in the clinical study (if required by local law/regulations).

7.7 Baseline

The baseline visit can be a standalone visit or can be performed on the same day as enrollment, but the visit must be prior to the insertion procedure.

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

- Inclusion/Exclusion Assessment
- Subject Demographics, Medical History
- Medications

7.8 Procedure

The insertion procedure will be performed in accordance with the standard insertion practice and in accordance with the Medtronic Reveal LINQ insertion instructions which are located within the respective clinician manual. The following information is required to be collected during the procedure visit:

- Procedure information (physician, location of procedure, duration, procedure technique, etc.)
- Device information (model, serial numbers, etc.)
- Device/Monitor Data
    - Submit device data via CareLink transmission, or transfer from a programmer printout to the eCRF
- Adverse Events assessment

7.9 Subject Follow-up

All subjects are followed in-office in accordance with the standard care practices of their respective care provider. However, in addition to the scheduled follow up visits, real time reporting is required for arrhythmia events and actions taken. Follow-up data collection is required at minimum every 6 months (+/- 3 months) post-insertion as shown in Figure 1.

The following information will be collected within the follow-up windows shown in Figure 1:

- Subject Arrhythmia/Symptom Status
- Treatments
    - Assess subject status and/or review subjects medical records for occurrence of any of the following treatments and indicate whether they were triggered by the Reveal LINQ ICM data review or any other reason:
        - AF ablation
        - Cardioversion (electrical and/or pharmacological)
        - Implant of cardiac rhythm system

        - Medication changed/administered
        - Revascularization (PCI and/or CABG)
        - Or other cardiac treatment
- Device/Monitor Data
    - New Diagnoses as a result of Reveal LINQ ICM data
    - Actions taken as a result of monitor data review
    - Submit complete device data via device transmission (i.e., CareLink), or transfer from a printout to the eCRF
- Medications (if the subject received an AF Ablation since Reveal LINQ ICM implant)
- Imaging testing results
    - Medtronic requests that the site send any copies of these test results completed as part of standard of care by the time the subject is exited from the study
- Adverse Events Assessment

7.9.1 Follow-up Due to AF Ablation

Subject follow-up may also include:

- Ablation Procedure
    - Collected for each ablation procedure that occurs post Reveal LINQ ICM insertion
        - Payer information
        - Heart Rhythm Status
        - Procedure Information
        - Ablation Strategy
        - Device Information
        - Imaging/Navigation
        - Procedure Results
        - Discharge
        - Adverse Event Assessment
- AF follow-up
    - If an AF ablation(s) occurred after Reveal LINQ ICM insertion, AF follow-up information is collected at all follow-up visits
        - Recurrent atrial arrhythmias
        - AF ablation related adverse event assessment and description
- AF Status
    - If an AF ablation(s) occurred after Reveal LINQ ICM insertion, AF status is collected at follow-up visits in which the subject experienced recurrent atrial fibrillation since the previous follow-up
        - AF Status details
        - Cardiac Medications History

7.9.2 Modes of Data Collection

The study employs multiple methods of data collection to ensure the most robust and reliable registry dataset is available. Modes of collection may include such methods as:

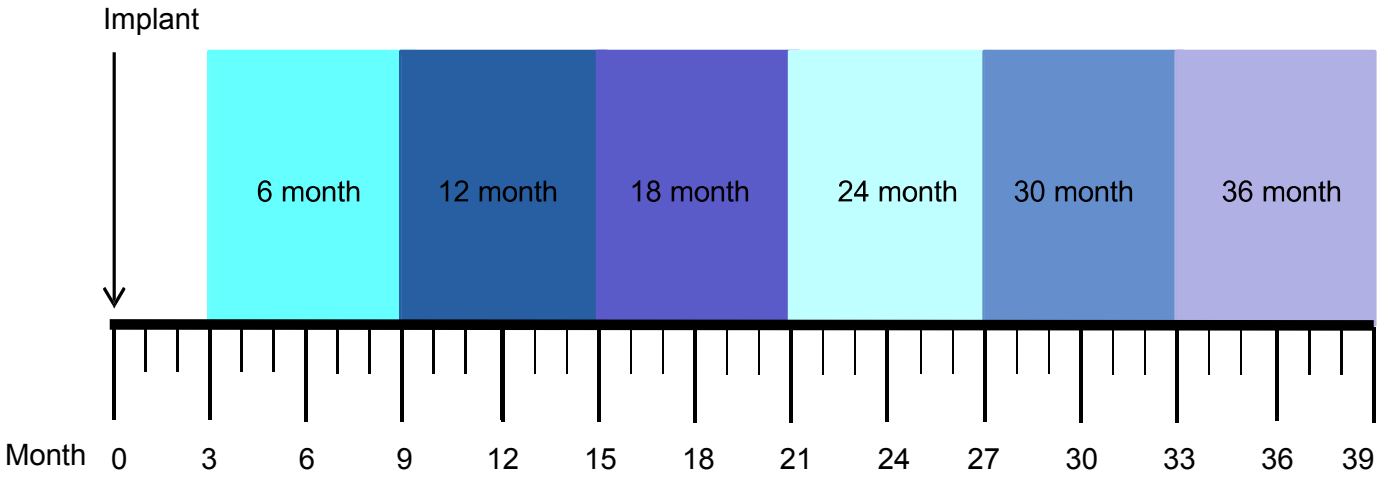
- In-office subject clinic visit
- Remote monitor transmissions (e.g., CareLink) review with no subsequent in-office assessment

- Chart review for reportable events

7.9.3 *Frequency of Follow-up*

Follow-up data collection as described in section 7.9.2 is required at minimum every 6 months (+/- 3 months) post-insertion as shown in Figure 1. These follow-up windows ensure regular subject status assessments are completed. Data may be collected more than once within each designated follow-up window.

Figure 1 Minimum* Required Reveal LINQ Registry Follow-up Schedule



* In addition to the scheduled follow up visits, real time reporting is required for Arrhythmia Events and Actions Taken. Data may be collected more than once within each designated follow-up window.

7.9.4 *Arrhythmia Event and Action Taken Assessment (ongoing)*

Data may be collected more than once within each designated follow-up window as real time reporting is required for Arrhythmia Events and Actions Taken.

- Arrhythmia Event
  - Regardless if action is taken, any time a new arrhythmia is recorded on the device a follow-up form is required
- Action Taken
  - If an action is taken as a result of an arrhythmia, a follow-up form is required. Actions include:
    - Medication change
    - Treatment
      - AF ablation
      - Cardioversion (electrical and/or pharmacological)
      - Implant of cardiac rhythm system
      - Medication changed/administered
      - Revascularization (PCI and/or CABG)
      - Or other cardiac treatment
    - Diagnostic work up
      - CT/MRI/PET Scan, X-Ray/Fluoroscopy, Cardiac Catheterization, Biopsy, Echocardiogram, Exercise Stress Test, Venous Ultrasound,

Radionuclide ventricular cardiography/MUGA, Tilt test, electrongencephalography (EEG), Electromyography (EMG), Laboratory test, Doppler of carotids/intracerebral arteries and other

7.9.5 Follow-up Duration

Subjects are followed until:

- Death or exit,
- Implanted device becomes inactive or explanted (with no related adverse events pending further treatment) , or
- Subject has been followed for a minimum of 3 years (i.e. 1096 days)

7.10 System Modification

A system modification will be reported if the Reveal LINQ ICM requires modification (e.g. explant, repositioning, replacement, etc.). In the event of a system modification, the follow-up schedule for the subject will remain unchanged. At a minimum the following types of data are collected for a system modification procedure:

- General relevant modification information (reason for modification, actions taken)
- Device information (model, serial numbers, etc.)
- Events assessment

A procedure report should be obtained to ensure all available modification information including any reportable adverse events are submitted.

In the event of a system modification, the follow-up schedule for the subject will remain unchanged unless the modification results in the subject no longer being study eligible in which case the subject must be exited from the study. Sites should make every effort to return all explanted devices.

It is recommended that all products be returned when possible for analysis. Procedures for returning products vary by geographic location. Please contact your local Medtronic field representative for more information or to obtain prepaid postage mailer kit.

7.11 Study Exit

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

Subjects may be exited from the study under the following circumstances:

- Study Closure
- Lost to follow-up

- No eligible product was implanted
- Inclusion/Exclusion criteria not met
- Subject chooses to withdraw (e.g. consent withdrawal)
- Physician deems withdrawal necessary (e.g. medically justified, failure of subject to maintain adequate study compliance)
- Reveal LINQ system is inactive
- Subject has been followed for 3 years

The following information is required to be collected at study exit on the study exit e-CRF:

- Date of exit
- Reason for exit

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

7.12 Subject Death

All deaths must be reported to Medtronic as soon as possible after the clinician/site coordinator first learns of the death.

Death Classification

Cause of death will be reported along with the clinician's assessment of product relatedness (See Appendix G for definitions)

Death Data Collection

For all subject deaths deemed to be product related, sufficient supporting documentation will be required in order to properly adjudicate and classify the subject's death. Provide as much of the following information as possible:

- Death certificate (if allowed by state/local law)
- Death summary/hospital records (if allowed by state/local law)
- Autopsy report (if allowed by state/local law)
- Device Data if applicable and available

Further supporting evidence that is not originally provided by the site may be requested by Medtronic to aid in the adjudication of the death.

8. STUDY DEVIATIONS

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

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

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

All study deviations must be reported on the Study Deviation e-CRF regardless of whether medically justifiable, pre-approved by Medtronic, an inadvertent occurrence, or taken to protect the subject in an emergency. The deviation description must be recorded with an explanation for the deviation. In the occurrence of a corrupted device interrogation file, Medtronic may request a deviation to document that a readable interrogation file is unavailable.

In the event the deviation involves a failure to obtain a subject's consent, or is made to protect the life or physical well-being of a subject in an emergency, the deviation must be reported to the Ethics Committee per local requirement and Medtronic as soon as possible. Reporting of all other study deviations should comply with Ethics Committee policies and/or local laws and must be reported to Medtronic as soon as possible upon the site becoming aware of the deviation. Reporting of deviations must comply with Ethics Committee policies, local laws, and/or regulatory agency requirements.

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

9. ADVERSE EVENTS AND DEVICE DEFICIENCIES

Reporting and analysis of safety data are mandated by regulatory authorities worldwide. Medtronic has established procedures in conformity with worldwide regulatory requirements to ensure appropriate reporting of safety information. This study is conducted in accordance with these procedures and regulations.

Since the safety reporting requirements and classification systems vary for each regulatory agency, requirements from all geographies are taken into account for the collection and reporting of safety information.

The Reveal LINQ ICM is approved with demonstrated evidence of safety and effectiveness for their intended use. It is not the purpose of the study to demonstrate product safety and effectiveness for the purpose of obtaining product approval nor to obtain approvals for expanded indications of use, new material or design change for medical device already on the market.

For the Reveal LINQ registry, all AEs occurring after consent that are potentially system related or procedure related will be collected, as well as:

- Stroke
- Transient ischemic attack (TIA)
- Bleeding events, and
- Ablation-related events
    - Espophageal injury, phrenic nerve injury, PV stenosis/occlusion, silent microembolismsm, late hematoma, pseudoaneurysm, AV fistula, dry cough, hemoptysis, other

In all geographies, Unavoidable AEs, listed in Table 5 need not to be reported if resolved within the timeframe specified.

9.1 Adverse Event Assessment

9.1.1 Adverse Events

AE definitions are provided in Table 5. AEs that are potentially system related or procedure related as well as stroke, TIA, bleeding events, and ablation-related events will be collected and reported to Medtronic during the study, starting from the time the subject completes consent. Reporting of these events to Medtronic will occur on the AE eCRF.

Each AE must be recorded on a separate AE eCRF and include a description of the event, the diagnosis, the date of event onset, the date the site became aware of the event, the relatedness and seriousness of the event, diagnostic tests and procedures performed, actions taken as a result of the event, and the outcome of the event. Documented pre-existing conditions are not considered AEs unless the nature or severity of the condition has worsened. Additionally, detected arrhythmias (including AF) for which no intervention is made are not reportable as AEs. In all geographies, Unavoidable AEs, listed in Table 5 need not to be reported if resolved within the timeframe specified.

For AEs that require immediate reporting (see Table 7), initial reporting may be done by phone, or on the CRF completing as much information as possible. The AE CRF must be completed as soon as possible.

In case the investigator requires information from the sponsor in an emergency situation, the investigator can contact the study sponsor (Table 1).

An assessment for Device Related, Procedure-Related Events as well as stroke, TIA, bleeding events, and ablation-related events will be conducted at each subject follow-up. Submit any

additional supporting evidence which could assist in the assessment and review of reported events e.g. device transmissions and/or device uploads.

9.1.2 Device Deficiencies

Device deficiency information will be collected throughout the study and reported to Medtronic. Device deficiencies that did not lead to an Adverse Event should be reported as a device deficiency only.

9.1.3 Processing Updates and Resolution

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

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

At the time of study exit, all AEs with an outcome of “Unresolved, further actions or treatment planned” must be reviewed and an update to the original AE must be reported. At a minimum, if there are no changes to the description, relatedness, test and procedures or actions taken, the outcome must be updated to reflect “Unresolved at time of study closure.”

9.2 Adverse Event and Device Deficiency Definitions

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

Where the definition indicates “device”, it refers to any device used in the study. Refer to Appendix I for event definitions. Every effort has been made to align study definitions with the ISO 14155:2011 standard but since the study is not within the scope of ISO, minor modifications have been made to better align with the purpose of the study. Specifically, the reference to the term “investigational” has been removed from the definitions with all other content unchanged.

Table 5: Adverse Event Definitions

General	
Adverse Event (AE) (ISO 14155-2011, 3.2)	Any untoward medical occurrence, unintended disease or injury, or untoward clinical signs (including abnormal laboratory findings) in subjects, users or other person, whether or not related to the medical device Note 1: This definition includes events related to the medical device or the comparator Note 2: This definition includes events related to the procedure involved Note 3: For users or other persons, this definition is restricted to the medical device.

Adverse Device Effect (ADE) (ISO 14155:2011, 3.1)	Adverse event related to the use of a medical device. Note 1: This definition includes any adverse event resulting from insufficient or inadequate instructions for use or the deployment, implantation, installation, or operation, or any malfunction of the medical device. Note 2: This definition includes any event resulting from user error or from intentional misuse of the medical device
Device Deficiency (DD) (ISO 14155:2011, 3.15)	Inadequacy of a medical device with respect to its identity, quality, durability, reliability, safety or performance. NOTE: Device deficiencies include malfunctions, use errors and inadequate labeling
Relatedness	
Procedure Related	An adverse event that occurs that is directly related to the implantation or modification of the Reveal LINQ system.
System Related	An adverse event that results from the presence or performance (intended or otherwise) of any component of the system (including: Reveal LINQ ICM, Programmer, Patient Assistant, and MyCareLink Patient Monitor).
Seriousness	
Serious Adverse Event (SAE) (ISO 1455-2011, 3.37)	An Adverse Event that: a) led to a death, b) led to a serious deterioration in the health of the subject, that either resulted in 1. a life-threatening illness or injury 2. a permanent impairment of a body structure or a body function 3. in-patient hospitalization or prolongation of existing hospitalization 4. medical or surgical intervention to prevent permanent impairment to body structure or a body function c) led to foetal distress, foetal death or a congenital abnormality or birth defect. Note: Planned hospitalization for a pre-existing condition without serious deterioration in health is not considered a serious event
Serious Adverse Device Effect (SADE) (ISO14155-2011, 3.36)	Adverse device effect that has resulted in any of the consequences characteristic of a serious adverse event
Unanticipated Serious Adverse Device Effect (USADE) (ISO14155:2011, 3.42)	Serious adverse device effect which by its nature, incidence, severity or outcome has not been identified in the current version of the risk analysis report. Note: Anticipated serious adverse device effect (ASADE) is an effect which by its nature, incidence, severity or outcome has been identified in the risk analysis report.

<table>
<tr><th colspan="2">Other</th></tr>
<tr><td>Unavoidable Adverse Event</td><td>An Adverse Event inherent to a surgical procedure that is expected to occur in all subjects for a projected duration according to the Investigator’s opinion, including, but not limited to:
<table>
<tr><th>Event Description</th><th>Time (hrs) from end of Procedure</th></tr>
<tr><td>Anesthesia related nausea / vomiting</td><td>24 hrs</td></tr>
<tr><td>Low-grade fever (<100^{O}F or < 37.8^{O}C)</td><td>48 hrs</td></tr>
<tr><td>Pocket site / incisional pain</td><td>72 hrs</td></tr>
<tr><td>Mild to moderate bruising / ecchymosis</td><td>168 hrs (7 days)</td></tr>
<tr><td>Sleep problems (insomnia)</td><td>72 hrs</td></tr>
<tr><td>Back pain related to laying on the table</td><td>72 hrs</td></tr>
<tr><td>Shoulder pain / discomfort / stiffness / related to shoulder immobilization during procedure</td><td>72 hrs</td></tr>
</table></td></tr>
<tr><td>Infection</td><td>Infection will be defined as deep incision site or superficial infection.

Deep incision site are classified as pain, redness, or drainage at incision site requiring the device to be removed or IV antibiotics administered.

Superficial infections are defined as redness beyond procedure expectation and oral antibiotics administered.

For both deep incision and superficial infections, a physician directed intervention must occur for the event to be defined as an infection.</td></tr>
</table>

9.3 Adverse Events and Deficiency Classification

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

The site will report the clinician’s assessment of the event relative to relatedness (e.g. device or procedure) and seriousness. Upon receipt of AEs at Medtronic, a Medtronic representative will review the AE /device deficiency for completeness and accuracy and when necessary will request clarification and/or additional information from the Investigator. Medtronic will utilize MedDRA, the Medical Dictionary for Regulatory Activities, to assign a MedDRA term for each AE based on the information provided by the investigator.

Regulatory reporting of all safety events, which may include SAEs and device deficiencies that could have led to an SADE, will be completed according to local regulatory requirements.

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

Table 6: Adverse Event classification responsibilities

What is classified?	Who classifies?	Classification Parameters
Relatedness	Investigator	System-related (including: Reveal LINQ ICM, Programmer, Patient Assistant, and MyCareLink Patient Monitor), Procedure-related
	Sponsor	System-related (including: Reveal LINQ ICM, Programmer, Patient Assistant, and MyCareLink Patient Monitor), Procedure-related
Severity	Investigator	SAE, SADE
	Sponsor	SAE, SADE, USADE, Complication or Observation (for all system or procedure related AEs), Life Threatening
Diagnosis	Investigator	Based on presenting signs and symptoms and other supporting data
	Sponsor	MedDRA term assigned based on the data provided by Investigator
Death Classification	Investigator	Sudden Cardiac, Non-sudden Cardiac, Non-Cardiac, Unknown

9.4 Adverse Event and Device Deficiency Reporting Requirements

Regulatory reporting of AEs/DDs will be completed according to local regulatory requirements. Refer to Table 7: Adverse Event Reporting Requirements for a list of required investigator reporting requirements and timeframes, and of required Medtronic reporting requirements and timeframes. Each geography has the responsibility to follow current local reporting requirements.

The investigator is required to report SAEs and SADEs/USADEs to Medtronic immediately, and to the Ethics Committee per local requirements. Medtronic is also required to report these events to the local regulatory authority based on their requirements. It is the responsibility of the investigator to abide by any additional AE/DD reporting requirements stipulated by the Ethics Committee responsible for oversight of the study.

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

The reporting of product complaints is not part of the clinical study and should be done in addition to the Adverse Event reporting requirements. 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.

Table 7: Adverse Event Reporting Requirements

Serious Adverse Events (SAEs)	
Investigator submit to:	
Medtronic	**EMEA:** Immediately after the investigator first learns of the event or of new information in relation with an already reported event. *(ISO 14155 and local law)* **All other geographies:** Report to the sponsor, without unjustified delay, all serious adverse events.
Ethics Committee	**All geographies:** Submit per local Ethics Committee requirement.
Regulatory authorities	**All geographies:** As per local reporting requirement.
Sponsor submit to:	
Regulatory authorities	**All geographies:** Submit to regulatory authority per local reporting requirement.
Ethics Committee	**All geographies:** Submit to Ethics Committee per local reporting requirement.
Serious Adverse Device Effects (SADEs) including Unanticipated Serious Adverse Device Effects(USADEs)	
Investigator submit to:	
Medtronic	**EMEA:** Immediately after the investigator first learns of the event or of new information in relation with an already reported event. *(ISO 14155 and local law)* **All other geographies:** Submit in a timely manner after the investigator first learns of the event.
Regulatory authorities	**All geographies:** As per local reporting requirement.
Ethics Committee	**All geographies:** Submit per local Ethics Committee requirement.
Sponsor submit to:	
Regulatory authorities	**All geographies:** Submit to regulatory authority per local reporting requirement.
Ethics Committee	**All geographies:** Submit to Ethics Committee per local reporting requirement.
Adverse Device Effects	
Investigator submit to:	
Medtronic	**EMEA**: Immediately after the investigator first learns of the effect. *(ISO 14155 and local law)* **All other geographies:** Submit in a timely manner after the investigator first learns of the effect.
Regulatory authorities	**All geographies:** As per local reporting requirement.
Ethics Committee	**All geographies:** Reporting timeframe as per local Ethics Committee requirement.
Sponsor submit to:	
Regulatory authorities	**All geographies:** Submit to regulatory authority per local reporting requirement.

Ethics Committee	**All geographies:** Submit to Ethics Committee per local reporting requirement.
All other reportable Adverse Events	
Investigator submit to:	
Medtronic	**All geographies:** Submit in a timely manner after the investigator first learns of the event.
Regulatory Authorities	**All geographies:** Submit to regulatory authority per local reporting requirement.
Ethics Committee	**All geographies:** Submit to Ethics Committee per local reporting requirement.
Sponsor submit to:	
Regulatory authorities	**All other geographies:** Submit to regulatory authority per local reporting requirement.
Device Deficiencies	
Investigator submit to:	
Medtronic	**All geographies:** Submit in a timely manner after the investigator first learns of the event.
Regulatory Authorities	**All geographies:** Submit to regulatory authority per local reporting requirement.
Ethics Committee	**All geographies:** Submit to Ethics Committee per local reporting requirement.

10. RISK ANALYSIS

Medtronic follows rigorous Quality Assurance and Control procedures throughout the life of a product, from the business analysis phase through development, market release, and post-market surveillance.

There are no incremental risks introduced to the subject as a result of participation in this study. Risks and Risk Mitigations to the subject identified below are consistent with those outlined in the device manual.

There may be other discomforts and risks related to the device system and/or this study that are not foreseen at this time.

Risks and Risk Mitigations

Possible risks associated with the Reveal LINQ include but are not limited to the following:

- Risks associated with a minor surgical procedure (ex. Slight risk of infection)
- Sensitivity to the device

10.1 Risk Minimization

The potential risks associated with the Reveal LINQ were identified and have been successfully mitigated. Any potential risks associated with this study are further minimized by selecting qualified investigators and training study personnel on the Clinical Investigation Plan.

In addition, investigators will be actively involved in the insertion and follow-up of the subjects implanted with the Reveal LINQ system.

Risks will be minimized by careful assessment of each subject prior to, during, and after insertion of the Reveal LINQ. Prior to insertion, it is recommended subjects undergo a complete cardiac evaluation.

After insertion, subjects will be followed at regular intervals. The investigator must interrogate the Reveal LINQ and assess for any adverse events.

- Risks associated with a minor surgical procedure
- Slight risk of infection
- Sensitivity to the device

10.2 Potential Benefits

The Reveal LINQ may offer no benefit. The potential benefits of having the Reveal LINQ include more intensive follow-up treatment and frequent device transmissions and/or continuous monitoring enabling more precise detection of arrhythmias. This better precision to detect arrhythmias may lead to clinicians having better data to quantify arrhythmia burden. The information gained from this study could result in the improved detection and management of arrhythmias. Additionally, information collected from this study may assist in the design of new product(s)/therapy(ies) and/or instructions for use. The System may not offer a direct clinical benefit to study subjects. The information collected from this study may assist in the design of new product(s)/therapy(ies) and/or instructions for use.

11. PLANNED STUDY CLOSURE, EARLY TERMINATION OF STUDY OR STUDY SUSPENSION

11.1 Planned study closure

Study Closure is a process initiated by distribution of a study closure letter. Study closure is defined as closure of a clinical study that occurs when Medtronic and/or regulatory requirements have been satisfied per the Clinical Investigation Plan and/or by a decision by Medtronic or regulatory authority), whichever occurs first. The study closure process is complete upon distribution of the Final Report or after final payments, whichever occurs last. Ongoing Ethics Committee oversight is required until the overall study closure process is complete. Refer to the Study Exit section for additional information regarding study exit procedures.

11.2 Early termination or suspension

Medtronic may limit enrollment when sufficient enrollment to effectively evaluate product performance and survivability is achieved (Refer to Section 12). Any enrollment closures will be communicated to sites along with the rationale for closure.

To ensure a widespread distribution of data and minimize site bias in study results, the maximum number of subjects who may have a Reveal LINQ inserted at a single site is fifteen percent (15) of total projected enrollment in a given geography based on enrollment allocations. Sites that enroll faster than others will be allowed to do so in order to maintain an adequate overall study enrollment rate, but may not exceed the maximum number of insertions per site.

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

i. Study-wide termination or suspension

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

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

ii. Investigator/site termination or suspension

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

- Failure to obtain initial Ethics Committee approval or annual renewal of the study

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

11.3 Procedures for termination or suspension

iii. 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 MEC/IRB/Head of Medical Institution approval lapse, the investigator will promptly inform the MEC/IRB/Head of Medical Institution
- In the case of study termination, the investigator must inform the subjects and may inform the personal physician of the subjects to ensure appropriate care and follow-up is provided
- In the case of a study suspension, subject enrollment must stop until the suspension is lifted by Medtronic
- In the case of a study suspension, enrolled subjects should continue to be followed out of consideration of their safety, rights and welfare

iv. Investigator-initiated

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

v. Ethics committee-initiated

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

- Subjects already enrolled should continue to be followed in accordance with MEC/IRB/Head of Medical Institution policy or its determination that an overriding safety concern or ethical issue is involved
- The investigator will inform his/her institution (where required per local requirements)
- The investigator will promptly inform the subjects, or legally-authorized designees or guardians and/or the personal physician of the subjects, with the rationale for the study termination or suspension

12. STATISTICAL METHODS AND DATA ANALYSIS

Medtronic employees or designees will perform all statistical analyses. Additionally, a separate Statistical Analysis Plan (SAP) will be developed to further describe statistical methods, pre-specified data handling rules, and pre-specified analyses that will be included in study reports. 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. Additional exploratory analyses of the data may be conducted as deemed appropriate. Missing data will not contribute to the objectives unless specified otherwise within the analysis methods.

The study is observational in nature. Sample size calculations for the study objectives provide information on the reliability of the estimates. The registry data is intended to benefit and support interests of patients, hospitals, clinicians, payers, and industry. Overall study enrollment size is determined by number of engaged study centers and enrollment potential at each study center. At the same time, data analysis may be carried out throughout the study without having all enrolled subjects completing study required follow-ups.

12.1 Primary Objective #1

Characterize clinical actions initiated by Reveal LINQ arrhythmia detection.

i. Analysis Methods

This objective is descriptive in nature. New onset of arrhythmias diagnosed as results of ICM data review, and the subsequent clinical actions taken are reported through CRFs.

Study sites will review device recorded arrhythmia episodes via remote transmission or at a regularly scheduled clinic visit. Clinical treatments may be prescribed upon diagnosis.

Summary statistics will be obtained for frequencies of diagnosis and treatment. Frequencies of each action taken, such as medication changes, surgical intervention, new cardiac device implant, etc. will be obtained.

ii. Determination of Subjects/Data for Analysis

All enrolled subjects who are diagnosed with an arrhythmia detected by Reveal LINQ will be included in analysis.

iii. Sample Size

There is no statistical hypothesis formulated for this analysis therefore there is no sample size for this objective.

12.2 Primary Objective #2

Estimate procedure-related acute infection rate (up to 30 days post insertion procedure).

i. Analysis Methods

The post insertion procedure visit can be either in office visit or CareLink visit. Infection events will be reported by study sites upon awareness. The acute infection rate will be calculated by dividing the number of subjects with infection events within 30 days post insertion procedure by the number of subjects in the risk set (the analysis cohort). Two-sided 95% confidence interval will be calculated using the Exact Binomial method. Additionally, rate for infection SAE may be calculated (see Appendix for SAE definition).

ii. Determination of Subjects/Data for Analysis

A subject will be included in the analysis cohort for this objective if one of the following criteria is met:

a) A subject who undergoes a Reveal LINQ insertion procedure (following subject's consent to the study) and completes a minimum of one visit at a time point ≥ 30 days post insertion procedure will be included for the analysis.

b) A subject will be included in the analysis if an infection event is reported regardless if the subject has completed 30 day follow-up.

c) A subject with a Reveal LINQ device explanted after a successful implant procedure that occurred prior to 30 days post insertion procedure will be included in the analysis cohort.

d) A subject who undergoes a Reveal LINQ implant procedure without having a Reveal LINQ device chronically implanted will be included in the analysis with a confirmation of patient status at ≥ 30 days post implant.

iii. Sample Size

The study will enroll sufficient number of subject to ensure a robust sample size to estimate acute infection rate. It is assumed the acute infection rate will be less than 5%. The confidence interval width (Lower limit to upper limit) for the infection rate estimate is demonstrated in Table 8. A minimum of 1200 subjects undergoing Real LINQ implant procedure will provide a 2-sided 95% confidence interval with a width of 2.6%, assuming infection rate is 5%.

Table 8 Sample Size Calculation for Estimating Acute Infection Rate

Sample Size	Event rate Assumption	Lower Limit	Upper Limit	Confidence Interval Width
100	5%	1.6%	11.3%	9.6%
200	5%	2.4%	9.0%	6.6%
300	5%	2.8%	8.1%	5.3%
400	5%	3.1%	7.6%	4.5%
500	5%	3.3%	7.3%	4.0%
600	5%	3.4%	7.1%	3.7%
700	5%	3.5%	6.9%	3.4%
800	5%	3.6%	6.7%	3.2%
900	5%	3.7%	6.6%	3.0%
1000	5%	3.7%	6.5%	2.8%
1100	5%	3.8%	6.5%	2.7%
1200	5%	3.8%	6.4%	2.6%
1500	5%	4.0%	6.2%	2.3%
2000	5%	4.1%	6.0%	2.0%
2300	5%	4.1%	6.0%	1.8%

12.3 [redacted]

13. DATA AND QUALITY MANAGEMENT

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

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

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

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

Device data from Reveal LINQ ICM interrogations and CareLink transmissions will be uploaded to secure servers. Save-to-media data collected at office visits will be sent to Medtronic. Upon receipt, device data will be maintained with databases and retrieved for analysis and reporting.

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

14. WARRANTY/INSURANCE INFORMATION

14.1 Warranty

Warranty information is provided in the product packaging for the Reveal LINQ and additional copies are available upon request.

Outside the US, Medtronic maintains appropriate clinical 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 insurance statement/certificate will be provided to the Ethics Board.

14.2 Insurance (Europe, Middle East, Africa)

Medtronic Bakken Research Center B.V. is a wholly owned subsidiary of Medtronic, Inc., which as the parent company of such entity 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 Trial insurance statement/certificate will be provided to the Ethics Committee.

14.3 Insurance (Japan)

Medtronic Japan Co., Ltd. is a wholly owned subsidiary of Medtronic, Inc., which as the parent company of such entity maintains appropriate clinical trial 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, insurance provisions will be provided to the Ethics Committee/Institutional Review Board.

14.4 Insurance (Greater China)

Medtronic (Shanghai) Management Co., Ltd is a wholly owned subsidiary of Medtronic, Inc., which as the parent company of such entity maintains appropriate clinical trial 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 Trial insurance statement/certificate will be provided to the Ethics Committee.

15. MONITORING

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

The sponsor or a regulatory authority may audit or inspect the study center to evaluate the conduct of the study. The clinical investigator(s)/institution(s) shall allow study related monitoring, audits, Ethics Board review and regulatory inspection 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 print outs 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 inspection by a regulatory body immediately.

15.1 Monitoring Visits

Frequency of monitoring visits may be based upon subject enrollment, duration of the study, study compliance, number of adverse events, number of deviations, findings from previous monitoring visits and any suspected inconsistency in data that requires investigation. Regulatory documents may be reviewed at each study site. Monitoring for the study, including site qualification visits, site initiation visits, interim monitoring visits, and closeout visits, will be done in accordance to the study-specific monitoring plan. Monitoring will be planned either at the study site, via telephone, or electronically to assure compliance with the study clinical investigation plan. Site activation, periodic visits and study closure visits will occur either on-site, via email or via telephone.

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

16. REQUIRED RECORDS AND REPORTS

16.1 Investigator records

The investigator is responsible for the preparation and retention of the records cited below. The following records are subject to inspection and must be retained for a period of two years (or longer as local law or hospital administration requires) after the date on which the investigation is terminated.

- All correspondence between the IRB/MEC, sponsor, monitor, and the investigator that pertains to the investigation, including required reports.
- Subject's case history records, including:
    - Signed and dated informed consent form personally signed by subject
    - Observations of adverse events/adverse device effects/device deficiencies
    - Medical history
    - Insertion and follow-up data
    - Documentation of the dates and rationale for any deviation from the protocol
- List of investigation sites
- All approved versions of the CIP and addendums, and PIC or DRF form (all approved versions).
- All subject and investigator completed DRF or CF forms (Authorizations, US only)
- Signed and dated Clinical Trial Agreement.
- Current curriculum vitae of principal investigators.
- Documentation of delegated tasks.
- IRB/MEC approval documentation. Written information that the investigator or other study staff, when member of the IRB/MEC, did not participate in the approval process. Approval documentation must include the Ethics Board composition, where required per local law.
- Study training records for site staff.
- Subject ID log (if applicable)
- Final Study Report including the statistical analysis.
- Any other regulatory authority or required records

Sites are responsible for ensuring practicing clinicians are appropriately licensed/qualified.

16.2 Investigator reports

The investigator is responsible for the preparation (review) and submission of the reports (reported per the country-specific collection requirements) to Medtronic and/or the Ethics Board cited in Table 9. In addition, if an Ethics Board takes any action with respect to the study, copies of all pertinent documentation must be forwarded to Medtronic in a timely manner. Reports are subject to inspection and to the retention requirements as described above for investigator records.

Investigator reporting requirements for safety data are listed in Table 7: Adverse Event Reporting Requirements. The investigator shall prepare and submit in a complete, accurate and timely manner the reports listed in this section.

Table 9: Investigator Reports applicable for all geographies per Medtronic requirements

Report	Submit to	Description/Constraints
Withdrawal of IRB/EC approval	Sponsor and Relevant Authorities	The investigator must report a withdrawal of approval by the reviewing IRB/EC of the investigator's part of the investigation as soon as possible.
Study Deviations	Sponsor and IRB/EC	Any deviation from the clinical investigation plan shall be recorded together with the explanation of the deviation. Notice of deviations from the CIP to protect the life or physical well-being of a subject in an emergency shall be given as soon as possible. Except in such emergency, prior approval is required for changes in the plan or deviations.
Failure to obtain informed consent	Sponsor and Ethics Committee	Informed consent shall be obtained in writing and documented before a subject is enrolled into the clinical study.
Final Report	IRBs/ECs and Relevant Authorities	This report must be submitted within 3 months of study completion or termination, or per local requirements.

Table 10: Investigator reports applicable to Japan per Ethical Guidelines on Medical Research involving Human Beings

Report	Submit to	Description/Constraints
Withdrawal of IRB/EC approval	Sponsor, IRB/EC, and Chief executive of the research implementing entity	The principal investigator of the research shall report to the chief executive of the research implementing entity with respect to matters required.
Progress Report	IRB/EC and Chief executive of the research implementing entity	The principal investigator shall report to the chief executive of the research implementing entity, with respect to the progress of the research in accordance with specifications prescribed in the research protocol.
Study Deviations	Sponsor, IRB/EC, and Chief executive of the research implementing entity	The investigator shall report deviations if required.

16.3 Sponsor records

Medtronic will maintain the following records for each site:

- All correspondence which pertains to the investigation
- Signed Investigator Trial Agreements and current curriculum vitae of principal investigator and curriculum vitae of authorized designees where required as well as delegation documentation
- All approved informed consent templates, data review files and Authorization forms and other information provided to the subjects and advertisements, including translations
- Copies of all IRB/MEC approval letters and relevant IRB/MEC correspondence and IRB/MEC voting list/roster/letter of assurance
- Names of the institutions in which the clinical study will be conducted
- Names/contact addresses of monitors
- Statistical analyses and underlying supporting data
- Final report of the clinical study
- The Clinical Investigation Plan
- Study training records for site personnel and Medtronic personnel involved in the study
- Insurance certificates
- Any other records that local regulatory agencies require to be maintained.

16.4 Sponsor reports

Medtronic shall prepare and submit the following complete, accurate, and timely reports listed in the tables below (by geography). In addition to the reports listed below, Medtronic shall, upon request of reviewing IRB/EC, regulatory agency or FDA, provide accurate, complete and current information about any aspect of the investigation. Medtronic reporting requirements for safety data are listed in Table 7 of the Adverse Event section.

Participating sites will have access to their own study data for ad hoc reporting.

Table 11: Sponsor Reports

Report	Submit to	Description
Progress Report	• Regulatory Authority	Progress reports will be submitted to regulatory authority as required, and to physicians & Ethics Boards as requested.
Withdrawal of Ethics Board approval	• Participating Sites • Regulatory Authority	Notification within five working days after the sponsor first learns of the withdrawal of approval. To be reported to Regulatory Authorities as required.
Final report	• Investigators, IRB/MEC	A final report will be submitted to the investigators and IRBs/MECs within three months after completion or termination of this study.
Study deviation	• Investigators	Site specific study deviations will be submitted to investigators periodically.

Medtronic records and reports will be maintained in a password-protected document management system, and paper documents (where applicable) will be stored in stored in secured file cabinets at Medtronic during the course of this study. After closure of the study Medtronic will archive records and reports indefinitely.

Appendix A: Draft data collection elements (Case Report Forms)

Draft Case Report Forms for the Reveal LINQ Registry will be provided under separate cover upon request. Final CRFs will be provided to sites via the electronic data management system after the site has fulfilled all requirements for database access.

Appendix B: Publication plan

Publications from the Reveal LINQ Registry study will be handled according to Cardiac Rhythm Heart Failure Standard Operating Procedures and as indicated in the Clinical Trial Agreement.

Publication Committee

The Reveal LINQ Registry study team has formed an Oversight Committee. This committee will manage study publications with the goal of publishing findings from the data. The Oversight Committee Charter is available under separate cover.

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

Management of Primary, Secondary and Ancillary Publications

The Oversight Committee, with Medtronic representatives will serve as the Publication Committee. The Publication Committee reviews, prioritizes, and manages all publications including primary, secondary and ancillary publications. Primary and secondary publications are those that address analyses of any or all primary objectives or ancillary objectives, respectively, as specified in the Clinical Investigation Plan.

An ancillary publication is any publication that does not address the study objectives identified in the Clinical Investigation Plan. They include publications proposed and developed by 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 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.

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) in addition to Medtronic authorship criteria. 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 committee. The selected authors will be responsible for drafting the publication. All selected authors must fulfill the authorship conditions stated above to be listed as authors, and all contributors who fulfill the conditions must be listed as authors.

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

Transparency

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

- a final report, describing the results of all objectives and analysis, will be distributed to all investigators, MECs 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 as well as local regulatory databases where required by local law
- disclosing conflicts of interest of the co-authors of publications according to the policies set forth by the corresponding journals and conferences
- making an individual sites study data accessible to the corresponding investigator after the completion of the study, if requested

Appendix C: Informed consent templates and Data Review Files

Geography-specific PIC and DRF templates will be provided under separate cover.

Appendix D: Participating Investigators and Institutions

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

Appendix E: Ethics Committee List

A complete list of participating Ethics Committees and their Chairperson(s) will be distributed under a separate cover when available.

Appendix F: Additional information for Japanese centers

Other required information for Japanese centers, such as detailed contact information of Medtronic Japan, names of monitors, detailed CRF instruction, etc. not outlined in the Clinical Investigational Plan will be provided under a separate cover.

Appendix G: Committees

The Reveal LINQ Registry study will utilize an Oversight Committee to manage study publications. Committee membership rosters will be maintained at Medtronic and will be made available upon request.

A Data Monitoring Committee (DMC) is not needed for this study. The study is considered non-significant risk for study participants, thus the need for additional safety oversight beyond Medtronic's already rigorous safety monitoring processes is not required.

Appendix H: Labeling

Labeling and package for all products used in this study will follow the local regulatory requirements.

Labeling and reference/technical manuals for the Reveal LINQ will be provided under separate cover. Labeling for all other market approved system components can be found with each package insert.

Appendix I: Definitions

Abnormal Battery Depletion: Any battery depletion rate which is faster than expected given an implanted devices programmed settings or usage conditions.

Atrial Fibrillation: Atrial Fibrillation is a supraventricular tachyarrhythmia characterized by uncoordinated atrial activity with consequent deterioration of atrial mechanical function. On the electrocardiogram (ECG), atrial fibrillation is characterized by the replacement of consistent P waves with rapid oscillations or fibrillation waves that vary in amplitude, shape and timing, associated with an irregular, frequently rapid ventricular response when atrioventricular conduction is intact.

Atrial Flutter: Atrial Flutter is characterized by a sawtooth pattern of regular atrial activation called flutter waves on the ECG, particularly visible in leads II, III, aVF and v1

Bleeding Event- An episode of internal or external bleeding classified into the following categories:

> Life-threatening/disabling – fatal bleeding (BARC type 5) or bleeding in a critical organ, such as intracranial, intraspinal, intraocular, or pericardial necessitating pericardiocentesis, or intramuscular with compartment syndrome (BARC type 3b and 3c) or bleeding causing hypovolemic shock or severe hypotension requiring vasopressors or surgery (BARC type 3b) or overt source of bleeding with drop in hemoglobin of > 5g/dL or whole blood or packed red blood cells (RBCs) transfusion >4 units (BARC type 3b)
>
> Major bleeding (BARC type 3a) – overt bleeding either associated with a drop in the hemoglobin level of at least 3.0 g/dL or requiring transfusion of 2 or 3 units of whole blood/RBC, or causing hospitalization or permanent injury, or requiring surgery AND does not meet the criteria of life-threatening or disabling bleeding
>
> Minor bleeding (BARC type 2 or 3a depending on severity) – any bleeding worth of clinical mention (e.g. access site hematoma) that does not qualify as life- threatening, disabling, or major

Cardiac Arrest: cardiac arrest is the sudden cessation of cardiac activity so that the victim becomes unresponsive, with no normal breathing and no signs of circulation. If corrective measures are not taken rapidly, this condition progresses to sudden death. Cardiac arrest should be used to signify an event as described above that is reversed, usually by CPR, and/or defibrillation or cardioversion, or cardiac pacing. Sudden cardiac death should not be used to describe events that are not fatal.

Cardiovascular Mortality: Any of the following criteria:

- Death due to proximate cardiac cause (e.g. myocardial infarction, cardiac tamponade, worsening heart failure)
- Death caused by non-coronary vascular conditions such as neurological events, pulmonary embolism, ruptured aortic aneurysm, dissecting aneurysm, or other vascular disease
- All procedure-related deaths, including those related to a complication of the procedure or treatment for a complication of the procedure
- All valve related deaths including structural or nonstructural valve dysfunction or

other valve related adverse events
- Sudden or unwitnessed death
- Death of unknown cause

Non-Cardiovascular Morality: Any death in which the primary cause of death is clearly related to another condition (e.g. trauma, cancer, suicide)

Clinical Performance (ISO14155-2011): Behavior of a medical device or response of the patient(s) to the medical device in relation to its intended use, when correctly applied to appropriate patient(s).

Data Query: A standard form used to request clarification of Registry collected data

Death:

- Sudden cardiac: Witnessed instantaneous in a previously stable subject. This may occur with or without preceding signs or symptoms, or may occur immediately following sudden dyspnea, lightheadedness, or palpitations.

  Unwitnessed. Subject found dead who at time of last witnessed contact was in usual state of health without medical complaints or obvious difficulty. This applies to subjects dying during sleep. Note: Whereas most sudden deaths seem to result from cardiac arrhythmias, sudden death may also result from non-cardiac processes (e.g., acute pulmonary embolus, rupture of abdominal aortic aneurysm). In most cases, documentation of the actual cause of death is missing.

- Non-sudden cardiac. Includes deaths of subjects in acute pulmonary edema; with severe, progressive HF; cardiogenic shock; or after recent cardiac surgical procedure.

- Non-cardiac. Vascular death (thromboembolic event, acute hemorrhage, CVA, dissecting aneurysm), or non-cardiovascular death (e.g., trauma, renal failure, cancer, sepsis, suicide).

- Unknown. No information available regarding death event.

Deviation: instance(s) of failure to follow, intentionally or unintentionally, the requirements of the clinical plan (Protocol and associated Addendum (if applicable)).

Device Data: stored data from a medical device saved to a media (e.g. USB, floppy disk) which is transferable to a data management system or data directly transferred to a data management system via a direct upload or transmission e.g. pacemaker, ICD, neurostimulator, etc.

Echocardiography (Echo): Diagnostic method which uses sound waves to record imaging of the heart and the heart's movement. Transthoracic Echo is done through the chest wall while transesophageal echo is done through the esophagus

Electrical Data: Data that describes the electrical characteristics of some medical devices including, but not limited to: impedance, threshold, and sensing amplitude measurements e.g. implanted cardiac rhythm devices

Failure to Sense/Undersensing (cardiac): Intermittent or complete loss of sensing or failure to detect the intended intrinsic cardiac signals (atrial or ventricular) during non-refractory periods at programmed sensitivity settings.

Heart Failure: Heart failure is defined as physician documentation or report of any of the following clinical symptoms of heart failure described as unusual dyspnea on light exertion, recurrent dyspnea occurring in the supine position, fluid retention; or the description of rales, jugular venous distension, pulmonary edema on physical exam, or pulmonary edema on chest x-ray. A low ejection fraction alone, without clinical evidence of heart failure does not qualify as heart failure.

Hospitalization: An overnight hospital admission, where admission date and discharge date are different

Implanted: When surgical incisions are closed (implant pocket closed).

Insertable/Implantable Loop Recorder (ILR) / Insertable Cardiac Monitor: A programmable device which continuously monitors a patient's ECG and other physiological parameters and used to aid in the diagnosis of a suspected cardiac arrhythmia

Lost to Follow-Up: A subject who will no longer be followed in the Registry due to unwillingness or inability to return to the clinic for follow-up or a subject who cannot be located for subsequent follow-up

Oversensing (cardiac): Misinterpretation of cardiac or non-cardiac events as cardiac depolarization, (e.g. T-waves, skeletal muscle potentials, lead noise, and extra cardiac electromagnetic interference (EMI)).

Procedure-Related Event: An adverse event that occurs that is directly related to the implantation or modification of the Reveal LINQ system.

Programmer Upload: The electronic transfer of device data from a device programmer to the data management system.

Remote Data Transmission: secure transmission of stored medical device data to clinics, physicians, and/or Medtronic, i.e. Medtronic's CareLink Network

Stroke: Loss of neurological function caused by an ischemic or hemorrhagic event with residual symptoms lasting at least 24 hours after onset or leading to death

Syncope: Sudden loss of consciousness with loss of postural tone, not related to anesthesia, with spontaneous recovery as reported by patient or observer. Patients may experience syncope when supine.

Transient Ischemic Attack: A focal neurological deficit (usually corresponding to the territory of a single cerebral vessel) that resolves spontaneously with any evidence of residual deficient at 24 hours.

Undersensing: Intermittent or complete loss of sensing or failure to detect the intended intrinsic cardiac signals (atrial or ventricular) during non-refractory periods at programmed sensitivity settings, see also Failure to Sense.

Ventricular Tachycardia: Ventricular Tachycardia is a cardiac arrhythmia of 3 or more consecutive complexes in duration emanating from the ventricles at a rate of >100 bpm (cycle length: <600 ms).

Appendix J: Modifications to the clinical investigation plan

Change from Post Surveillance Registry (PSR) CIP V4.0 to Reveal LINQ Registry CIP V1.0		
Applicable Sections	**Change**	**Rationale**
Section 2.2	Study Description: The study is expected to be conducted at approximately 100 study sites globally with approximately 2,300 subjects contributing to total enrollment numbers. Participating geographies are expected to include, but are not limited to: the United States, Europe Middle East and Africa (EMEA), China and Japan.	Description of sites, subjects and geographies within the Reveal LINQ Registry
Section 6.1	Primary Objective: V.4: Characterize clinical actions initiated by Reveal LINQ AF detection. V.1: Characterize clinical actions initiated by Reveal LINQ arrhythmia detection.	To support reporting on clinical actions initiated by Reveal LINQ for all arrhythmias detected
Section 6.3	Inclusion criteria: • Subject or legally authorized representative provides written authorization and/or consent per institution and geographical requirements • Subject is intended to have a Reveal LINQ ICM inserted in the next 30 days • Subject consent prior to Reveal LINQ ICM insertion	Specific to Reveal LINQ product and consent prior to insertion for data collection and reporting

Section 7.3	Site activation: Additional document collection requirements added	Business requirement
Section 7.9	Follow-up: • Changed from required at minimum every 12 months to every 6 months post-insertion. • Added: Medtronic requests that the site send any copies of imaging testing results completed as part of standard of care by the time the subject is exited from the study Added section for Arrhythmia Event and Action Taken Assessment (ongoing)	More frequent and robust data collection/reporting
Section 9	Adverse Events: Device deficiency collection added	Added safety collection
Change from Reveal LINQ Registry CIP V1.0 to V2.0		
Applicable Sections	**Change**	**Rationale**
Table 6	System-related description	List of options errant