Medtronic

Alleviating Pain · Restoring Health · Extending Life

REVEAL AF

Clinical Investigation Plan

Version 2

12-APR-2013

Medtronic, Inc. 8200 Coral Sea Street NE Mounds View, MN U.S.A. 55112 1-800-328-2518	Medtronic, Bakken Research Center B.V. Endepolsdomein 5 6229 GW Maastricht The Netherlands +31-43-35-66-566

TABLE OF CONTENTS

LISTING OF TABLES

LISTING OF FIGURES

CONTACT INFORMATION

The clinical study will be sponsored by:

Medtronic, Inc.
8200 Coral Sea Street NE
Mounds View, MN U.S.A. 55112
1-800-328-2518

Medtronic, Bakken Research Center B.V.
Endepolsdomein 5
6229 GW Maastricht
The Netherlands
+31-43-35-66-566

STEERING COMMITTEE

Medtronic, as the study sponsor, will maintain study oversight. The role of the steering committee is to provide input into study design and implementation.

1 INTRODUCTION

1.1 Study purpose

Medtronic, Inc. is sponsoring REVEAL AF a prospective, single arm, open-label, multi-center, post-market interventional clinical study to determine, via continuous monitoring with the Reveal XT implantable cardiac monitor (ICM) or newer approved version (referred to in the remainder of the document as Reveal ICM), the incidence of atrial fibrillation (AF) in patients suspected to be at high risk for having AF and to understand how physicians manage these patients once AF has been detected. Furthermore, the study will seek to identify what patient characteristics are most predictive of developing AF. This information may facilitate the ability to identify those patients that are at highest risk for developing AF, and for whom Reveal ICM may be most beneficial and potentially cost saving.

1.2 Study Scope

The study is expected to be conducted at approximately 60 clinical centers located in the United States (~45 centers) and Europe (~15 centers). Based on previous studies of comparable scope and magnitude, it is estimated that centers will identify, on average, about 6-10 eligible potential study subjects.

Up to 450 subjects are planned to be enrolled into the study, to have approximately 400 patients implanted with the Reveal ICM. To ensure that the data are derived from a widespread spectrum of centers and thereby minimize center bias, a maximum number of 40 subjects will be implanted at a single center. In addition to ensure a robust dataset is available for subgroup analysis, a minimum of 70 subjects with a $CHADS_2$ score of 2, 3, or ≥4 per the inclusion criteria, will be implanted in each of these three subgroups. If needed, enrollment will be halted for a given $CHADS_2$ subgroup to ensure a minimum of 70 subjects are implanted with a $CHADS_2$ score of 2, 3, and ≥4, respectively. Centers that enroll faster than others will be allowed to do so in order to maintain an adequate overall study enrollment rate, but not exceed the maximum number implanted per site.

2 BACKGROUND AND JUSTIFICATION

Atrial fibrillation (AF) is the most common diagnosed cardiac arrhythmia[1,2], with the number of cases in the adult US population estimated at approximately 3 million and in the European Union 4.5 million cases are estimated[3,4,5]. AF is associated with significant morbidity and mortality due to cerebrovascular complications such as stroke; which lead to a substantial economic impact on the health care system[7,8]. Therefore, the ability to identify AF is paramount for guiding preventative therapy decisions in patients suspected of, or who have clinical risk factors (e.g. congestive heart failure or hypertension), for having AF or a stroke. However, the incidence of AF in patients suspected to be at high risk for having AF is not known.

Several aspects make AF difficult to diagnosis, such as patient symptoms not being reliably correlated with AF episodes, the frequency of the episodes (i.e. paroxysmal vs. persistent), and frequency of ECG monitoring[8-13]. It is well established that with intermittent and symptom based monitoring, there is low sensitivity to accurately identify patients with AF episodes. Studies have shown that of the AF episodes on a pacemaker

log, only 13% to 21% of those AF episodes had symptoms as reported by the patient[14, 15]. Given the limitations of intermittent monitoring and symptoms as an index of AF, continuous cardiac monitoring may provide an important tool in both the diagnosis and follow-up management of AF.

Symptomology such as dyspnea, chest pain, palpitations, dizziness, or fatigue, are common reasons for patients to visit a physician for assessment[16] and may be indicators of the development of AF[17]. However, as stated above patient symptoms are poorly correlated with AF episodes and also, they are non-specific and may result from other causes. Certain patient comorbidities have been shown to be associated with the development of AF and stroke. Physicians estimate the risk of stroke in AF patients using either the $CHADS_2$ or CHA_2DS_2-VAS_c scoring system [18, 19]. The $CHADS_2$ scoring system is based on the following risk factors; congestive heart failure, hypertension, age greater than 75 years, diabetes, and prior stroke or transient ischemic attack (doubled). The more recently developed scoring system of CHA_2DS_2-VAS_c is based on the factors of congestive heart failure, hypertension, age ≥ 75 (doubled), diabetes, stroke (doubled)– vascular disease, age 65-74, and sex category. A higher score in either system is associated with an increased rate of stroke or TIA. Therefore, these scores are used to guide anticoagulant therapy decisions for the treatment of AF. AF therapy also, may include restoring and maintaining normal sinus rhythm, and/or control of the ventricular rates. Additional risk factors such as coronary artery disease, renal impairment, sleep apnea, and chronic obstructive pulmonary disease have also been shown to be risk factors associated with AF[20]. For the current study, given there is not a unified way to estimate AF development in patients that are at high risk of developing AF, elements from the $CHADS_2$ or CHA_2DS_2-VAS_c scoring systems will be utilized to define the high risk patient population[21].

3 SYSTEM DESCRIPTION AND INTENDED USE

The study will be conducted using the components of the Medtronic Reveal ICM device. Depicted in Figure 1 and outlined in Table 1 below are the components for the Reveal XT ICM. The Medtronic Reveal ICM system is being used within the clinical investigation plan (CIP) in accordance with the indications for the device. The Reveal ICM is indicated for:

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

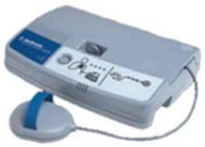
Figure 1. Components of the Medtronic Reveal XT ICM system.

(Not drawn to scale)

Reveal XT
Insertable Monitor

Reveal XT Patient
Assistant

Medtronic CareLink
Programmer



Medtronic CareLink
Monitor

Instructions for use of the devices are provided in their respective manuals. Study system components are being used without modification.

Table 1: System component information

Model Number	Component	Market-released
Model 9529 with FullView™ Software (or later Medtronic releases)	Reveal XT Insertable Monitor	Market-released
Model 2090 with FullView™ Software (or later Medtronic releases)	Medtronic CareLink Programmer	Market-released
9539 (or later Medtronic releases)	Reveal XT Patient Assistant	Market-released
2490G (or later Medtronic releases)	Medtronic CareLink Monitor	Market-released

Note: The labels for the Reveal ICM components are available in English and where available in the local language.

3.1 Reveal Insertable Cardiac Monitor

The Reveal ICM (model 9529 with FullView™ software Model SW007 or later Medtronic releases) is a leadless device that is typically implanted under the skin in the region of the thorax. Two electrodes on the body of the device continuously monitor the patient's subcutaneous ECG. The device can store up to 22.5 min of ECG recordings from the patient-activated episodes and up to 27 min of ECG recordings from automatically detected arrhythmias. When the ECG storage log within the monitor is full, the ECG

record from the most recent episode will overwrite the ECG data from the oldest stored episode for that same arrhythmia category. Documentation of episode occurrence will be retained.

A Vector Check tool is incorporated in the packaging of the Reveal XT. The Vector check tool enables the implanting physician to select the most optimal implantation site while the Reveal ICM is still in the sterile package. Future approved Reveal ICM devices can be used with similar functionality.

3.2 Medtronic CareLink Programmer

The Medtronic CareLink Programmer (Model 2090 with FullView™ software Model SW007 or later Medtronic releases) is used to program the Reveal ICM to detect arrhythmias with various pre-specified characteristics. In addition, the programmer allows the physician to view, save, and print the ECG records currently held within the Reveal ICM.

3.3 Reveal Patient Assistant

The Reveal Patient Assistant (Model 9539 or later Medtronic releases) is a battery-operated, hand-held telemetry device that enables the patient, on experiencing symptoms potentially indicative of a cardiac event, to manually trigger the Reveal ICM to collect and store an ECG record. When the recording is manually triggered in this way (i.e., the Symptoms button is pressed), the Patient Assistant device also shows the patient whether it successfully received the telemetry transfer from the Reveal ICM, as well as whether the battery of the Patient Assistant device is low.

Lastly, the patient can use a query button on the Patient Assistant device for direct feedback about whether the Reveal has registered an arrhythmia and/or whether criteria have been met for the patient to take action to contact the physician or clinic. The notification criteria are selected and pre-programmed by the care provider.

3.4 Medtronic CareLink Monitor

The CareLink Monitor (Model 2490G or later Medtronic releases) is a device that enables the device diagnostic data (which includes ECG data) to be transmitted directly from the Reveal ICM to the Medtronic CareLink Network for review by the physician.

3.5 Additional: Medtronic CareLink network

The Medtronic CareLink network is an internet-based remote service for monitoring patients with implanted Medtronic cardiac devices. The physician can access the CareLink network, a secured network with restricted access, to review the device data that has been uploaded from the implanted Reveal monitor.

4 REGULATORY COMPLIANCE

The REVEAL AF clinical study is a multicenter, post market, interventional clinical trial. The study was designed to reflect the good clinical practice principles outlined in ISO 14155:2011. These include the protection of the rights, safety and well-being of human subjects, controls to ensure the scientific conduct and credibility of the clinical investigation and the definition of responsibilities of the sponsor and investigators. Information regarding the safety and efficacy of the Reveal ICM has previously been evaluated and are summarized in the Clinical Evaluation Report, Version 3.0, for

Medtronic's Insertable Cardiac Monitors. For the Reveal AF study, the Reveal ICM system will be used in accordance with the approved label. The objectives of this post-market interventional clinical study are not to evaluate the safety and efficacy of the Reveal ICM.

The study will additionally be conducted in compliance with the Clinical Investigation Plan (CIP) and the applicable local laws and regulations of each participating country, including data protection laws and any requirements imposed by the local Competent Authority (CA) and Ethics Committee (EC) and Institutional Review Board (IRB).

The principles of the Declaration of Helsinki have been implemented through the patient informed consent process, EC/IRB approval, data protection, study training, clinical study registration, preclinical testing, risk benefit assessment and publication policy. In addition, compliance with US Food and Drug Administration (FDA) 21 CFR parts 11 is required for all participating geographies.

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

In the United States this is a non-investigational device study and is exempt from 21 CFR 812, and the study will be conducted in compliance with relevant local laws which are US Title 21 CFR parts

- 50: Protection of Human Subjects
- 56: Institutional Review Boards

In Europe, each country will comply with its local laws and the Active Implantable Medical Device Directive (AIMDD) as applicable.

Approval of the CIP or CIP amendments is required from the following groups prior to any study procedures at a clinical study center: Medtronic, geography-specific regulatory authorities (if regulatory approval is required), and an EC/IRB.

5 METHODOLOGY

5.1 Study design

The REVEAL AF study is a prospective, single arm, open-label, multi-center, post-market interventional study to evaluate the incidence of AF in patients that are suspected to be at high risk of having AF, as defined by a modified $CHADS_2$ score as defined in the inclusion criteria. Prior to initiating any study specific procedures, patients must sign and date an informed consent form (ICF) to be enrolled in the study. Up to 450 subjects are planned to be enrolled into the study, to have approximately 400 patients implanted with the Reveal ICM. Inclusion/Exclusion criteria will be evaluated and the patients' medical history and baseline information will be collected and then the Reveal ICM device will be implanted. Enrolled subjects who have a successful Reveal ICM implant will then be followed for a minimum of 18 months to monitor for the detection of AF, and up to a maximum of 30 months or until the last subject has completed their 18 month follow-up visit. During the follow-up period, subjects will have in-office visits every 6 months and will transmit device data via CareLink® on a monthly basis. The total duration of enrollment is anticipated to last approximately 24 months and the study duration is anticipated to last approximately 42 months.

5.2 Study objectives

5.2.1 Primary objective

Determine the incidence rate of atrial fibrillation lasting greater than or equal to six minutes in patients who are at high risk of having atrial fibrillation.

5.2.2 Secondary objectives

- Identify predictors of AF onset in patients who are at high risk of having atrial fibrillation.
- Characterize the timing and nature of clinical actions relative to detection of AF in patients who are at high risk of having atrial fibrillation.

5.2.3 Exploratory objectives

- Characterize AF burden over time in patients who are at high risk of having atrial fibrillation.
- Characterize the presence of non-atrial arrhythmias in patients who are at high risk of having atrial fibrillation.
- Characterize Quality of Life over time in patients who are at high risk of having atrial fibrillation.
- Characterize healthcare utilization in patients who are at high risk of having atrial fibrillation.
- Identify predictors of progression to persistent AF in patients who are at high risk of having atrial fibrillation.

5.3 Subject selection criteria

Subjects will be screened to ensure they meet all of the inclusion and meet none of the exclusion criteria. Institutional Review Board / Medical Ethics Committee (IRB/EC) approval of the REVEAL AF CIP and ICF must be obtained prior to enrolling patients in the study.

5.3.1 Inclusion criteria

- Patient meets the approved indications to receive the Reveal ICM
- Patient is suspected, based on symptomatology and/or demographics, of having atrial fibrillation or at high risk of having AF, as determined by the clinical investigator
- Patient has a $CHADS_2$ score ≥ 3 OR has a $CHADS_2$ score = 2 with at least one of the following documented:
    - Coronary artery disease
    - Renal impairment (GFR 30-60 ml/min)
    - Sleep apnea
    - Chronic obstructive pulmonary disease

Note: stroke/TIA criterion as part of the $CHADS_2$ score for this trial is limited to either an ischemic stroke or TIA, which occurred more than one year prior to enrollment.

- Patient is 18 years of age or older
- Patient has a life expectancy of 18 months or more
- Patient, or legally authorized representative, is willing to sign and date the consent form
- Patient is willing and able to be remotely monitored (i.e., eligible for enrollment into the Medtronic CareLink Network)

5.3.2 Exclusion criteria

- Patient has a documented history of AF or atrial flutter
- Patient had an ischemic stroke or TIA within past year prior to enrollment
- Patient has a history of a hemorrhagic stroke
- Patient is currently implanted with an IPG, ICD, CRT-P, or CRT-D device
- NYHA Class IV Heart Failure patient
- Patient had heart surgery within previous 90 days prior to enrollment
- Patient had an MI within the previous 90 days prior to enrollment
- Patient is taking chronic immuno-suppressant therapy
- Patient is taking an anti-arrhythmic drug
- Patient is contraindicated for long term anticoagulation medication
- Patient is taking a long-term anticoagulation medication
- Any concomitant condition which, in the opinion of the investigator, would not allow safe participation in the study (e.g., drug addiction, alcohol abuse, emotional / psychological diagnosis)
- Patient is enrolled in another study that could confound the results of this study, without documented pre-approval from Medtronic study manager
- Patient has a creatinine clearance <30 ml/min (completed within past 6 months prior to enrollment) or is on dialysis
    - Note: if the clinical investigator suspects the renal dysfunction to be reversible a single repeat creatinine clearance assessment can be made.

5.3.3 Point of enrollment

A subject is considered enrolled upon signing the ICF.

5.4 Randomization

No randomization will be employed. All subjects will receive a Medtronic Reveal ICM.

5.5 Minimization of Bias

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

- Subjects will be screened to confirm eligibility for enrollment in keeping with the inclusion/exclusion criteria.

- Subjects will be characterized at baseline on demographic factors as well as a wide variety of clinical factors related to cardiovascular status and potential risk for AF.
- To ensure a widespread distribution of data between centers, the maximum number of implanted subjects per center is 40 subjects.
- Data collection requirements and study procedures will be standardized across all centers and geographies.
- All study center personnel and Medtronic personnel will be trained on their respective aspects of the study using standardized training materials. All study clinicians will be trained on and required to follow the CIP.
- A statistical analysis plan will be developed prior to analyzing data which will document all pre-specified analyses and analysis methods.
- An AF Adjudication Committee comprised of individuals experienced with identifying AF will review the device EGM records to ensure AF was appropriately identified.

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

6 STUDY PROCEDURES

All clinical investigators managing the subject's condition during the study must be qualified practitioners who are experienced in the diagnosis and medical management of arrhythmias such as AF. Clinical investigators must have the capability and be willing and able to manage CareLink® data and enforce data transmission compliance effectively. Implanting physicians must be experienced in handling and implanting cardiac monitoring devices.

6.1 Site initiation and activation

During the activation process, Medtronic will train site personnel on the CIP, relevant standards and regulations, informed consent process, and data collection and reporting tools for the study. If new members join the investigational site team, they will receive training by Medtronic (or designee) on the applicable clinical investigation requirements before contributing to the clinical investigation.

Prior to performing study related activities, all sites must have EC/IRB approval, as applicable for that geography, and Medtronic has provided written acknowledgement that all pre-study documentation has been received and all training has been completed.

All local and regional regulatory requirements will be fulfilled prior to center activation and enrollment of subjects into the study. Requirements for activation vary by geography, and may include, but are not limited to:

- Signed and dated non-disclosure (confidentiality) agreement/IRB approval letter for the current version of the CIP and Medtronic approved ICF
- Regulatory approval (e.g. Competent Authority (CA) approval) or notification (if required per geography)
- Investigator(s) Curriculum Vitae (CV) on file with sponsor (Unites States)

- Signed and dated Curriculum Vitae (CV) of the Investigator(s) and all key participants in the study on file with sponsor (Europe)
- Signed and dated Clinical Trial Agreement (CTA) on file with sponsor
- Signed and dated documentation of training of required study personnel
- Delegation and Training documentation
- Insurance certificate (if required per geography)

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

Technical training (e.g. product overview, Reveal ICM programming, implant procedures, CareLink®), either initial or refresher, must be completed by the physicians and other site personnel in accordance with their respective roles in the study.

Signed training documentation must be maintained to document and verify completion of the training on the study procedures prior to performing study related activities.

6.2 Equipment requirements

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

- Computer with high speed internet and Windows Internet Explorer for data entry (version 6 or 8 or other compatible version)
- Market released Medtronic CareLink programmer (Model 2090 or future equivalent)
- Equipment required to complete and obtain results of an echocardiogram (if the subject has not had an echocardiogram performed within the previous 6 months prior to enrollment)
- Ability to collect, process and ship blood samples to a central laboratory
- Ability to conduct an external ECG monitor of a minimum of 24 hours or able to obtain results of external ECG monitoring.

The maintenance and calibration of the equipment used for this study will be assessed by the study center (according to their standard procedures). Programmer calibration will not be monitored by the clinical investigation team, but will be maintained by Medtronic field representatives as per standard practice.

6.3 Data collection

Clinical data are collected at designated time points throughout the study. Medtronic field personnel may provide support on how to complete and/or correct data on data collection worksheets, where appropriate. Medtronic personnel are not allowed to complete or correct data collected. A web-based application tool, Remote Data Capture (RDC) will be used for data entry. This tool has Electronic Case Report Forms (e-CRFs) which can be accessed via an Internet browser. Data will be collected using an electronic data management system for clinical studies. Data will be stored in a secure, password-protected database which will be backed up on a daily basis. Data will be reviewed using programmed and manual data checks. Data queries will be made available to study

centers for resolution. Study management reports may be generated to monitor data quality and study progress. The investigator is responsible for the preparation (review and signature) of the e-CRF. The requirements for data collection and study visit schedules are summarized in Table 2.

Table 2: Data collection and study procedures

Study Procedure	Baseline Visit	Implant Visit	Follow-up Office Visit	Unscheduled Visit
Informed Consent	X			
Inclusion/Exclusion	X			
Medical History	X			
Subject Demographics	X			
Height/Weight	X			
HR/BP	X			
Physical Exam	X			
Symptom assessment	X		X	X
External ECG assessment	X			
Echocardiogram	X			
Cardiovascular medications	X	X	X	X
Biomarker blood draw	X			
Treatment decision/actions			X	X
Device Location		X		
Device Interrogation/data transfer		X	X	X
QoL Questionnaire (EQ5D)	X		X	
HCU assessment		X	X	X
Assessment of cardiovascular procedures			X	X
Patient conducted CareLink Transmission	Will occur monthly following Reveal ICM implant			
Device Deficiencies	Upon Occurrence			
Death				
Adverse Event				
System Modification				
Study Deviation				
Study Exit				

6.4 Patient informed consent process

Patient informed consent is defined as legally effective, documented confirmation of a subject's (or their legally authorized representative or guardian) voluntary agreement to participate in a particular clinical investigation after information has been given to the subject on all aspects of the clinical investigation that are relevant to the subject's decision to participate. This process includes obtaining an ICF and an Authorization to Use and Disclose Personal Health Information/Research Authorization/other privacy language when required by law that has been approved by the investigation center's EC/IRB and Medtronic, and signed and dated by the subject (or their legally authorized representative or guardian). A subject may only consent after information has been given to the subject on all aspects of the clinical investigation that are relevant to the subject's decision to participate.

Prior to enrolling subjects, each investigational center's EC/IRB will, as required by geography approve the CIP, ICF, and the Authorization to Use and Disclose Personal Health Information/Research Authorization/other privacy language. The document(s) must be controlled (i.e. versioned and dated) to ensure it is clear which version(s) were approved by the EC/IRB. Any adaptation of the sample ICF must be approved by Medtronic and the EC/IRB reviewing the application prior to enrolling subjects. EC/IRB approval must be accompanied with and EC/IRB roster or letter of compliance.

Each investigational center's EC/IRB will also be required to approve subject recruitment materials and other information that will be provided to the subject.

Prior to initiation of any study-specific procedures, patient informed consent must be obtained from the subject (or their legally authorized representative or guardian). Likewise, privacy or health information protection regulation in other geographies may require subjects to sign and date additional forms to authorize centers to submit subject information to the study sponsor. The ICF and Authorization to Use and Disclose Personal Health Information/ Research Authorization / other privacy language as required by law must be given to the subject (or their legally authorized representative or guardian) in a language he/she is able to read and understand. The process of patient informed consent must not be conducted using coercion or undue improper influence on or inducement of the subject to participate by the investigator or other center personnel.

The process of obtaining patient informed consent shall:

- Not waive or appear to waive the subject's legal rights
- Use language that is non-technical and understandable by the subject
- Provide ample time for the subject to read and understand the ICF and to ask questions, receive answers and consider participation
- Include a personally dated signature by the subject (or authorized legal representative) acknowledging that participation in the study is voluntary
- Europe: Include a personally dated signature by the principal investigator or authorized designee responsible for conducting the informed consent process

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

In the event the subject cannot read and/or write, witnessed (impartial third party) patient informed consent will be allowed, provided detailed documentation of the process is recorded in the subject's case history and the witness signs and dates the ICF patient informed consent. The subject should "make his/her mark" (sign or otherwise physically mark the document so as to indicate consent) on the ICF as well. The ICF 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 or a copy of the signed and dated ICF must be filed at the study center. An original or copy of the signed and dated ICF and signed Authorization to Use and Disclose

Personal Health Information / Research Authorization / other privacy language as required by law must be provided to the subject. When a patient signs and dates the ICF, he/she is considered a subject enrolled in the study.

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

Any changes to a previously approved ICF throughout the course of the study must be approved by the EC/IRB reviewing the application and the study sponsor before being used to consent a prospective study subject. The document(s) must be controlled (i.e. versioned and and/or dated) to ensure it is clear which version(s) were approved by the EC/IRB. If new information becomes available during the course of the study that could affect subjects' future health and/or medical care, this information shall be provided to subjects in written form. If relevant, approval may be requested from subjects to confirm their continued participation.

6.5 Enrollment and baseline

When a patient signs and dates the ICF, he/she is considered a subject enrolled in the study and the patient chart is to be noted accordingly that the subject is enrolled in the study. Study-related information collection and testing may begin only after the ICF has been signed and dated.

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

- Informed Consent
- Inclusion/Exclusion assessment
- Demographics
- Medical history
- Physical Exam
- Symptomatology
- External ECG assessment

  Note: If a subject has not had an external monitoring (minimum of 24 hour monitor) performed within the previous 90 days prior to enrollment, he or she must complete this test prior to Reveal ICM implant. If AF was diagnosed on the external ECG monitor the subject will be exited from the study.

- Echocardiogram

  Note: If a subject has not had an echocardiogram performed within the previous 6 months prior to enrollment, he or she must complete this test prior to Reveal ICM implant. If AF was diagnosed on the echocardiogram the subject will be exited from the study.

- Blood sample collection and analysis:
    - Five blood tubes (one plasma, three serum and one whole blood) will be collected, processed, and sent to the central laboratory for analysis of biomarkers that are considered potential predictors of identifying patients who are at high risk for AF.
        - One 6 mL tube of blood will be collected and processed for plasma for B-type Natriuretic Peptide (BNP) analysis. The residual from the tube will be kept in long-term storage for future analysis.
        - Two 5 mL tubes of blood will be collected and processed for serum for Troponin-I, C-reactive protein (CRP), and thyroid-stimulating hormone (TSH) testing. The residuals from these three tubes will be kept in long-term storage for future analysis.
        - One 5 mL tube of blood will be collected, processed for serum and kept in long-term storage for future analysis.
        - One 4 mL tube of whole blood will be collected for genetic testing such as genotyping single nucleotide polymorphisms (SNP).
    - Patients, who have completed their baseline visit under Version 1 CIP, will have these 5 blood samples collected at their next scheduled visit, provided consent was obtained for collection of these blood samples.
    - Specifics regarding the acquisition of these specimens, necessary supplies, and shipping information, under separate cover, will be provided to all study centers by the central laboratory.
- QOL questionnaire: EQ-5D
- Cardiovascular medications
- Heart Rate, Blood Pressure, Height, Weight

6.6 Implant

Implantation must be performed within 6 weeks following study enrollment (dated signature of the ICF). The implant procedure will be performed in accordance with the hospital's standard implant practice and in accordance with the Medtronic Reveal ICM implant instructions (for instance, determine preferred implant site and device position with Vector Check tool, create tight subcutaneous pocket, and suture).

After the Reveal ICM device is implanted, the surgical team will perform diagnostic testing specific to R-wave sensing to ensure that the Reveal ICM device is accurately identifying R-waves and calculating heart rate from R-R intervals per standard implant recommendations. The programmer ECG trace with marker annotations is used to evaluate R-wave sensing and adjust gain as necessary to prevent under- or over-sensing. Ideally, this should be done at the time of implantation, and then repeated post-operatively when the study participant is awake shortly and before discharge from the hospital.

The following information will be collected during the implant visit:

- Reveal ICM device serial number
- Reveal ICM device implant location and orientation

- Device interrogation and data transfer (e.g. save-to-disk, USB data transfer)
- Cardiovascular medications assessment
- Healthcare utilization assessment

6.6.1 Programming Requirements

Table 3 below outlines the programming parameters for which there are required settings.

Table 3: ICM device programming requirements

Parameter	Required Setting
Type of AT/AF detection	AF only
AF Detection	Balanced sensitivity
AT/AF Record ECG of	≥6 minutes
Ectopy Rejection	ON
FVT ECG recording	OFF
VT ECG recording	OFF
Brady ECG recording	OFF
Asystole ECG recording	OFF
AT/AF ECG recording	ON

6.7 Reprogramming

The Reveal ICM device is to be programmed according to Table 3. Reprogramming of the parameters that are off may be done only if needed for clinical reasons. However, they should be reprogrammed again back to the initial settings as soon as clinically feasible and a study deviation should be reported.

6.8 Subject CareLink Transmissions

Subjects are required to have their Reveal ICM interrogated monthly via CareLink transmissions following successful Reveal ICM implant. For the monthly CareLink transmissions that would coincide with a scheduled follow-up visit (i.e. 6-month follow-up visit), a CareLink transmission is not required but a device interrogation and data transfer (e.g. save-to-disk, USB data transfer) is still required at the follow-up visit.

CareLink transmission data will be automatically transferred to the Medtronic Data Warehouse for CareLink. If unavailable, centers may be required to submit CareLink reports by uploading them to a secure server or sending printed versions of the CareLink reports to Medtronic.

6.9 Scheduled follow-up visits

After receiving notice of successful implantation, Medtronic will provide the target dates and windows for each visit to the implanting center. Follow-up visits at 6 months, 12 months, and 18 months post implant are required for all subjects. After the 18 month follow-up visit,

the subject will continue to have a follow-up in-office visit at 24 and 30 months or until the last subject has completed their 18 month follow-up visit, whichever comes first. Table 4 documents the required follow-up schedule and visit windows.

Should a subject visit fall outside the pre-specified window, or is not performed (missing visit), a deviation is to be reported. Data analyses will include late follow-up visits, so a late visit is preferred over a missed visit. However, the original visit schedule must be maintained for all subsequent follow-up visits.

Table 4: Follow-up schedule and visit windows

Study Follow-up Visit	Window (time post-implant)		
	Window Start (time post-implant)	Target (time post-implant)	Window End (time post-implant)
Follow-up 1: 6 mo	152 days (22 weeks)	182 days (26 weeks)	212 days (30 weeks)
Follow-up 2: 12 mo	334 days (48 weeks)	365 days (52 weeks)	395 days (56 weeks)
Follow-up 3: 18 mo	516 days (74 weeks)	546 days (78 weeks)	576 days (82 weeks)
Follow-up 4: 24 mo	700 days (100 weeks)	730 days (104 weeks)	760 days (108 weeks)
Follow-up 5: 30 mo	881 days (126 weeks)	911 days (130 weeks)	941 days (134 weeks)

The following information will be collected during follow-up visits:

- Cardiovascular medications assessment
- Symptomatology
- Treatment decisions/actions taken
- QOL questionnaire: EQ-5D
- Healthcare utilization assessment
- Device interrogation
- System modifications (if applicable)
- Assessment to determine if cardiovascular related procedures (i.e. echo, treadmill stress test, chest x-ray, etc) were completed since prior visit.

6.10 Unscheduled visits

An unscheduled visit is defined as any unplanned visit for cardiovascular related reasons made to the study site. Unscheduled visits will be entered onto an unscheduled visit case report form. Data collection requirements at an unscheduled visit comprise:

- Cardiovascular medications assessment
- Symptomatology
- Treatment decisions/actions taken
- Healthcare utilization assessment
- Device interrogation
- System modifications (if applicable)
- Assessment to determine if cardiovascular related procedures (i.e. echo, treadmill stress test, chest x-ray, etc) were completed since prior visit

6.11 Healthcare Utilization

All cardiovascular-related Health Care Utilizations (including hospitalizations, emergency department visits, outpatient treatment involving overnight stay, urgent care, or outside clinic visits) will be collected and should be reported on a Health Care Utilization case report form. Note: A HCU eCRF is not to be completed for any visit made to the study center, whether the visit was for a scheduled study follow-up or an unscheduled follow up visit. For follow-up/unscheduled visits to the study center, only the follow up/unscheduled, eCRF, as appropriate, is required. Cardiovascular related Healthcare Utilization (HCU) information should be reported upon center awareness and assessed at all scheduled/unscheduled follow-up visits. Any visit where changes occur to CIP required programming parameters is considered cardiovascular-related. For HCUs involving changes to CIP required programming parameters, both an initial and final device interrogation will be required and two copies should be made, one for Medtronic and one for the subject's file.

6.12 System Modification

A system modification will be reported in the event that the Reveal ICM device requires invasive modification, i.e., the implanted monitor is repositioned, replaced or explanted. If the modification consists of repositioning or replacement, the follow-up schedule for the subject will remain unchanged. If the Reveal ICM is explanted without replacement prior to the 18 month follow-up, the subject will be exited from the study. If the Reveal ICM is explanted and a Medtronic IPG, ICD, or CRT device is implanted the subject can continue participation in this study (see Section 7 for handling of explanted Reveal ICM). For subjects who receive a Medtronic IPG, ICD, or CRT device and continues in the study, Table 5 outlines the recommended programming for these devices. The other parameters for these devices are to be programmed based on the investigators opinion.

Table 5 Recommended programming parameters for Medtronic IPG, ICD or CRT devices

Parameter	Recommended Setting
Atrial preference pacing (APP)	OFF
Atrial rate stabilization (ARS)	OFF
Post-mode switch overdrive pacing (PMOP)	OFF
Atrial Anti-tachycardia pacing (ATP)	OFF
AT/AF detection and EGM collection	Nominal

For a system modification the following activities are required:

- Reason(s) for modification
- Pre-modification: device interrogation with download
- Post-modification: device interrogation with download (if the modification involved only repositioning or explant with replacement)
- Healthcare utilization assessment

6.13 Study Exit

Once a subject is enrolled every effort should be made to keep the subject in the study. Study exit of a subject before study closure and reason for subject withdrawal must be documented in the patient medical chart and on the e-CRFs. All data available through the time of the subject exit will be used for the study analyses.

Subjects may be exited from the trial for any of the following situations:

- Subject has completed follow-up
- Subject was not successfully implanted with Reveal ICM
- Subject lost to follow-up
- Subject death
- Subject has AF or atrial flutter diagnosed via the external ECG monitoring conducted prior to Reveal ICM implant.
- Subject had Reveal ICM monitor explanted prior to18 month follow-up and did not receive a study approved replacement
- Subject chose to withdraw (e.g., consent withdrawal, relocation to another geographic location)
- Investigator deemed withdrawal necessary (e.g., medically justified, inclusion/exclusion criteria not met, failure of subject to maintain adequate study compliance)

6.13.1 Lost to follow-up

If the subject is determined to be lost to follow-up, the details regarding 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. Any additional regulations set forth by the governing IRB or MEC must be followed.

6.13.2 Subject-initiated and investigator withdrawal

If the subject wishes to withdraw from the study, or the investigator deems withdrawal necessary, the center is required to document the subjects' exit and reason for withdrawal. Upon withdrawal from the study, no further study data will be collected for the subject and no additional study visits will occur. The subject will continue to receive standard medical care comparable to what he or she would have received had Reveal ICM been implanted without being enrolled in a study.

6.13.3 Study exit upon sponsor request

In the event that study exit occurs upon sponsor request, no further study data will be collected for the subject and no additional study visits will occur. The subject will continue to receive standard medical care comparable to what he or she would have received had the Reveal ICM been implanted without being enrolled in a study.

6.14 Medications

Information on cardiovascular medications will be collected at the baseline visit and throughout the follow-up visits for the subject. Also, information regarding medications given for non-cardiac disorders that may, in the investigator's opinion, affect heart rate

(e.g., a beta adrenergic antagonist administered topically to treat glaucoma) will be collected.

No specific medications are required for the study. The only medications that are excluded from use during the study would be investigational medications.

7. DEVICE STORAGE, HANDLING AND TRACEABILITY

The Reveal ICM system used in this study is commercially available (no investigational components). There are no additional instructions for storage, use and handling for the Reveal ICM system components than the ones covered in the product manuals that are packaged with the devices. No traceability of the Reveal ICM is required.

7.1 Final product disposition

It is not a study requirement to return explanted devices to Medtronic. However, any Reveal ICM that is explanted due to device adverse effects or device malfunction should be returned to Medtronic for analysis. Similarly, if the subject dies during the study, explant of the Reveal ICM and its return to Medtronic for analysis is recommended, if local laws permit this. Prior to explant, the device should be interrogated and data downloaded or a CareLink transmission performed, if at all possible.

When the Reveal ICM or other system component is returned to Medtronic, internal product reporting systems may be used to gather additional information about the returned item. To receive a Returned Product Mailer Kit, contact your local Medtronic field personnel or the REVEAL AF Clinical Trial Leader.

8. STUDY DEVIATIONS

A study deviation is defined as a situation or event within a study that represents non-compliance with the CIP, or non-compliance with other study documents such as the CTA. The investigator should contact Medtronic in situations where the investigator anticipates or contemplates a decision to deviate. The investigator should also contact Medtronic to discuss circumstances in which a deviation will apply to all visits going forward, and if so to determine if it is appropriate to capture such circumstances in a single deviation report. Such circumstances might be a medically justifiable condition, or other unforeseen situations that will continue (e.g. subject permanently refusing a specific, but non-essential (not contributing to primary endpoint) measurement or procedure).

The investigator does not need to contact Medtronic when a deviation from the CIP is necessary to protect the safety, rights or physical well-being of a subject in an emergency or for non-emergency situations that are both unforeseen and 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).

All study deviations must be reported on the Study Deviation CRF independent of the reason for the deviation (i.e. whether medically justifiable, an inadvertent occurrence, or whether taken to protect the subject in an emergency). The deviation must be recorded with an explanation for its occurrence.

Medtronic is responsible for analyzing deviations, assessing their significance, and identifying any additional corrective and/or preventive actions (e.g. initiating an amendment to the CIP, conducting additional training). Repetitive or serious investigator compliance issues may represent a need to initiate a corrective action plan with the investigator and site, and in some cases, necessitate freezing enrollment until the problem is resolved, or terminating the investigator's participation in the study.

8.1 Reporting timelines

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 Medtronic and to the IRB/MEC within the time required by IRB/MEC policies, local laws and/or the local supervising regulatory agency. For all other study deviations, it is expected that reporting to Medtronic will occur as soon as possible after the center becomes aware that the deviation has occurred. On a periodic basis, Medtronic will provide center-specific reports to investigators that will summarize information about all the various deviations that have occurred at the investigational site.

9 ADVERSE EVENTS AND DEVICE DEFICIENCIES

Timely, accurate, and complete reporting and analysis of safety information for clinical studies are crucial for the protection of subjects, investigators and the sponsor. 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.

9.1 Adverse Event (AE) and Device Deficiency Assessment

9.1.1 Adverse Events

All cardiovascular-related adverse events as well as all serious adverse events (SAEs) will be collected throughout the study duration, beginning at the time that the ICF is signed and dated. Retrospective reporting of SAE's must be performed for subjects enrolled under the previous version of the CIP. These events will be reported to Medtronic on an Adverse Event electronic case report form (e-CRF).

Each reportable AE must be reported separately and will include a description of the event, the diagnosis, the date of event onset, the date the site became aware of the event, seriousness of the event, diagnostic tests and procedures performed, actions taken as a result of the event, relatedness of the event, and the outcome of the event.

The completed eCRF must be sent to Medtronic per the reporting timelines in Section 9.5.

In case the AE is related to the market approved device during the study, post market surveillance is also applicable and the investigator is responsible for immediate reporting of the product complaint via the regular channels for market released products.

9.1.2 Device Deficiencies

Device deficiency information will be collected throughout the study and reported to Medtronic. A Device Deficiency is an 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.* A Device Deficiency that did not lead to a reportable AE should be reported as a Device Deficiency only. Retrospective reporting of Device deficiencies must be performed for subjects enrolled under the previous version of the CIP.

Device deficiencies that did not lead to an AE but could have led to a Serious Adverse Device Effect (SADE) (i.e., if suitable action had not been taken, if intervention had not been made, or if the circumstances had been less fortunate) require immediate reporting (refer to section 9.5 for reporting requirements).

9.1.2 Processing Updates and Resolution

For any changes in the 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 reported. All AEs must be followed until the AE has been resolved, is unresolved with no further actions planned, subject exit/death, or until study closure, whichever occurs first.

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, test and procedures or actions taken, the outcome must be updated to reflect "Unresolved at time of study exit / death / study closure."

9.2 Adverse Event definitions, classification and reporting

9.2.1 Adverse Event Definitions

Table 6: Adverse Event definitions

General	
Adverse Event (AE)	Any untoward medical occurrence, intended disease or injury, or untoward clinical signs (including abnormal laboratory findings) in subjects, users or other persons, whether or not related to the investigational medical device. – NOTE 1: This definition includes events related to the investigational medical device or the comparator. – NOTE 2: This definition includes events related to the procedures involved. – NOTE 3: For users or other persons, this definition is restricted to events related to investigational medical devices.

Adverse Device Effect (ADE)	Adverse event related to the use of an investigational medical device NOTE 1: This definition includes adverse events resulting from insufficient or inadequate instructions for use, deployment, implantation, installation, or operation, or any malfunction of the investigational medical device. NOTE 2: This definition includes any event resulting from use error or from intentional misuse of the investigational medical device.
Device Deficiency (DD)	Inadequacy of a medical device with respect to its identity, quality, durability, reliability, safety or performance NOTE: Device deficiencies include malfunctions, use errors, and inadequate labeling.
Seriousness	
Serious Adverse Event (SAE)	adverse event that a) led to death b) led to a serious deterioration in the health of the subject, that either resulted in • a life-threatening illness or injury, or • a permanent impairment of a body structure or a body function, or • in-patient hospitalization or prolonged hospitalization, or • medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function, c) led to fetal distress, fetal death or a congenital abnormality or birth defect. NOTE Planned hospitalization for a pre-existing condition, or a procedure required by the CIP, without serious deterioration in health, is not considered a serious adverse event
Serious Adverse Device Effect (SADE)	Adverse device effect that has resulted in any of the consequences characteristic of a serious adverse event.
Relatedness	
Cardiovascular Related	An adverse event relating to the heart and the blood vessels or the circulation. This includes all arrhythmias, strokes, TIAs, etc.

9.2.2 Adverse Event and Device Deficiency classification and reporting

Upon receipt of AEs at Medtronic, a Medtronic representative will review the AE 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 medical term for each AE based on the information provided by the investigator.

Regulatory reporting of AEs and device deficiencies that could have led to an SADE will be completed according to local regulatory requirements. Refer to Table 9 for a list of required investigator and Medtronic reporting requirements and timeframes. It is the responsibility of the investigator to comply with any additional AE reporting requirements set by the local EC/IRB responsible for oversight of the study.

AEs will be classified as outlined below:

Table 7: Adverse Event classification responsibilities

What is classified?	Who classifies?	Classification Parameters
Severity	Investigator	seriousness
Diagnosis	Investigator	Based on presenting signs and symptoms and other supporting data
	Sponsor	MedDRA term assigned based on the data provided by Investigator

9.3 Subject death

9.3.1 Death data collection

All subject deaths must be reported by the investigator to Medtronic as soon as the investigator first learns of the death using a Death e-CRF. The Reveal ICM should, if possible, be explanted and returned to Medtronic for analysis if permitted by local laws.

If possible, prior to explant, the Reveal ICM should be interrogated, and the data downloaded. If any system component is returned to Medtronic, internal return product reporting systems may be used to gather additional information about the returned device/component.

In summary, the following data will be collected:

- Date of death
- Detailed description of death
- Cause of death
- Relatedness to device system and/or procedure
- Device interrogation(if possible)
- Device disposition information

9.3.2 Death classification and reporting

Sufficient information will be required in order to properly classify a subject death. The Investigator shall classify each subject death in accordance with the following definitions:

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

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

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

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

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

Table 8: Subject death classification responsibilities

What is classified?	Who classifies?	Classification Parameters
Relatedness	Investigator	Reveal ICM system or procedure
Death Classification	Investigator	Cardiac, Sudden Cardiac, Non-sudden Cardiac, Non-cardiac, Unknown

Regulatory reporting of subject deaths will be completed according to local regulatory requirements. Refer to Table 9 for a list of required investigator and sponsor reporting requirements and timeframes.

9.4 Market-released reporting requirements

All devices used in this study are market released. It is the responsibility of the investigator to report all product complaints and malfunctions immediately via the regular channels for market approved, CE marked products. The reporting of product complaints and malfunctions is not part of the clinical study and should be done in addition to the Adverse Event reporting requirements.

9.4.1 Europe:

Product Complaint: Any written, electronic or oral communication that alleges deficiencies related to the identity, quality, durability, reliability, safety, effectiveness or performance of a device after it is released for distribution.

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

A serious deterioration in the state of health can include:

1. Life-threatening illness
2. Permanent impairment of a body function or permanent damage to a body structure
3. A condition necessitating medical or surgical intervention to prevent a) or b)
4. Any indirect harm as a consequence of an incorrect diagnostic or in vitro diagnostic test results when used within manufacturer's instructions for use
5. Fetal distress, fetal death or any congenital abnormality or birth defects

Note: Not all incidents lead to death or serious deterioration in health. The non-occurrence of such a result might have been due to other fortunate circumstances or to the intervention of healthcare personnel. It is sufficient that: an incident associated with a device happened, and the incident was such that, if it occurred again, it might lead to death or serious deterioration in health.

Vigilance Reporting: A system used to notify the Competent Authority (CA) about incidents with regard to medical devices that carry the CE-mark. This system requires a manufacturer to notify the CA of incidents immediately upon learning of them (ref: MEDDEV 2.12-1 rev 5 (Guidelines on a Medical Device Vigilance System), April 2007)"

9.4.2 United States:

Medical Device Reporting (MDR) Requirements for User Facilities
General Reminder for Investigators:

Per FDA regulations, Device User Facilities are required to report Medical Device Reports (MDR) on market approved products (21 CFR 803, subpart C) A Device User Facility is defined as a hospital, an ambulatory surgical facility, a nursing home, an outpatient treatment facility, or an outpatient diagnostic facility which is not a physician's office.

9.5 Adverse Event and Device Deficiency records and reporting requirements

Adverse Events will be recorded and reported according to local regulatory requirements. Refer to Table 9 for adverse event reporting requirements. It is the responsibility of the Investigator to abide by the adverse event reporting requirements stipulated by the centers' EC/IRB.

The investigator is required to report these events to Medtronic as noted in Table 9, and to the EC/IRB per local requirements. Medtronic is also required to report these events to the local competent authority based on their requirements

Table 9: Adverse Event Reporting Requirements

Serious Adverse Events (SAEs)	
Investigator submit to:	
Medtronic	**Europe:** Immediately after the investigator first learns of the event. (ISO 14155 and local law) **All other geographies:** Submit in a timely manner after the investigator first learns of the event.
EC/IRB	**Europe:** Submit to EC/IRB per local reporting requirement **All other geographies:** Submit per local EC requirement.
Sponsor submit to:	
Regulatory authorities	**Europe:** Submit to Competent Authority per local reporting requirement.
EC/IRB	**Europe:** Submit to EC/IRB per local reporting requirement.
All other reportable Adverse Events (cardiovascular-related) and Deaths	
Investigator submit to:	
Medtronic	**All geographies:** Submit in a timely manner after the investigator first learns of the event.
Regulatory authorities	**All geographies:** Submit or report as required per local reporting requirement.
EC/IRB	**All geographies:** Submit per local EC/IRB requirement.

Sponsor submit to:	
Regulatory authorities	**Europe:** Submit to Competent Authority per local reporting requirement, as applicable
EC/IRB	**Europe:** Submit to EC/IRB per local reporting requirement.
Device Deficiencies with SADE potential	
Investigator submit to:	
Medtronic	**Europe**: Immediately after the investigator first learns of the deficiency or of new information in relation with an already reported deficiency. **All other geographies**: Submit or report as required per local reporting requirements.
Ethics Board	Submit per local EC requirement.
Regulatory authorities	Report immediately after the investigator first learns of the event if required according to local law.
Sponsor submit to:	
Regulatory authorities	**All geographies**: Submit or report as required per local reporting requirements.
Ethics Board	**All geographies**: Submit per local Ethics Board requirement.
All other Device Deficiencies	
Investigator submit to:	
Medtronic	**All geographies**: Submit in a timely manner after the investigator first learns of the deficiency.
Regulatory Authorities	**All geographies**: Submit or report as required per local reporting requirement.
EC	**All geographies**: Submit per local EC 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. All the equipment and the implantable devices in the REVEAL AF study are market-released in all participating countries (for instance, FDA approved for USA, and CE mark for Europe) and are used in accordance with medical, technical, and ethical standards and in accordance with their approved and intended use. There are no incremental risks introduced to the subject as a result of participation in the REVEAL AF study. Devices should be handled according to the Clinical Manual.

There are potential risks and discomforts associated with receiving a subcutaneous insertable cardiac monitor. Standard risks as described in the Reveal ICM Clinician Manual are:

- Device rejection phenomena including local tissue reaction
- Device migration
- Pocket infection and erosion through the skin

The risks identified above will be minimized by careful assessment of each subject prior to, during, and after implant of the Reveal ICM.

10.1 Risk Minimization

The potential risks associated with the Reveal ICM system have been identified and mitigated. Any potential risks associated with this study are minimized by selecting qualified investigators and training study personnel on the CIP.

Risks will be minimized by careful assessment of each subject prior to, during, and after implant of the Reveal ICM. Medtronic has also attempted to minimize risk to subjects by ensuring the investigators will be involved with the diagnosis, referral for implant (as necessary), the implant and follow-up of the subjects implanted with the Reveal ICM system. Prior to implant, it is recommended subjects undergo a complete cardiac evaluation.

Medtronic has further minimized the possibility of risks by implementing and maintaining quality control measures into device production, providing guidelines for subject selection and evaluation, and providing appropriate and adequate instructions and labeling.

After implantation, subjects in the Reveal AF clinical study will be followed at regular intervals to monitor the condition of the implanted system. At each CIP required in office follow-up, the investigator must interrogate the Reveal ICM device to verify appropriate function, evaluate sensing characteristics, and to determine if there are any adverse events.

10.2 Potential Benefits

Participation in the REVEAL AF study may offer no direct personal benefit to individual subjects. Subjects may benefit from continuous ECG monitoring with the Reveal ICM, as this monitoring could result in diagnosis of AF (or other arrhythmias) and comprehensive evaluation of symptoms on an earlier and more conclusive basis than what would be possible without an implantable monitor. Subjects may also benefit from being evaluated in-office at 6 month intervals as required by the study visit schedule.

The information gained from this study could result in the improved management of AF in individuals who are at high risk for stroke. Additionally, information collected from this study may assist in the design of new product(s)/therapy(ies) and/or instructions for use.

10.3 Risk-to-Benefit Analysis

Since the Reveal ICM device is a market-released (FDA approved for USA and CE mark for Europe) device used in accordance with its approved and intended use, the risks associated with the device are the same as would be the case if the subject received the device outside the study context. There are no additional tests or assessments required that add risks compared to standard of care. The study requirements for careful selection, training, and monitoring of the participating physician and for detailed in-office evaluation of the subject at 6 month intervals carry potential benefits that might not be present if the subject received the device without participating in the study. Hence, for individual subjects, participation in the study has greater benefit than risk. Moreover, the value of the knowledge to be gained by conducting this clinical study outweighs the potential risks to study participants.

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 an initial study closure letter. Study closure is defined as closure of a clinical study that occurs when Medtronic and/or regulatory requirements have been satisfied per the CIP and/or by a decision by Medtronic or regulatory authority, whichever occurs first. Continued IRB/MEC oversight is required until the overall study closure process is complete. The study closure process is complete upon distribution of the Final Report or after final payments. With regard to individual subjects, no dedicated closure visit will occur in association with overall study closure, and no medical care as defined by the study will be provided to the subject following overall study closure.

11.2 Early termination or suspension

Early termination of the study is the closure of a clinical study that occurs prior to meeting defined endpoints. This is possible for the whole study, or for a single study center.

Study suspension is a temporary postponement of study activities related to enrollment and distribution of the product. This is possible for the whole study or a single center.

11.2.1 Study-wide termination or suspension

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

- Observed/suspected performance different from the product's design intent
- Decision by Medtronic or by a regulatory body
- Technical issues during the manufacturing process

11.2.2 Investigator/center termination or suspension

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

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

11.3 Procedures for termination or suspension

If the termination or suspension is initiated by Medtronic, by an investigator, or by an EC/IRB, Medtronic will inform the regulatory authority(ies) where by local geography.

11.3.1 Medtronic-initiated

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

11.3.2 Investigator-initiated

- The investigator will inform Medtronic and provide a detailed written explanation of the termination or suspension
- The investigator will promptly inform the institution (where required per regulatory requirements)
- The investigator will promptly inform the MEC/IRB.
- The investigator will promptly inform the subjects and/or the personal physician of the subjects to ensure that 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

11.3.3 EC/IRB 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 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

12.1 Primary Objective

Determine the incidence rate of AF lasting greater than or equal to six minutes in patients who are at high risk of having AF.

12.1.1 Hypothesis

The purpose of the objective is to estimate the incidence of AF in this patient population, and thus no pre-specified hypotheses will be tested.

12.1.2 Endpoint Definition

AF will be defined as an arrhythmic episode lasting at least 6 minutes in duration and adjudicated to be AF.

12.1.3 Performance Requirements

A 95% two-sided confidence interval will be generated for the 18 month event rate. There is no pre-specified threshold for success.

12.1.4 Rationale for Performance Criteria

Because the rate of AF is unknown in this population, the purpose of this objective is simply to estimate what the incidence rate over 18 months is for this population. Thus, a threshold for success is not necessary for this objective.

12.1.5 Sample Size Determination

The sample size requirement for this objective was chosen to generate a 95% two-sided confidence interval for the 18 month incidence rate of AF that would be approximately 10 percentage points in width. To assess the sample size requirement, data from a subset of the CONNECT study subjects comparable to the target population (ICD subjects with no history of AF or stroke but possessing a CHADS score of at least 3 or of 2 along with coronary artery disease) was used to estimate the likely incidence rate in this population. CONNECT study subjects were only followed through 15 months, but based on the available data the extrapolated 18 month event rate was estimated to be between 16% and 20%. Assuming an event rate of 20% at 18 months and 10% attrition per year, a sample size of 292 would ensure an 80% chance of generating a confidence interval with 10% width (i.e., 14.4% to 24.4%). However, due to the secondary goal of identifying a subset of high risk patients most likely to have undiagnosed AF, it is desirable to allow for greater representation of the underlying population by using a sample of up to 400 patients implanted. Given it is expected that approximately 5-10% of the subjects enrolled in the study will have AF detected via external ECG monitoring, up to 450 subjects will be enrolled in the study.

12.1.6 Analysis Methods

Arrhythmic episodes identified by the device as AF and lasting 6 or more minutes will be stored by the device with EGM data, so that the episodes can be adjudicated to confirm they are truly AF. The time to first such episode with EGM

data available will be determined for each subject. If a subject does not experience an endpoint during follow-up, the subject will be censored at the date of their last device interrogation. Time 0 will be the date of device implant. A Kaplan-Meier event curve will be generated, along with 95% confidence bounds. Only adjudicated AF episodes will be included for analysis.

12.1.7 Determination of Subjects/Data for Analysis

Subjects who were successfully implanted with the Reveal ICM will be included in the analysis cohort. For those subjects who do not complete follow-up or receive a Medtronic IPG, ICD, or CRT during the course of the study, the analysis will include all data up to the point of their last useable interrogation. However, subjects will be excluded from analysis based on the following CIP violations that would affect endpoint analysis:

- Subject had AF prior to the Reveal ICM implant
- Subject did not satisfy the $CHADS_2$ score inclusion criterion at time of study enrollment
- Subject was taking an anti-arrhythmic medication at time of enrollment

12.2 Secondary Objective #1: Predictors of AF

12.2.1 Identify predictors of AF onset in patients who are at high risk of having AF

Hypothesis

Let $h_0(t)$ denote the hazard rate for patients at high risk of AF developing AF. Consider a set of baseline characteristics X_1, X_2 … It is assumed that if these particular characteristics affect a patient's risk of developing AF, the effects have the form

$$h(t) = h_0(t)\exp(\beta_1 X_1 + \beta_2 X_2 + \ldots)$$

The null hypothesis is that these covariates have no effect on a patient's risk of developing persistent AF. In other words,

H_0: $\beta_i = 0$ for all i

H_A: $\beta_i \neq 0$ for some i

12.2.2 Endpoint Definition

AF will be defined as an arrhythmic episode lasting at least 6 minutes in duration and adjudicated to be AF.

12.2.3 Performance Requirements

The null hypothesis will be rejected if the p-value for any of the covariates listed in section 12.2.5 is less than 0.05.

12.2.4 Sample Size Determination

Based on the data from the CONNECT trial, it is assumed that approximately 16 to 20% of subjects will experience an AF event in their first 18 months of follow-up. Assume there is a single baseline comorbidity which divided patients into those with a lower prevalence of AF (e.g. 7-11% chance of experiencing AF in the first 18 months of having an ILR) and those with higher prevalence of AF (e.g. 22%

chance of experiencing AF in the first 18 months of having an ILR). Under this assumption and the assumption of 10% attrition per year, the following table provides power estimates for the comorbidity being shown to be significant in affecting the risk of experiencing AF, 400 total implanted subjects. In addition, it is expected that approximately 5-10% of the subjects enrolled in the study will have AF detected via external ECG monitoring; therefore, up to 450 subjects will be enrolled in the study.

Table 10: Power Calculations for Predictor Objective Assuming 10% Annual Attrition

Cohort Sample Size	Fraction of Cohort With Comorbidity	18 Month Event-free Rate with Comorbidity	18 Month Event-free Rate without Comorbidity	Power for detecting significant difference
400	25%	78%	88%	78.9%
400	30%	78%	88%	78.5%
400	35%	78%	88%	82.6%
400	45%	78%	88%	84.4%
400	25%	78%	90%	90.1%
400	35%	78%	90%	94.5%

12.2.5 Analysis Methods

The following baseline measurements will be evaluated in testing for predictors of persistent AF:

- Diabetes
- Heart Failure
- Age
- Hypertension
- Renal impairment
- COPD
- BMI
- BNP
- C-reactive protein
- Troponin-I
- TSH
- Prior stroke occurring >1 year ago
- Coronary artery disease
- Sleep apnea
- Family History
- Vascular disease
- Gender

A Cox proportional hazards model will be fit with each predictor simultaneously. Each subject's response will be the time until the subject experiences AF as

defined in section 12.2.2. If a subject does not experience AF during follow-up, the subject will be censored at their last device interrogation. Time 0 will be the date of implant. Age, BMI, BNP, C-reactive protein, Troponin-I, and TSH will be considered continuous variables in the model, while the other covariates will be treated as binary variables.

12.2.6 Determination of Subjects/Data for Analysis

Subjects who were successfully implanted with Reveal ICM will be included in the analysis cohort. For those subjects who do not complete follow-up or receive a Medtronic IPG, ICD, or CRT during the course of the study, the analysis will include all data up to the point of their last useable interrogation. However, subjects will be excluded from analysis based on the following CIP violations that would affect endpoint analysis:

- Subject had AF prior to the Reveal ICM implant
- Subject was taking an anti-arrhythmic medication at time of enrollment

12.3 Secondary Objective #2: Clinical Actions for AF

Characterize the timing and nature of clinical actions relative to detection of AF in patients who are at high risk of having AF.

12.3.1 Hypothesis

There are no pre-specified hypotheses for this objective, as the goal of the objective is to characterize clinical actions in response to AF detection.

12.3.2 Endpoint Definition

Actions taken in response to awareness and management of AF as identified by the clinician will be considered endpoints. AF might be an individual episode, or cumulative AF burden from the device's daily AF trending diagnostic, or it could be identified by some other means.

12.3.3 Performance Requirements

There are no performance requirements for this objective, as the purpose is simply to characterize the timing of clinical actions in response to awareness of AF.

12.3.4 Sample Size Determination

There is no sample size requirement for this objective.

12.3.5 Analysis Methods

Descriptive statistics will be used to summarize the actions taken when AF is identified by the clinician. This will include a breakdown of what types of actions are taken in response to awareness of AF. A Kaplan-Meier curve will be generated with Time 0 as the time of first AF diagnosis, and the event time as the time from Time 0 to the first action taken for AF. Annualized rates of specific actions (e.g. cardioversions, initiation of OAC, etc.) will be generated in 6 month intervals.

12.3.6 Determination of Patients/Data for Analysis

Subjects who were successfully implanted will be included in the analysis cohort for that. However, subjects will be excluded from analysis based on the following CIP violations:

- Subject had AF prior to the Reveal ICM implant
- Subject did not satisfy the $CHADS_2$ score inclusion criterion at time of study enrollment
- Subject was taking an anti-arrhythmic medication at time of enrollment

12.4 Exploratory Objective #1: AF Burden

Characterize AF burden over time in patients who are at high risk of having AF.

12.4.1 Hypothesis

There are no pre-specified hypotheses for this objective. The purpose of the objective is to estimate incidence of different amounts of daily AF in this patient population.

12.4.2 Endpoint Definition

For analyses showing the incidence of pre-defined amounts of device-detected AF in a single day, the following endpoints will be used:

- A day with at least 6 minutes of device-detected AF
- A day with at least 30 minutes of device-detected AF
- A day with at least 1 hour of device-detected AF
- A day with at least 6 hours of device-detected AF

These endpoints will be defined by device classification of arrhythmias rather than adjudication of arrhythmias.

12.4.3 Performance Requirements

There are no performance requirements for this objective, as the purpose is simply to estimate the incidence of different daily amounts of AF in this patient population.

12.4.4 Sample Size Determination

There is no sample size requirement for this objective.

12.4.5 Analysis Methods

To assess the development of pre-specified amounts of AF over time, Kaplan-Meier event curves will be generated for each of the endpoints described in section 12.4.2. Time 0 will be defined as the day of implant. For each curve, if a subject does not experience the corresponding endpoint during follow-up, the subject will be censored at the last device interrogation. AF burden beyond the first such event will be summarized by determining, for each day, the percentage of subjects experiencing each of the endpoints, and plotting the percentage for each such endpoint over time.

12.4.6 Determination of Patients/Data for Analysis

Subjects who were successfully implanted with Reveal ICM will be included in the analysis cohort. For those subjects who do not complete follow-up or receive a Medtronic IPG, ICD, or CRT during the course of the study, the analysis will include all data up to the point of their last useable interrogation. However, subjects will be excluded from analysis based on the following CIP violations:

- Subject had AF prior to the Reveal ICM implant
- Subject was taking an anti-arrhythmic medication at time of enrollment

12.5 Exploratory Objective #2: Non-atrial Arrhythmias

Characterize the presence of non-atrial arrhythmias in patients who are at high risk of having AF.

12.5.1 Hypothesis

There are no pre-specified hypotheses for this objective. The purpose of the objective is to estimate non-atrial arrhythmic activity in this patient population.

12.5.2 Endpoint Definition

Endpoints for this objective will be the following:

- Asystole (as defined by the device),
- Ventricular arrhythmias (as defined by the device),
- Bradycardia (as defined by the device).

These episodes will not be adjudicated, and so the device classifications will be used. Additionally, episodes classified by the device as AF but adjudicated to be asystole, ventricular arrhythmias, or bradycardia will also be counted as endpoints.

12.5.3 Performance Requirements

There are no performance requirements for this objective, as the purpose is simply to characterize rates of non-atrial arrhythmias as recorded by the device.

12.5.4 Sample Size Determination

There is no sample size requirement for this objective.

12.5.5 Analysis Methods

Stored device data will be collected via CareLink transmissions or in-office device interrogations. All non-atrial arrhythmias occurring within the follow-up period and reported by the device will be included in the analysis. Kaplan-Meier event curves will be generated to show the rate of first device detection of arrhythmias for each type. Descriptive statistics will also be provided for rates of each type of non-atrial arrhythmia.

12.5.6 Determination of Patients/Data for Analysis

Subjects who were successfully implanted with Reveal ICM will be included in the analysis cohort. For those subjects who do not complete follow-up or receive a

Medtronic IPG, ICD, or CRT during the course of the study, the analysis will include all data up to the point of their last useable interrogation.

However, subjects will be excluded from analysis based on the following CIP violations:

- Subject had AF prior to the Reveal ICM implant
- Subject did not satisfy the $CHADS_2$ score inclusion criterion at time of study enrollment
- Subject was taking an anti-arrhythmic medication at time of enrollment

12.6 Exploratory Objective #3: Quality of Life

Characterize Quality of Life over time in patients who are at high risk of having AF.

12.6.1 Hypothesis

There is no pre-specified hypothesis for this objective. The purpose of the objective is to estimate average Quality of Life over time, as measured by the EQ-5D Quality of Life questionnaire.

12.6.2 Endpoint Definition

The endpoints will be defined as the EQ-5D index score at each of the following time points: baseline, 6 months, 12 months, and 18 months.

12.6.3 Performance Requirements

There are no performance requirements for this objective, as the purpose is to characterize quality of life, as measured by the EQ-5D index score, over time in this population.

12.6.4 Sample Size Determination

There is no sample size requirement for this objective.

12.6.5 Analysis Methods

Subjects will be asked to complete the EQ-5D questionnaire at baseline, 6, 12, 18, 24, and 30 months. Descriptive statistics will be used to summarize the results at each time point.

12.6.6 Determination of Patients/Data for Analysis

Subjects who were successfully implanted with Reveal ICM will be included in the analysis cohort. Missing QOL data will not be imputed for analysis. However, subjects will be excluded from analysis based on the following CIP violations:

- Subject had AF prior to the Reveal ICM implant
- Subject did not satisfy the $CHADS_2$ score inclusion criterion at time of study enrollment
- Subject was taking an anti-arrhythmic medication at time of enrollment

12.7 Exploratory Objective #4: Healthcare Utilization

Characterize healthcare utilization in patients who are at high risk of having AF.

12.7.1 Hypothesis

There are no pre-specified hypotheses for this objective. The purpose of the objective is to characterize the rate of healthcare utilizations in this patient population.

12.7.2 Endpoint Definition

The following will be considered endpoints:

- Cardiovascular related Inpatient Hospitalizations
- Cardiovascular related Outpatient/Procedure Visits
- Cardiovascular related ED visits
- Cardiovascular related Urgent Care Visits
- Cardiovascular related Unscheduled Clinic Visits
- Device-related visits
- Renal-related visits
- Syncope-related visits
- Dyspnea-related visits

12.7.3 Performance Requirements

There are no performance requirements for this objective, as the purpose is simply to characterize rates of CV healthcare utilization in this patient population.

12.7.4 Sample Size Determination

There is no sample size requirement for this objective.

12.7.5 Analysis Methods

Annualized rates of each of the endpoints in section 12.7.2 will be generated, both overall and in 6 month intervals (e.g. CV inpatient hospitalization rate in first 6 months, months 6-12, etc.) to evaluate whether the rates change over time.

12.7.6 Determination of Patients/Data for Analysis

Subjects who were successfully implanted with Reveal ICM will be included in the analysis cohort. However, subjects will be excluded from analysis based on the following CIP violations:

- Subject had AF prior to the Reveal ICM implant
- Subject did not satisfy the $CHADS_2$ score inclusion criterion at time of study enrollment
- Subject was taking an anti-arrhythmic medication at time of enrollment

12.8 Exploratory Objective #5: Progression to Persistent AF

Identify predictors of progression to persistent AF in patients who are at high risk of having AF.

12.8.1 Hypothesis

Let $h_0(t)$ denote the hazard rate for patients at high risk of AF developing persistent AF. Consider a set of baseline characteristics X1, X2, … It is assumed that if these particular characteristics affect a patient's risk of developing persistent AF, the effects have the form

$$h(t) = h_0(t)\exp(\beta_1 X_1 + \beta_2 X_2 + \ldots)$$

The null hypothesis is that these covariates have no effect on a patient's risk of developing persistent AF. In other words,

H_0: $\beta_i = 0$ for all i

H_A: $\beta_i \neq 0$ for some i

12.8.2 Endpoint Definition

Persistent AF will be defined as 7 consecutive days with 23+ hours of device-detected AF, or less than 7 consecutive days with 23+ hours of device-detected AF due to a cardioversion.

12.8.3 Performance Requirements

The null hypothesis will be rejected if the p-value for any of the covariates listed in section 12.8.5 is less than 0.05.

12.8.4 Sample Size Determination

There is no sample size requirement for this objective.

12.8.5 Analysis Methods

The following baseline measurements will be evaluated in testing for predictors of persistent AF:

- Diabetes
- NYHA
- Age
- Hypertension
- Renal impairment
- COPD
- BMI
- BNP
- C-reactive protein
- Troponin-I
- TSH
- Prior stroke occurring >1 year ago
- Coronary artery disease

- Sleep apnea
- Family History
- Vascular disease
- Gender

A Cox proportional hazards model will be fit with each predictor simultaneously. Each subject's response will be the time until the subject experiences persistent AF as defined in section 12.8.2. If a subject does not experience persistent AF during follow-up, the subject will be censored at their last device interrogation. Time 0 will be the date of implant. Age, BMI, BNP, C-reactive protein, Troponin-I, and TSH will be considered continuous variables in the model, while the other covariates will be treated as binary variables. A Kaplan-Meier curve will be generated estimating freedom from persistent AF in this population.

For those subjects who experience a first AF episode as defined in section 12.1.2, a similar analysis will be done with Time 0 as the date of that first AF episode.

12.8.6 Determination of Patients/Data for Analysis

All subjects who were successfully implanted with Reveal ICM will be included in the analysis cohort. For the analysis evaluating time to progression from first AF onset to persistent AF, only subjects with an AF episode satisfying the primary endpoint definition will be included. For those subjects who do not complete follow-up or receive a Medtronic IPG, ICD, or CRT during the course of the study, the analysis will include all data up to the point of their last useable interrogation. However, subjects will be excluded from analysis based on the following CIP violations:

- Subject had AF prior to the Reveal ICM implant
- Subject was on an anti-arrhythmic medication at time of enrollment

12.9 General considerations

Data from all study centers will be pooled for analysis. Standard statistical methods will be employed to summarize and analyze the data.

The Statistical Analysis Plan (SAP) will include a comprehensive description of the statistical methods and reports to be included in the final study report. Any change to the data analytic 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.

Confidence intervals and any statistical significance testing will employ an alpha level of 0.05 unless otherwise stated. Tests of hypotheses will be two-tailed.

12.10 Missing data

If a subject is exited prior to study closure, his/her data will be included in analyses through the last date for which the center in contact with the subject for the healthcare utilization and Quality of Life objectives. For objectives with endpoints defined by device data (e.g. predictors of AF, incidence of AF, progression of persistent AF), only data through a subject's last device interrogation will be used.

For the AF predictor objectives, if one or more baseline covariates is missing for a subject, multiple imputation may be performed to assess robustness of results to missing data.

12.11 Adjustments for Covariates

No adjustments for covariates are planned, except in the case of evaluating predictors of AF.

12.12 Subgroup analysis

Multiple regression techniques will be used to determine whether there are characteristics or combination of characteristics present at baseline that have significant ability to predict which subjects will ultimately be found to have AF.

13. DATA AND QUALITY MANAGEMENT

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

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

For source documentation, the center study team must sign and date any copies or printouts of original source document with a statement that this is a true preproduction of the original source document and any discrepancies shall be explained in writing. Site study team must mark patient files for participation in the study.

Device interrogation data collected at follow up visits shall be sent to Medtronic and a copy must be kept on site. Device data from transmissions will be uploaded to secure servers. Upon receipt, device data will be maintained with secure databases and retrieved for analysis and reporting.

The sponsor may audit and a regulatory authority may inspect the study center to evaluate the conduct of the study. If a regulatory authority announces that an inspection of the study center will occur, this announcement must be provided to Medtronic immediately. The clinical investigator(s)/institution(s) shall allow study-related monitoring, audits, EC/IRB review, and regulatory inspection(s) by providing direct access to source data/documents. Confidentiality of data shall be observed by all parties at all times throughout the clinical study. All data shall be secured against unauthorized access.

14. WARRANTY/INSURANCE INFORMATION

14.1 Warranty

Warranty information is provided in the product packaging for the commercially released Reveal ICM system. Additional copies are available upon request.

14.2 Insurance (Europe)

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 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 EC/IRB.

15. MONITORING

It is the responsibility of Medtronic to ensure proper monitoring of this clinical investigation. Trained Medtronic personnel, or delegates appointed by Medtronic, will perform monitoring at the study center to ensure that the study is conducted in accordance with the CIP, the CTA, and applicable regulatory supervisory requirements including those of the EC/IRB. Monitoring is also performed to ensure that Regulatory documentation is up-to-date, to ensure that other records and reports are properly maintained, and to review source documents against eCRF entries. Medtronic, or its delegates, must therefore be allowed access to the subjects' case histories (clinic and hospital records, and other source data/documentation) when so requested as per the ICF, Research Authorization (where applicable) and CTA.

15.1 Monitoring Visits

Frequency of monitoring visits may be based on subject enrollment, duration of the study, study compliance, findings from previous monitoring visits and any suspected inconsistency in data that requires investigation. Regulatory documents (e.g., EC/IRB approval letters and CTAs) will be reviewed at each study center. Subject data will be monitored against source documentation (e.g., clinic and hospital charts). Monitoring for the study will be done in accordance to the study monitoring plan.

Monitoring visits will be conducted periodically to assess center study progress, the investigator's adherence to the CIP, regulatory compliance including but not limited to EC/IRB approval and review of the study, maintenance of records and reports, and review of source documents against subject eCRFs. Monitors verify center regulatory and study compliance by identifying findings of non-compliance and communicating those findings along with recommendations for preventative/corrective actions to center personnel. Communication with the center personnel occurs during the visit and following the visit via a written follow up letter. Monitors may work with study personnel to determine appropriate corrective action recommendations and to identify trends within the study or at a particular center. Study closure visits may be conducted via telephone, letter or an on-site visit at each enrolling study center according to the monitoring plan.

16. REQUIRED RECORDS AND REPORTS

16.1 Investigator records

The investigator has overarching responsibility for the preparation and retention of the records cited below. All of the below records, with the exception of case history records, case report forms, and other documents directly related to subjects, should be kept in the Study Center File (i.e., the study binder provided to the investigator). Electronic Case

Report Forms (eCRFs) may be maintained and signed electronically within the electronic data capture system during the trial.

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 study is terminated:

- All key correspondence between the MEC/IRB, sponsor, monitor, Competent Authority and/or the investigator that pertains to the study, including required reports.
- Subject's case history records, including:
  - Signed and dated ICF. In U.S. signed and dated by subject. Signed and dated by subject and investigator as required by geography.
  - Observations of Adverse Events
  - Medical history
  - Implant (when applicable) and follow-up data
  - Source for all eCRF elements
  - Documentation of the dates and rationale for any deviation from the CIP
- All approved versions of the CIP.
- Executed CTA.
- Investigator(s) Curriculum Vitae (CV) (Unites States)
- Current, signed and dated Curriculum Vitae (CV) of the Principal Investigator and all key members in the study (Europe)
- Documentation of delegated tasks.
- MEC/IRB approval documentation. Written information that the investigator or other study staff, when member of the MEC/IRB, did not participate in the approval process.
- Study training records for center staff (this includes anyone listed on the delegated task list).
- Insurance certificates (as required by geography).
- Any other records that IRB/EC or local regulatory agencies require to be maintained.
- Final Study Report including the statistical analysis.
- Subject screening log
- Monitoring Log
- Site specific ICF

16.2 Investigator reports

The investigator is responsible for the preparation (review and signature) and submission to the sponsor of all eCRFs, adverse events, deaths, and any deviations from theCIP. If any action is taken by an IRB/MEC with respect to this clinical study, copies of all pertinent documentation must be forwarded to Medtronic in a timely manner. Reports are subject to inspection and to the retention requirements as described above for investigator records.

Investigator reporting requirements for items related to Safety data are listed in Section 9.5. Table 11 and Table 12 below cover the investigator reporting requirements for all other reports. The investigator shall prepare and submit in a complete, accurate and timely manner the reports listed in this section.

Table 11: Investigator reports applicable to the United States

Report	Submit to	Description/Constraints
Withdrawal of IRB/MEC approval	Sponsor	The investigator must report a withdrawal of approval by the reviewing IRB/MEC of the investigator's part of the investigation within 5 working days.
Study Deviations	Sponsor and IRB/MEC	Reporting of study deviations should comply with MEC/IRB policies and/or local laws and must be reported to Medtronic as soon as possible upon the center becoming aware of the deviation.
Final Report	IRBs/MECs	This report must be submitted within 6 months of study completion or termination.
Failure to obtain informed consent	Sponsor and IRBs/MECs	Informed consent shall be obtained in writing from the subject and the process shall be documented before any procedure specific to the clinical investigation is applied to the subject

Table 12: Investigator reports applicable to Europe

Report	Submit to	Description/Constraints
Withdrawal of IRB/MEC approval	Sponsor	The principal investigator or authorized designee shall promptly inform the sponsor and enrolled subjects at his/her study site, as appropriate.
Progress Report	Sponsor and IRB/MEC	Provide if required by local law or MEC/IRB.
Study Deviations	Sponsor and IRB/MEC	The principal investigator shall document and explain any deviation from the approved CIP that occurred during the course of the clinical investigation The principal investigator shall promptly report any deviations from the CIP that affect the rights, safety or wellbeing of the subject or the scientific integrity of the clinical investigation, including those which occur under emergency circumstances, if required by the EC, CIP or national regulation,
Failure to obtain informed consent	Sponsor and IRBs/MECs	Informed consent shall be obtained in writing from the subject and the process shall be documented before any procedure specific to the clinical investigation is applied to the subject
Significant new information	Subject	If new information becomes available that can significantly affect a subject's future health and medical care, this information shall be provided to the subject(s) affected in written form. If relevant, all affected subjects shall be asked to confirm their continuing informed consent in writing

16.3 Sponsor records

Medtronic shall maintain the following accurate, complete, and current records:

- All key correspondence which pertains to the investigation

- Signed CTAs, current signed and dated curriculum vitae (CVs) of principal investigator and as required by geography CVs of key members of the investigation center team, documentation of delegated task.
- All signed and dated case report forms submitted by investigator, samples of ICF, and other information provided to the subjects
- Copies of all EC/IRB approval letters and relevant EC/IRB correspondence
- Correspondence with regulatory authorities as required by local geographies
- Names of the institutions in which the clinical investigation will be conducted
- Notification, correspondence and approval of authorities as required by national legislation
- Insurance certificates (as required by geography)
- Forms for reporting any AEs
- Names/contact addresses of monitors
- Statistical analyses and underlying supporting data
- Final report of the clinical investigation
- The CIP and study related reports
- Study training records for center personnel, Medtronic personnel and others involved in the study
- Any other records that local regulatory agencies require to be maintained.
- Investigator selection reports
- Monitoring visit reports, follow-up letters and any additional correspondence
- Blank set of CRFs

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/MEC, regulatory agency provide accurate, complete and current information about any aspect of the investigation. Safety data Medtronic reporting requirements are listed in Section 9.5 of the Adverse Event section.

Table 13: Sponsor reports for the United States

Report	Submit to	Description/Constraints
Premature termination or suspension of the clinical investigation	Investigators IRB/MEC Relevant authorities Head of the Institution	Provide prompt notification of termination or suspension and reason(s).
Final report	Investigators, IRB/MEC,	A final report will be submitted to the investigators, and IRBs/MECs within six months after completion or termination of this study.
Study deviation	Investigators	Site specific study deviations will be submitted to investigators periodically.

Table 14: Sponsor reports for Europe

Report	Submit to	Description/Constraints

Report	Submit to	Description/Constraints
Premature termination or suspension of the clinical investigation	Investigators IRB/MEC Relevant authorities Head of the Institution	Provide prompt notification of termination or suspension and reason(s))
Withdrawal of IRB/MEC approval	Investigators Head of Institution IRB/MEC relevant authorities	Investigators, IRBs/MECs will be notified only if required by local laws or by the IRB/MEC.
Withdrawal of CA approval	Investigators Head of Institution IRB/MEC relevant authorities	Investigators, IRBs/MECs will be notified only if required by local laws or by the IRB/MEC.
SAE Report	Regulatory authorities	Weekly cardiovascular SAE report, as required by local geography.
Progress Reports	IRB/MEC and relevant authorities	This report will be submitted only if required by the local geographies IRB//MEC).
Final report	Investigators, IRB/MEC, Regulatory authorities upon request	The investigator shall have the opportunity to review and comment on the final report. If a clinical investigator does not agree with the final report, his/her comments shall be communicated to the other investigator(s). The coordinating investigator shall sign the report. If no coordinating investigator is appointed, then the signature of the principal *i*nvestigator in each center should be obtained
Study deviation	Investigators	Ensure that all deviations from the CIP are reviewed with the appropriate clinical investigator(s), are reported on the case report forms and the final report of the clinical investigation Site specific study deviations will be submitted to investigators periodically.

Medtronic records and reports will be stored in locked file cabinets at Medtronic during the course of the study. Electronic versions of the reports will be kept on a password-protected document management system. After closure of the study, all records and reports will be archived indefinitely.

APPENDIX A: DRAFT CASE REPORT FORMS

Case report forms for the Reveal AF study will be provided under separate cover.

APPENDIX B: PRELIMINARY PUBLICATION PLAN

Publications from the REVEAL AF clinical study will be handled according to appropriate Medtronic Standard Operating Procedures and as indicated in the CTA. The final publication plan will be maintained under separate cover.

APPENDIX C: COMMITTEES

Steering Committee

The Steering Committee will guide decisions about study design and data collection in order to achieve a design that is robust but can be achieved given current physician practice, i.e. what is the standard approach to management of AF patients. They will also be responsible for:

- Guidance on overall study issues
- Assistance, as needed, with general study execution issues
- Providing representation for the study at major professional meetings
- Representing the study investigators
- Compositional leadership, as needed, for publications

Endpoint Adjudication Committee:

The endpoint adjudication committee will review Reveal ICM detected AF to determine if true AF was present. The committee will be comprised of: 1) the study center investigators, 2) Medtronic representative that are experienced with reviewing Reveal ICM detected AF (this could include but is not limited to FCEs), 3) a committee chairperson who is a physician (independent of study center and Medtronic) that is experienced at reviewing Reveal ICM detected AF. Medtronic will appoint the committee chairperson and the Medtronic representatives.

Initially, the endpoint adjudication will consist of the study center investigator and a Medtronic representative independently reviewing the Reveal ICM detected AF episodes. The study center investigator will document on an episode log eCRF for each device detected AF episode for which EGM was available and document if they agree or not if the device detected episode of AF is accurate. Independently, all device detected episodes with EGM will also be reviewed by a Medtronic representative. If the assessments by the study center investigator and the Medtronic personnel are in agreement, this outcome will be accepted as the final determination that AF did or did not occur. This outcome will be accepted for the data analysis.

For episodes in which the study center investigator's classification and the Medtronic representative's classification do not agree regarding whether the episode is AF, the episode will be reviewed by the committee chairperson. The outcome of the committee chairperson's review will be accepted as the final determination that AF did or did not occur. This outcome will be accepted for the data analysis.

Publication Committee:

The publication committee will be responsible for publication planning, authorship criteria, and the dissemination of study results.

APPENDIX D: STUDY OVERVIEW / SYNOPSIS

Title: Reveal AF

Purpose: The purpose of the REVEAL AF study is to determine, via continuous monitoring with the Reveal ICM device, the incidence of AF in patients suspected to be at high risk for having AF and to understand how physicians managed these patients once AF has been detected. Furthermore, the study will seek to identify what patient characteristics are most predictive of developing AF. This information may facilitate the ability to identify those patients that are at highest risk for developing AF, and for whom the Reveal ICM may be most beneficial and potentially cost saving.

Study Design: The REVEAL AF study is a prospective, single arm, open-label, multi-center, post-market interventional study to evaluate the incidence of AF in patients that are suspected to be at high risk of having AF, as defined by a modified $CHADS_2$ score as defined in the inclusion criteria. Prior to initiating any study specific procedures, patients must sign and date an ICF to be enrolled in the study. Up to 450 subjects are planned to be enrolled into the study, to have approximately 400 patients implanted with the Reveal ICM. Inclusion/Exclusion criteria will be evaluated and the patients' medical history and baseline information will be collected and then the Reveal ICM device will be implanted. Enrolled subjects who have a successful Reveal ICM implant will then be followed for a minimum of 18 months to monitor for the detection of AF, and up to a maximum of 30 months or until the last subject has completed their 18 month follow-up visit. During the follow-up period, subjects will have in-office visits every 6 months and will transmit device data via CareLink® on a monthly basis. The total duration of enrollment is anticipated to last approximately 24 months and the study duration is anticipated to last approximately 42 months.

Primary Objectives: Determine the incidence rate of atrial fibrillation lasting greater than or equal to six minutes in patients who are at high risk of having atrial fibrillation

Secondary Objectives:

- Identify predictors of AF onset in patients who are at high risk of having atrial fibrillation.
- Characterize the timing and nature of clinical actions relative to detection of AF in patients who are at high risk of having atrial fibrillation.

Inclusion Criteria:
Individuals enrolled in the study must meet all of the following criteria:

- Patient meets the approved indications to receive the Reveal ICM.
- Patient is suspected, based on symptomatology and/or demographics, of having atrial fibrillation or at high risk of having AF, as determined by the clinical investigator
- Patient has a $CHADS_2$ score ≥ 3 OR has a $CHADS_2$ score = 2 and at least one of the following documented:
    - Coronary artery disease
    - Renal impairment (GFR 30-60 ml/min)
    - Sleep apnea
    - Chronic obstructive pulmonary disease

    Note: stroke/TIA criterion as part of the $CHADS_2$ score for this trial is limited to either an ischemic stroke or TIA, which occurred more than one year prior to enrollment.
- Patient is 18 years of age or older
- Patient has a life expectancy of 18 months or more
- Patient, or legally authorized representative, is willing to sign and date the consent form
- Patient is willing and able to be remotely monitored (i.e., eligible for enrollment into the

Medtronic CareLink Network)

Exclusion Criteria:
Individuals who meet any of the following criteria are not eligible to be enrolled in the study:

- Patient has a documented history of AF or atrial flutter.
- Patient had an ischemic stroke or TIA within past year prior to enrollment
- Patient has a history of a hemorrhagic stroke
- Patient is currently implanted with an IPG, ICD, CRT-P, or CRT-D device
- NYHA Class IV Heart Failure patient
- Patient had heart surgery within previous 90 days prior to enrollment
- Patient had an MI within the previous 90 days prior to enrollment
- Patient is taking chronic immuno-suppressant therapy
- Patient is taking an anti-arrhythmic drug
- Patient is contraindicated for long term anticoagulation medication
- Patient is taking a long-term anticoagulation medication
- Any concomitant condition which, in the opinion of the investigator, would not allow safe participation in the study (e.g., drug addiction, alcohol abuse, emotional / psychological diagnosis).
- Patient is enrolled in another study that could confound the results of this study, without documented pre-approval from Medtronic study manager
- Patient has a creatinine clearance <30 ml/min or is on dialysis (completed within past 6 months prior to enrollment) or is on dialysis
    - Note: if the clinical investigator suspects the renal dysfunction to be reversible a single repeat creatinine clearance assessment can be made.

Device Description: The study will use the Medtronic Reveal ICM device which comprises of the Reveal insertable cardiac monitor (model 9529 with FullView™ Software or later Medtronic releases), the Medtronic CareLink Programmer (model 2090 with FullView™ Software or later Medtronic releases), the Reveal Patient Assistant (model 9538 or successor model), and the Medtronic CareLink Monitor (model 2490G or successor model). All components are market-released and will be used in accordance with labeling indications.

1809

APPENDIX E: INFORMED CONSENT TEMPLATES

Geography specific Informed Consent form templates will be provided under separate cover.

APPENDIX F: PARTICIPATING INVESTIGATORS AND INSTITUTIONS

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

APPENDIX G: EC/IRBLIST

At the time of completion of the REVEAL AF Clinical Investigation Plan (Version 2) center confirmation was not finalized. Therefore, a complete list of participating EC/IRBs and the Chairperson(s) will be distributed under a separate cover when available.

APPENDIX H: LABELING

Labeling for all the components of the market approved Reveal ICM system can be found with each package insert. Refer to the Clinician Manual for product details for the Reveal ICM.

APPENDIX I: MODIFICATIONS TO THE CLINICAL INVESTIGATION PLAN

Applicable Sections	Change	Rationale
Contact information	• Updated Contacts	• Added international contacts and CRO contact information
Section 1	• Updated number of sites in each geography • Added the ≥ symbol	• Study scope for geographies shifted • To clarify inclusion criteria
Section 3	• Inserted software model numbers • Updated component name	• Not previously included • Consistency of naming
Section 4	• Removed exception to ISO 14155 • Provided version of Clinical Evaluation Report	• ISO 14155 was used as a guidance for development of CIP to reflect good clinical practice • Not previously listed
Section 5	• Updated exclusion criteria regarding creatinine clearance	• Provided a window for how recent a value could be used for consideration of exclusion criteria
Section 6	• Updated equipment requirements with needed capabilities at sites for ECG and ECHO monitoring • Updated blood sample collection were 5 tubes will be collected and sent to Quest (CRO) and no blood samples will be sent for local analysis and how to manage patient already enrolled in the study. • Added system modification form and symptomatology to information collected	• Added clarity to sites equipment needs • • Blood sample collection process was finalized and updated as appropriate • Consistency with Table 3
Section 7	• Clarified information on storage, use, handling and traceability of the device	• Clarity of information
Section 9	• Updated AE collection to capture all SAEs and device deficiencies and guidance on retrospective collection of SAEs and device deficiencies.	• Meet competent authority reporting requirements
Section 10	• Included language specifying no additional tests required compared to standard of care	• To confirm no additional risk assumed by patients
Section 13	• Added device interrogation to be kept at site	• Guidance for site
Section 16	• Added documents to be maintained by Investigator and Sponsor • Added investigator requirement to report failure to obtain informed consent to their IRB	• Documents already being done by investigator and sponsor, thus added to CIP. • Thorough list of investigator reporting responsibilities
Throughout Document	• Switch terms after initial mention to acronyms e.g. IRB, ICF • Grammatical, spelling, and wording changes • Removed reference of MEA as possible geography for conducting the study • Clinical Investigational Plan added to footer • Added “and dated” when referring to signing	• Ease of reading • Ease of reading • MEA no longer within scope • Document clarity • To clarify enrollment specifications • AFEQT will no longer be collected

	of ICF • Removal of references to AFEQT questionnaire	

1874
1875

APPENDIX J: LITERATURE REVIEW, PRE-CLINICAL TESTING AND PREVIOUS INVESTIGATIONS

For the market released Reveal ICM, a literature review, summary of pre-clinical testing, previous clinical investigations, and market experience is available in the Clinical Evaluation Report and will be provided, upon request, to participating centers under separate cover.

APPENDIX K: BIBLIOGRAPHY

1. Fuster V, Ryden L, Cannom D, *et al.* ACC/AHA/ESC 2006 Guidelines for the Management of Patients with Atrial Fibrillation: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and the European Society of Cardiology Committee for Practice Guidelines *Circulation.* 2006, *114*: 257–354.

2. Go A, Hylek E, Phillips K, Chang Y, Henault L, Selby J, Singer DE. Prevalence of diagnosed atrial fibrillation in adults: National implications for rhythm management and stroke prevention. *JAMA.* 2001, *285*: 2370–5.

3. Naccarelli G, Varker H, Lin J, Schulman K. Increasing prevalence of atrial fibrillation and flutter in the United States. *Am J Cardiol*. 2009, *104*: 1534-9.

4. Fuster V, Ryden LE, Cannom DS, et al. Guidelines for the Management of Patients with Atrial Fibrillation: developed in collaboration with the European Heart Rhythm Association and Heart Rhythm Society. *Circulation*. 2006, 114:257-354.

5. Chugh SS, Blackshear JL, Shen WK, et al. Epidemiology and natural history of atrial fibrillation: clinical implications. *J Am Coll Cardiol.* 2001, 34:371-378.

6. Wattigney W, Mensah G, Croft J. Increasing trends in hospitalization for atrial fibrillation in the United States, 1985 through 1999: Implications for primary prevention. *Circulation*. 2003, *108*: 711-16.

7. Wolf P, Mitchell J, Baker C, Kannel W, D'Agostino R. Impact of atrial fibrillation on mortality, stroke, and medical costs. *Arch Intern Med*. 1998, *158*: 229-34.

8. Ziegler P, Koehler J, Mehra R. Comparison of continuous versus intermittent monitoring of atrial arrhythmias. *Heart Rhythm*. 2006. *3*: 1445–52.

9. Ziegler P, Glotzer, TV, Daoud EG, el at. Incidence of newly detected Atrial arrhythmias via implantable devices in patients with a history of thromboembolic events. *Stroke.* 2010, 41:256-260.

10. Tayal AH, Tian M, Kelly KM, et al. Atrial fibrillation detected by mobile cardiac out-patient telemetry in cryptogenic TIA or stroke. *Neurology.* 2008, 71:1696-1701.

11. Jabaudon D, Sztajzel J, Sievert K, et al. Usefulness of ambulatory 7-day ECG monitoring for the detection of atrial fibrillation and flutter after acute stroke and transient ischemic attack. *Stroke.* 2004, 353:1647-1651.

12. Bansil S, Karim H. Detection of atrial fibrillation in patients with acute stroke. *J. Stroke Cerebrovasc Dis.* 2004, 13:12-15.

13. Elijovich L, Josephson SA, Fung GL, et al. Intermittent atrial fibrillation may account for a large proportion of otherwise cryptogenic stroke: a study of 30-day cardiac even monitors. *J. Stroke Cerebrovasc Dis.* 2009. 18:185-189.

14. Quirino G, Giammaria M, Corbucci G, et al. Diagnosis of paroxysmal atrial fibrillation in patient with implanted pacemakers: relationship to symptoms and other variables. Pacing Clin Electrophysiol. 2009, 32:91-98.

15. Silberbauer JH, Veasey RA, Cheek E, et al., Electrophysiological characteristics associated with symptoms in pacemaker patients with paroxysmal atrial fibrillation. J Inter Card Electrophysiol. 2009, 26:31-40.

16. Thrall G, Lane D, Carroll D, Lip G. Quality of life in patients with atrial fibrillation: A systematic review. *Am J Med*. 2006, *119*: 448e1-419.

17. Gaynor S, Schuessler R, Bailey M et al. Surgical treatment for atrial fibrillation: Predictors of late reoccurrence. *J Thorac Cardiovas Surg* 2005, *129*: 104-11.

18. Welles CC, Whooley MA, Na B., et al. The $CHADS_2$ score predicts ischemic stroked in the absence of atrial fibrillation among subjects with coronary heart disease: Data from the Heart and Soul Study. *Am Heart J.* 2011, 162:555-561.

19. Lip G and Halperin, J. Improving stroke risk stratification in atrial fibrillation. *Am J Medicine. 2010, 123: 484-8.*

20. De Vos, CB, Pisters, R, Mieuwlaat, R., et al. Progression from Paroxysmal to Persistent Atrial Fibrillation. *J Am Coll Cardiol.* 2010. 55:725-731.

21. Ziegler PD, Glotzer TV, Daoud EG, et al. Detection of previously undiagnosed atrial fibrillation in patients with stroke risk factors and usefulness of continuous monitoring in primary stroke prevention. Am J Cardiol 2012 (in press).