Improve SCA Bridge Study
Clinical Study Protocol - Version 2.0
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Medtronic

Clinical Investigation Plan

Clinical Investigation Plan/Study Title	Improve SCA Bridge
Sponsor/Local Sponsor	**Medtronic, Inc. (Worldwide Sponsor)** Cardiac Rhythm and Heart Failure Clinical Research 8200 Coral Sea Street NE, MS: MVS33 Mounds View, MN 55112 **Medtronic (Shanghai) Management Co., Ltd.** 3rd Floor, No. 180. Rijing Road, China (Shanghai) Pilot Free Trade Zone, 200131, Shanghai, P.R.China **Medtronic (Taiwan) Ltd.** 2F, No.2, Sec.1, Dunhua S. Rd. Songshan Dist. Taipei City 105, Taiwan (R.O.C.) **Medtronic Malaysia Sdn Bhd** B-23-1 Level 23, The Ascent, Paradigm No 1 Jalan SS7/26A Kelaena Jaya 46301 Petaling Jaya, Selangor, Malaysia **PT Medtronic Indonesia** Gandaria 8 Office Tower, 36th Floor Unit A Jl. Sultan Iskandar Muda, Kebayoran Lama Jakarta 12240 - Indonesia **Medtronic Philippines Inc.** 29th Floor One World Place, 32nd St., City Center North, Bonifacio Global City Taguig City, 1634 Philippines **Medtronic International Ltd (Singapore Branch)** 49 Changi South Avenue 2 Singapore 486056

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2. Glossary

Term	Definition
AE	Adverse Event
ADE	Adverse Device Effect
CIP	Clinical Investigation Plan
CRT-D	Cardiac Synchronization Therapy- Defibrillator
CTA	Clinical Trial Agreement
Data Protection authorization	Authorization to Use and Disclose Personal Health Information/Research Authorization/other privacy language
DM	Data Management
eCRF	Electronic Case Report Form
EC	Ethics Committee
EP	Electrophysiologist
GCP	Good Clinical Practice
IC	Interventional Cardiologist
ICD	Implantable Cardioverter-Defibrillator
IRB	Institutional Review Board
LVEF	Left Ventricular Ejection Fraction
MEC	Medical Ethics Committee
MI	Myocardial Infarction
MSM	Medtronic Secure Messaging
NSTEMI	Non ST-Elevation Myocardial Infarction
PI	Principal Investigator

Term	Definition
RA	Right Atrial
RV	Right Ventricular
SAE	Serious Adverse Event
SADE	Serious Adverse Device Effect
SAP	Statistical Analysis Plan
SCA	Sudden Cardiac Arrest
SCD	Sudden Cardiac Death
SOC	Standard of care
STEMI	ST-Elevation Myocardial Infarction
USADE	Unanticipated Serious Adverse Device Effect

3. Synopsis

Title	Improve SCA Bridge
Sponsor	Medtronic Inc. Cardiac Rhythm and Heart Failure Clinical Research 8200 Coral Sea Street NE, MS: MVS33 Mounds View, MN 55112 55112
Local Sponsor	**Medtronic (Shanghai) Management Co., Ltd.** 3rd Floor, No. 180. Rijing Road, China (Shanghai) Pilot Free Trade Zone, 200131, Shanghai, P.R.China **Medtronic (Taiwan) Ltd.** 2F, No.2, Sec.1, Dunhua S. Rd. Songshan Dist. Taipei City 105, Taiwan (R.O.C.) **Medtronic Malaysia Sdn Bhd** B-23-1 Level 23, The Ascent, Paradigm No 1 Jalan SS7/26A Kelaena Jaya 46301 Petaling Jaya, Selangor, Malaysia **PT Medtronic Indonesia** Gandaria 8 Office Tower, 36th Floor Unit A Jl. Sultan Iskandar Muda, Kebayoran Lama Jakarta 12240 - Indonesia **Medtronic Philippines Inc.** 29th Floor One World Place, 32nd St., City Center North, Bonifacio Global City Taguig City, 1634 Philippines **Medtronic International Ltd (Singapore Branch)** 49 Changi South Avenue 2 Singapore 486056 **Medtronic Thailand (Limited)** 319 Chamchuri Square 27th Floor, Unit 1-16, Phayathai Road, Pathumwan Bangkok 10330, Thailand **Medtronic Korea Co. Ltd** 17F, Glass Tower, #534 Teneran-ro, Gangnam-gu Seoul, 06181, Korea

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Investigation Purpose	The purpose of the Improve SCA Bridge study is to characterize the care pathway flow of post-acute myocardial infarction (MI) patients as a result of standard assessments of left ventricular ejection fraction (LVEF) in the acute phase (≤14 days post- acute MI) and chronic phase (≥40-90 days post-acute MI).
Product Status	There is no investigational device under evaluation; subjects may be implanted, if referred and indicated, with any brand or model of market released Implantable Cardioverter-Defibrillator (ICD)/ Cardiac Synchronization Therapy- Defibrillator (CRT-D).
Primary Objective	Characterize the proportion of post-acute MI patients who are referred for sudden cardiac death (SCD) risk stratification and management.
Secondary Objective(s)	• Characterize the proportion of post-acute MI patients who are known to be indicated for an ICD/CRT-D within 12 months post-acute MI. • Characterize the proportion of post-acute MI patients who receive an ICD/CRT-D within 12 months post- acute MI. • Summarize the referral and implant refusal rationale. • Characterize the proportion of post-acute MI patients who experience cardiovascular mortality. • Determine how the ejection fraction evolves over 3 months following an acute MI.
Study Design	This study is a prospective, non-randomized, multi-site, global, post-market study. After enrollment, subjects will be followed up at 3-, 6- and 12-months. The 6- and 12-month follow up maybe completed either in-person or via phone. There is no investigational device; subjects can be implanted, if indicated and referred, with any brand or model of a market released ICD/CRT-D. The study is expected to be conducted at approximately 50 sites worldwide. Participating geographies are: China, India

	Subcontinent (including India, Bangladesh), Korea, Middle East, Africa, Central Asia, & Turkey (MEACAT) (including Egypt, Pakistan, Saudi Arabia, South Africa and Tunisia), South East Asia (SEA) (including Brunei, Indonesia, Malaysia, Philippines, Singapore and Thailand) and Taiwan. Additional countries could participate within these geographies. Each geography is expected to enroll approximately 200 subjects, with a total of approximately 1,200 subjects from 6 geographies. The sample size may vary by geographies, as it will depend on the mortality and drop-out rates and on the reason for referral at 3 months, which will differ across geographies and will be continuously monitored. The actual sample size may increase up to 2,400 subjects, depending on the observed mortality and drop-out rate between enrolment and 3-month visit, and on the observed proportion of subjects with a reason for referral at the 3-month visit. The study duration is expected to be approximately 24 months. This represents an estimated 12 months for subject enrollment and 12 months for subject follow-up for the last subject enrolled. Subjects are anticipated to be in the study for approximately 12 months. Prior to study site initiation, current referral information will be collected from sites, and investigators and other site clinical personnel will be provided with educational materials that address the importance of EF measurement and care pathway for post-MI patients.
Sample Size	Approximately 200 subjects per geography, with a total of approximately 1,200 subjects from 6 geographies. The sample size might be increased up to a maximum of 2,400 subjects, depending on the observed mortality and drop-out rates and on the observed proportion of subjects with reason for referral at 3-month.
Inclusion/Exclusion Criteria	**Inclusion Criteria** • Age 18 and above (or meet age requirements per local law) • Patients who have an acute Myocardial Infarction (MI) (STEMI or Non-STEMI) ≤ 30 days of study enrollment and have a LVEF <50% measurement ≤ 14 days post-acute MI • Willing and able to give valid Informed Consent

	Exclusion Criteria • Patient has previously received or currently implanted with an ICD or CRT-D • Patient has any contraindication for ICD/CRT-D • Patient has a life expectancy of less than 12 months • Patient who has had an EP referral within the last 12 months • Any exclusion criteria required by local law (e.g. pregnancy, breast feeding etc.) • Patient is unable (e.g. mental disorder) or unwilling to be compliant with the responsibilities as specified in the informed consent form. • Patient is enrolled in a concurrent study that has not been approved for concurrent enrollment by the Medtronic Clinical Trial Leader* **Concurrent enrollment with observational registry is allowed without approval from the Medtronic Clinical Trial Leader if the Principal Investigator confirms that the registry has no intervention beyond standard of care and may not confound study results prior to enrollment.*
Study Procedures and Assessments	The study requires an Enrollment/ Baseline visit, and 3-month, 6-month and 12-month follow-up visits.
Safety Assessments	Cardiovascular Adverse Events (AE) and all deaths will be collected (refer to Section 11 for AE Assessment)
Statistics	The purpose of the study is to characterize treatment patterns in different geographies for this population, and so descriptive statistics will primarily be used, and reported by geography. For the primary objective, a confidence interval will be reported.

4. Introduction

4.1. Background

Acute myocardial infarction (MI) is a life-threatening condition that occurs when the blood flow to the heart muscle is abruptly cut off, causing tissue damage. Fibrinolytic (thrombolytic) therapy, which prevents blood clots from growing and becoming problematic, may be used within the first few hours of symptom onset. Coronary revascularization, including percutaneous coronary intervention (PCI) and Coronary Artery Bypass Grafting (CABG) has been shown to improve patient symptoms from myocardial ischemia, increase long term survival, and is recommended as part of professional clinical guidelines[1]. However, if there is substantial damage to the heart muscle, the heart may be unable to pump an adequate amount of blood, which can lead to heart failure. Left ventricular dysfunction following an

acute MI identifies patients at higher risk of sudden cardiac arrest (SCA) and sudden cardiac death (SCD)[2]. SCD remains a leading cause of death in those who received revascularization, accounting for up to 40% of total deaths[3,4,5]. It is well established that the use of Implantable Cardioverter Defibrillators (ICDs) reduces the risk of mortality in patients with reduced LVEF. However, low ICD utilization in ICD-indicated patients worldwide (ranging from 30 to 50% in USA, 24% in Europe, 12% in Asia)[6] and persistent high post-PCI mortality rates suggest that barriers in this patient care pathway exist. In the U.S. from the National Cardiovascular Data Registry in 2001, the proportion of PCI cases to ICD cases is 4.5:1[7]; in China in 2013, the proportion of PCI cases to ICD and CRT-D cases is 148:1[8]. Considering that patients without PCI are even less likely to have an ICD implanted, the disparity in ratios will be at least as bad as the above when all MI patients are considered.

Known barriers to ICD utilization include reimbursement (by government or insurance) of devices, lack of evidence awareness by healthcare providers, and limited ability and willingness to pay due to patients' socioeconomic status and attitudes[6]. Greater uptake and patient acceptance generally occurs in regions with government reimbursement of ICDs and lower out-of-pocket patient cost; however, even in regions where this financial barrier is reduced, ICD referral rates remain low, suggesting challenges further upstream in the patient care pathway. Out of 2,000 ICD nonrecipients surveyed in a recent study[6], 55% of them were unaware of the benefits or needed more information on device therapy. Previous studies also suggested that physicians' awareness on the indications for ICD therapy is low[6]. This leads to low referral rates for ICD implantation which is noted to be an important barrier to ICD utilization. In addition to education and awareness, there is evidence that adherence to guidelines on post-MI care is variable.

Efforts have been made to improve and align guidelines-based clinical practice for prevention of SCD post-MI. For example, the ACC/AHA/ HRS guidelines for post-MI care[9] are widely accepted. In 2016, the Society of Cardiac Pacing and Electrophysiology, Chinese Society of Cardiology, Chinese Medical Association, and Heart Rhythm Committee of Chinese Medical Doctor Association jointly published an Expert Consensus Guideline for China: "Prevention of Sudden Cardiac Death after Revascularization to Coronary Heart Disease" [8] that details post-MI care and emphasizes the importance of regular evaluation of the LVEF, but adherence has been low.

Ways in which the upstream care pathway can be improved have not been effectively implemented to date. A reduced LVEF (LVEF ≤ 40%) for more than 40 days after a MI identifies patients at higher risk of SCD and current guidelines recommend LVEF reassessment during the convalescent months post-MI[10]. However, current practice is suboptimal, patient-reported LVEF reassessment at 6-month after acute MI was <40% in TRIUMPH registry that included patients with LVEF <40% at time of MI[11]. AMIQA study also shows LVEF reassessment was <50% during the convalescent post-MI months and 25% of post-MI patients with reduced LVEF had either no increase or a decline in LVEF[2]. Additionally, it is not known how many patients post MI have a LVEF that qualifies them for an ICD. This information is important because it provides visibility on areas to improve current revascularization approaches and sheds greater awareness on the magnitude of the ICD utilization problem in patients with reduced LVEF after MI.

This Improve SCA Bridge study will assess the care pathway for post-acute MI patients through standard assessment of LVEF and implementation of an educational tool to bridge the treatment pathway for patients who are indicated for an ICD/CRT-D as per AHA/ACC/HRS guideline[9]. This will help to understand the cause of low adherence of guidelines-based clinical practice and low ICD utilization, and to identify targets for action to improve guideline adherence.

4.2. Purpose

The purpose of the Improve SCA Bridge study is to characterize the care pathway flow of post-acute MI patients as a result of standard assessments of left ventricular ejection fraction in acute phase (≤14 days post- acute MI) and chronic phase (≥ 40-90 days post-acute MI). Specifically, how many patients are referred for sudden cardiac death (SCD) risk stratification and management, indicated for ICD/CRT-D implant, and how many receive such devices within 12 months of experiencing an MI. In addition, the current trial will characterize the impact from execution of the above-mentioned guidelines.

5. Objectives and Endpoints

5.1. Objectives

5.1.1. Primary Objective

To characterize the proportion of post-acute MI patients who are referred for sudden cardiac death (SCD) risk stratification and management.

5.1.2. Secondary Objectives

- Characterize the proportion of post-acute MI patients who are known to be indicated for an ICD/CRT-D* within 12 months post-acute MI.
- Characterize the proportion of post-acute MI patients who receive an ICD/CRT-D within 12 months post-acute MI.
- Summarize the referral and implant refusal rationale.
- Characterize the proportion of post-acute MI patients who experience cardiovascular mortality
- Determine how the ejection fraction evolves over 3 months following an acute MI.

** Indication as per the current AHA/ACC/HRS Guideline for ICD (or CRT-D) implant[9]*

5.2. Endpoints

5.2.1. Primary Endpoint

The endpoint will be defined as the clinician's determination to refer the subject for an SCD stratification and management. The reason for this referral could be any of the following:

- Subject's LVEF at 3 months determined to be up to 40%

- Subject experiences unexplained syncope, ventricular arrhythmia, AV block, clinically significant palpitations, new onset bundle branch block, conduction abnormalities, or symptomatic bradycardia.

5.2.2. Secondary Endpoints

- For the objective "Characterize the proportion of post-acute MI patients who are known to be indicated for an ICD/CRT-D within 12 months post-acute MI" the endpoint will be defined as whether a subject was indicated for an ICD/CRT-D device during follow-up.
- For the objective "Characterize the proportion of post-acute MI patients who receive an ICD/CRT-D within 12 months post-acute MI" the endpoint will be defined as whether a subject received an ICD/CRT-D device during follow-up.
- For the objective "Summarize the referral and implant refusal rationale" the outcome measure will be the proportion of patients with ICD indication, who were not referred, refused referral or refused implant. The denominator will count all patients with at least one of the below:
  (a) a reduced ejection fraction, as measured by the Left Ventricular Ejection Fraction (LVEF) being lower or equal than 40%.
  (b) ventricular arrhythmia, AV block, new onset bundle branch block, or conduction abnormalities as measured by ECGs.
  (c) unexplained syncope, clinically significant palpitations or symptomatic bradycardia as assessed by the physician

  The numerator will count the patients included in the denominator who were not referred, refused referral or refused implant of an ICD/CRT-D.
- For the objective "Characterize the proportion of post-acute MI patients who experience cardiovascular mortality" the endpoint will be defined as cardiovascular mortality.
- For the objective "Determine how the ejection fraction evolves over 3 months following an acute MI" each subject's LVEF will be measured at hospital discharge (i.e. within 14 days of MI), and at chronic phase (40-90 days post MI). The endpoint will be the change between the acute and the chronic measurement.

6. Study Design

This study is a prospective, non-randomized, multi-site, global, post-market study. There is no investigational device; subjects can be implanted, if indicated and referred, with any brand or model of a market released ICD/CRT-D.

The study is expected to be conducted at approximately 50 sites worldwide. Participating geographies are: China, India Subcontinent (including India, Bangladesh), Korea, Middle East, Africa, Central Asia, & Turkey (MEACAT) (including Egypt, Pakistan, Saudi Arabia, South Africa and Tunisia), South East Asia (SEA) (including Brunei, Indonesia, Malaysia, Philippines, Singapore and Thailand) and Taiwan. Additional

countries could participate within these geographies. Each geography is expected to enroll approximately 200 subjects, with a total of approximately 1,200 subjects from 6 geographies. The actual sample size may increase up to 2,400 subjects, depending on the observed mortality and drop-out rate between enrolment and three months follow-up and on the observed proportion of subjects with a reason for referral at the three months visit.

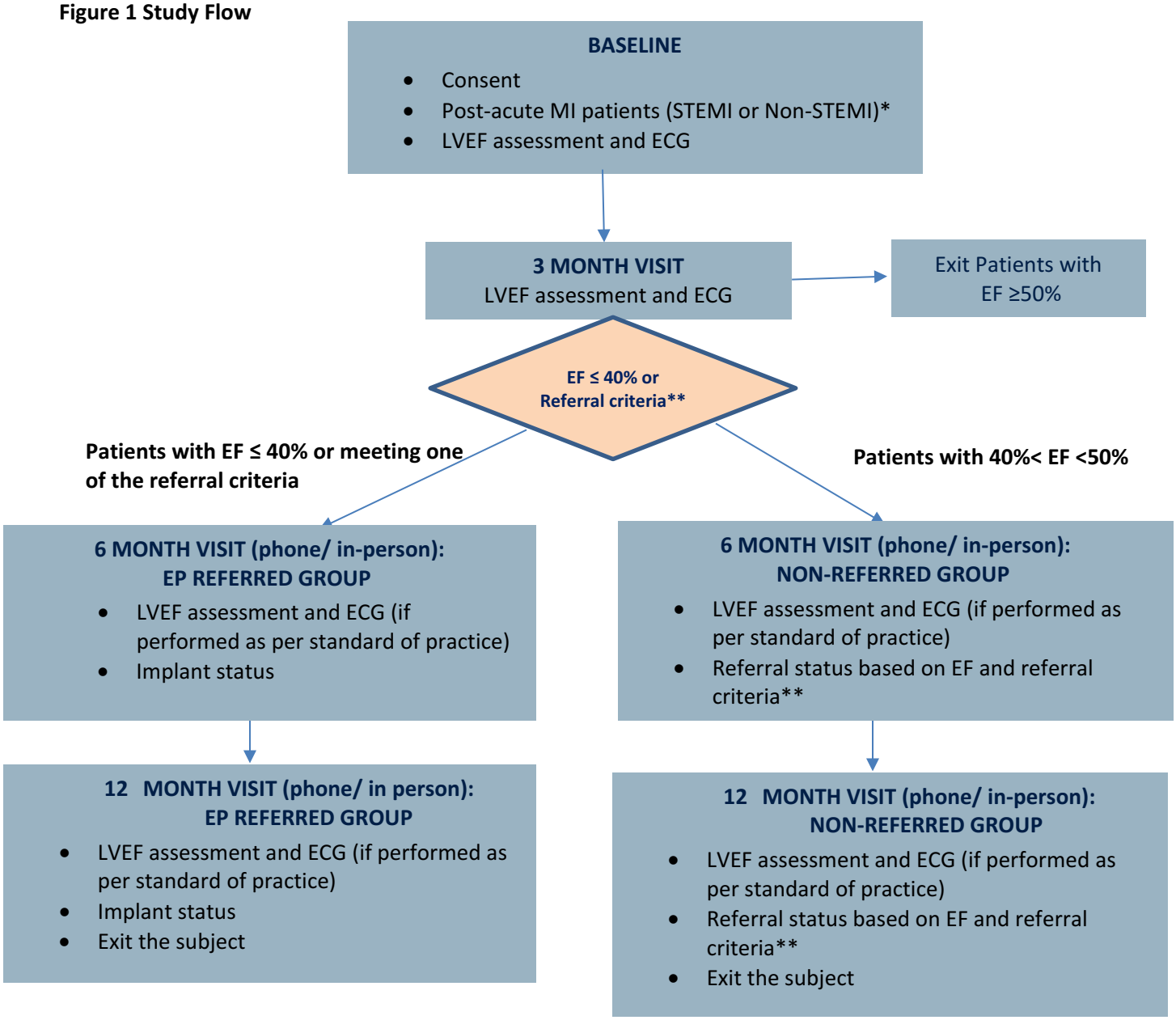
Prior to study site initiation, current referral information will be collected from sites, and investigators and other site clinical personnel will be provided with educational materials (available under a separate cover) that address the importance of EF measurement and care pathway for post-MI patients.

Methods incorporated in the study design to minimize potential bias include (but are not limited to):

- Subject demographics will be collected at baseline for potentially analyzing differences that may affect the endpoints.
- All study clinicians and Medtronic personnel will be trained on the corresponding aspects of the study using standardized training materials.
- All study clinicians and Medtronic personnel will be trained on and required to follow the Protocol.
- Sites will be encouraged to approach any eligible patients meeting inclusion/exclusion criteria
- Each geography is expected to enroll an approximate 200 subjects to have at least 80% power to achieve a moderate to high number of patients referred for SCD risk stratification and management.
- For each geography, sites where the same physician acts both as an interventional cardiologist and as an electrophysiologist will be limited to a maximum of 20% of the total sites in the geography, and approximately 20% of the total expected enrollments in the geography will be enrolled in these sites.
- To ensure a wide distribution of data between sites, the maximum enrollments per site will be no more than 20% of the total expected enrollment in the geography.

  See Figure 1 and Section 9 for further detail on study procedures and data collection as well as timepoints for data collection.

Figure 1 Study Flow



***For patient enrollment:** Patients must be enrolled ≤ 30 days post-acute MI and must have an EF < 50% measured ≤ 14 days post-acute MI.*

***Referral Criteria:** sustained VT, cardiac or unexplained syncope, clinically significant palpitations, new onset bundle branch block, conduction abnormalities, or symptomatic bradycardia.*

6.1. Duration

The study duration is expected to be approximately 24 months. The first enrollment is projected in Nov 2018. This represents an estimated 12 months for subject enrollment and 12 months for subject follow-up for the last subject enrolled. At approximately 12 months past the final study enrollment, centers will be notified that study closure is about to occur.

6.2. Rationale

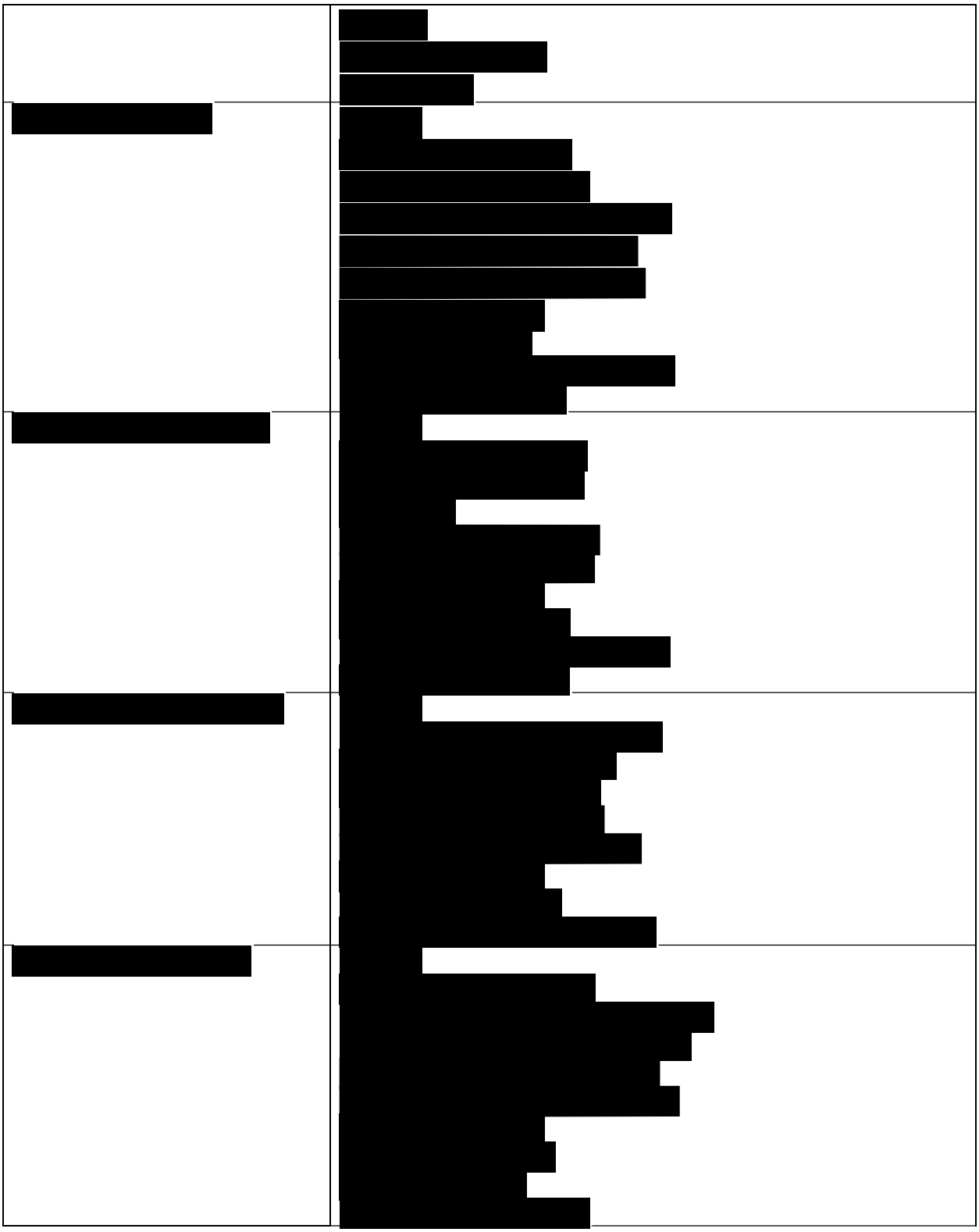
This study is characterizing the care pathway of post MI patients and understanding the evolution of LVEF for post MI patients, which will improve the management of this group of patients in prevention of SCD.

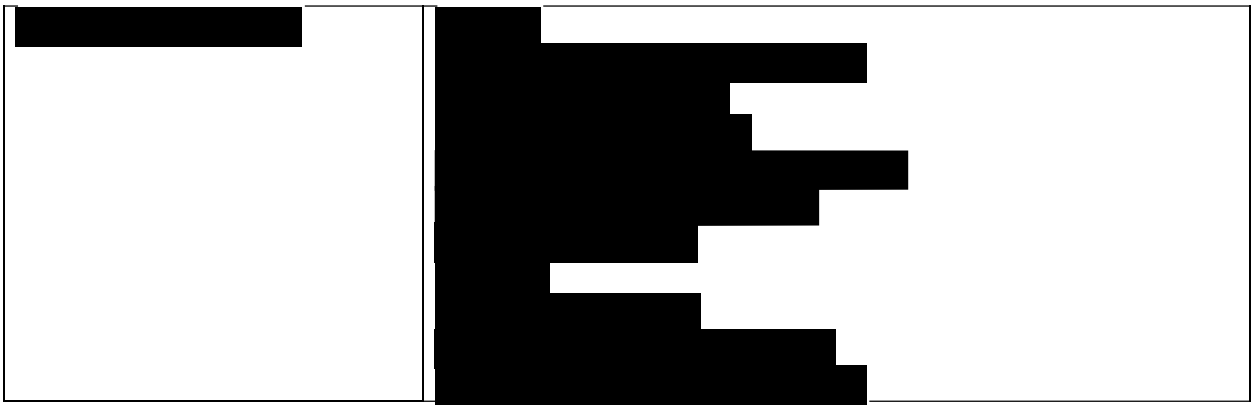
6.3. Study oversight

The study will utilize a Steering Committee (SC). The SC is responsible for the scientific content of the study and for providing input for the execution of the study. Members of the SC are study site investigators. The purpose of the SC is to provide unbiased opinions and expertise to Study design and process; support the execution of Study and provide guidance, feedback and direction to the clinical study. The SC is comprised of the members as indicated in Table 1 below.

Table 1: Steering Committee Members

Committee Member	Contact Information
[redacted]	[redacted]
[redacted]	[redacted]





7. Product description

7.1. General

There are no requirements for model or manufacturer of ICD/CRT-Ds implanted during the patient's follow-up. These devices can be any brand or model of market released ICD/CRT-D, and should be implanted as per the current AHA/ACC/HRS Guideline[9].

Subjects receiving a Medtronic device will have device data retrieved and analyzed by Medtronic as part of the study.

8. Selection of Subjects

8.1. Study Population

Patients of both genders who have had an acute MI ≤ 30 days of enrollment and have a LVEF <50% measurement ≤ 14 days post-MI will be approached regarding enrollment in the study. Patients implanted with ICDs or CRT-Ds or who have had an EP referral in the last 12 months will not be approached for this study.

8.2. Subject Enrollment

Subjects are considered enrolled in the study upon signing the Medtronic & Medical Ethics Committee (MEC)-approved Informed Consent Form. Informed consent must be obtained prior to performing any of the study-related procedures or entering any subject data in the eCRF. The complete informed consent process will include giving the patient adequate information about the study and ensuring that there is sufficient time to comprehend the information in the IC Form and have all questions answered before making a decision to participate in the study. Each site will be responsible for maintaining subject identification records (e.g. subject identification log).

8.3. Inclusion Criteria

The inclusion criteria are as follows:

- Age 18 and above (or meet age requirements per local law)
- Patients who have an acute Myocardial Infarction (MI)* (STEMI or non-STEMI) ≤ 30 days of study enrollment and have a LVEF <50% measurement ≤ 14 days post- MI
- Willing and able to give informed consent

** Strongly recommend following the ESC guideline[12] for acute MI definition.*

8.4. Exclusion Criteria

The exclusion criteria are as follows:

- Patient has previously received or currently implanted with an ICD or CRT-D
- Patient has any contraindication for ICD/CRT-D
- Patient's life expectancy of less than 12 months
- Patient who has had an EP referral within the last 12 months
- Any exclusion criteria required by local law (e.g. pregnancy or breast feeding etc.)
- Patient is unable (e.g. mental disorder) or unwilling to be compliant with the responsibilities as specified in the informed consent form.
- Patient is enrolled in a concurrent study that has not been approved for concurrent enrollment by the Medtronic Clinical Trial Leader*

**Concurrent enrollment with observational registry is allowed without approval from the Medtronic Clinical Trial Leader if the Principal Investigator confirms that the registry has no intervention beyond standard of care and may not confound study results prior to enrollment.*

9. Study Procedures

Prior to performing study related procedures, all sites must have EC approval and documentation of site initiation from Medtronic.

Medtronic representatives may perform the following activities at the study sites during the study if appropriately trained and under the supervision of the PI and/or appropriate delegate (e.g. appropriately trained and delegated sub-investigator):

- Study training relevant and pertinent to the involvement of personnel conducting study activities and Investigator responsibilities
- Technical support at all visits (e.g. performing device interrogations/save-to-media), but no electronic case report form (eCRF) data entry shall be performed by Medtronic personnel
- Monitoring activities
- Auditing activities

9.1. Investigator/Investigation Site Selection

The PI will provide oversight for the entire study team at his/her site, implement and manage the day-to-day conduct of the clinical study, ensure data integrity, and the rights, safety, and well-being of the subjects involved in the clinical study.

The PI shall:

- Be qualified by education, training, and experience to assume responsibility for the proper conduct of the clinical study.
- Be qualified practitioners and experienced in the management of post-MI subjects
- Be able to comply with applicable Institutional Review Board (IRB)/Ethics Committee (EC) and regulatory requirements
- If applicable, not to be debarred, disqualified, or working under sanctions in applicable regions

Additionally, the site:

- Has the required number of eligible subjects needed within the recruitment period
- Has one or more qualified Investigators, a qualified study team, and adequate facilities for the foreseen duration of the clinical study
- Needs to have specialized practitioners (e.g. Interventional Cardiologist and Electrophysiologist) to participate in the study and be complaint with this study protocol.

9.2. Site Initiation

During the initiation process (prior to subject enrollment), Medtronic will provide clinical study materials (e.g. Investigator Site File, database access codes etc.) and train site personnel on the Clinical Investigation Plan (CIP), relevant standards and regulations (if needed), informed consent, and data collection and reporting tools.

A Clinical Trial Agreement (CTA) shall be entered into effect by Medtronic, the participating investigation site and/or the Principal Investigator (PI) at each investigation site (per the local legal requirements), and returned, fully executed, to Medtronic prior to the commencement of any study activities. Financial aspects of conducting and reporting a study will be specified in the agreement. By signing and dating the agreement, the Investigator indicates compliance to the CIP.

Prior to performing study related activities, all sites must have IRB/EC approval, as applicable for that geography.

All local and regional regulatory requirements must be fulfilled prior to site initiation and enrollment of subjects into the study. Each study site must have written documentation of site and Investigator initiation before beginning any study-related activities. Requirements for initiation vary by geography, and may include, but are not limited to:

- Written documentation of EC approval of the current versions of the CIP and IC Form (approved versions must be retrievable from the IRB/EC approval letter or submission letter) and the corresponding voting list (as required per local law)

- Regulatory authority approval or notification (as required per local law)
- Executed CTA on file with Sponsor
- Current Curriculum Vitae (CV) of Investigators and key members of the investigation site team
- Documentation of delegated tasks
- Documentation of study site personnel training

Additional requirements imposed by the EC and regulatory authority shall be followed, if appropriate. Medtronic will provide each study site with documentation of study site/Investigator initiation; this letter must be received prior to subject enrollment. If new members join the study site team after site initiation, they will receive training on the applicable clinical study requirements relevant to their roles before contributing to the clinical study. Medtronic will provide the study site with documentation of the investigation site team initiation upon receipt of all required documentation.

In addition, all participating site staff must be trained on the current version of the CIP pertinent to their role in the study and must be delegated by the principal investigator to perform study related activities, which must be documented on the Delegated Task List. Site personnel performing only standard of care procedures and no study related activities throughout the study (including but not limited to ICD/ CRT-D implant) do not need to be trained on the CIP and delegated on the Delegated Task List.

9.3. Schedule of Events

Clinical data will be collected at the Baseline 3 month, 6 month, 12 month, and exit visits. In addition if applicable, clinical data will be collected with an exit or death, as well as unscheduled visits. Device data will be collected from device interrogations on Medtronic devices received during the period between the enrollment and exit until study closure; for non-Medtronic devices, device data will not be collected. Data will be collected using eCRFs using an electronic data management system for clinical studies. In addition to eCRF data, non-eCRF data will be collected including device interrogation files (for Medtronic implanted devices only). Surveys may also be used throughout the study.

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 study sites for resolution. Study management reports will be generated by Medtronic to monitor data quality and study progress. At the end of the study, the data will be frozen and retained indefinitely by Medtronic. Data Collection requirements are summarized in the table 2 below.

Table 2 Data Collection and study procedure requirements at subject visit

Study Procedure	Baseline	3 month visit	6 month visit	12 month visit	Study Exit
Patient informed consent	X				
Eligibility Verification (Inclusion/ exclusion assessment)	X				
Subject Demographics	X				
Acute MI information	X				
Medical History	X				
Cardiovascular Medications	X	X			
LVEF measurement	X	X*	X (collect if performed as per SOC)	X (collect if performed as per SOC)	
ECG	X	X (collect if performed as per SOC)	X (collect if performed as per SOC)	X (collect if performed as per SOC)	
Referral Status		X	X	X	X
Implant Status (if applicable)		X (if subject receives or has received device implant)	X (if subject receives or has received device implant)	X (if subject receives or has received device implant)	X (if subject receives or has received device implant)
Device Interrogation File (pdd) or CareLink Transmission for subjects implanted with Medtronic device only		X	X	X	X
Adverse Event	As they occur				
System Modification					
Study Deviation					
Subject Death					

** The LVEF measurement needs to be performed ⩾40 days post-acute MI for MI subjects without revascularization, or ⩾90 days post-revascularization for post-MI subjects with revascularization done.*

9.4. Subject Consent

Informed consent is defined as a legally effective documented confirmation of a patient's voluntary agreement to participate in a particular clinical study after the information has been given to the patient on all aspects of the clinical study that are relevant to the patient's decision to participate. This process

includes obtaining an Informed Consent Form (IC Form) and an Authorization to Use and Disclose Personal Health Information/Research Authorization/other privacy language (data protection authorization) as required by law that has been approved by the study site's IRB/EC, and Medtronic, and personally signed and dated by the patient and the PI or an authorized designee.
Prior to enrolling patients, each site must have documented IRB/EC approval of the IC Form (and data protection authorization, where applicable) as required by law. Any changes to a previously approved IC Form throughout the course of the study must be reviewed and approved by Medtronic and the IRB/EC reviewing the application before being used to obtain consent or re-consent a study subject. The document(s) must be controlled (i.e. versioned and dated) to ensure it is evident which version(s) were approved by Medtronic and the IRB/EC. All important new information should be provided in written form to new and existing subjects throughout the study. If relevant, all affected subjects must be asked to confirm their continuing informed consent in writing.

Prior to initiation of any study-specific procedures, informed consent must be obtained from the patient. Likewise, privacy or health information protection regulation may require patients to sign additional forms to authorize sites to submit subject information to the study sponsor. Obtaining informed consent must be conducted by the PI or an authorized designee, and the IC Form and a data protection authorization, as required by law, must be given to the patient in a language he/she is able to read and understand.
The process of obtaining informed consent shall:

- Ensure that the PI or an authorized designee conducts the informed consent process.
- Include all aspects of the clinical study that are relevant to the patient's decision to participate throughout the clinical study.
- Avoid any coercion or undue improper influence on, or inducement of the patient to participate.
- Not waive or appear to waive the patient's legal rights.
- Ensure the IC Form and a data protection authorization as required by law, are given to the patient in a non-technical language the patient is able to read and understand.
- Provide ample time and opportunity for the patient to read and understand the Informed Consent Form to inquire about details of the study, and to consider participation. All questions about the study should be answered to the satisfaction of the patient.
- Include a personally dated signature of the subject acknowledging that their participation in the study is voluntary.
- Include a personally dated signature by the PI, or authorized designee responsible for obtaining the informed consent, as required by local law.
- Provide the subject with a copy of the IC Form and a data protection authorization as required by law.
- Ensure subjects are notified of any significant new findings about the study that become available during the course of the study which are pertinent to the safety and well-being of the subject, as this could impact a subject's willingness to participate in the study.

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

In the event the subject cannot read and/or write, witnessed (impartial third party) informed consent will be allowed, provided detailed documentation of the process of obtaining the informed consent is recorded in the subject's case history and the witness signs and dates the Informed Consent Form. Informed consent shall be obtained through a supervised oral process. An impartial witness must be present throughout the process. The IC Form and any other information must be read aloud and explained to the prospective subject if allowed by local law. The witness signs and personally dates the IC Form attesting that the information was accurately explained and that informed consent was freely given. Whenever possible, the subject should "make his mark" (sign or otherwise physically mark the document so as to indicate consent) on the IC Form as well. The IC Form should document the method used for communication with the prospective subject and the specific means by which the prospective subject communicated agreement to participate in the study.

The original of the signed IC Form must be filed in the hospital/clinical chart and/or with the subject's study documents.

The IC Form and a data protection authorization as required by law must be available for monitoring, auditing, and regulatory inspections.

9.5. Enrollment/Baseline

When a patient and the PI or authorized designee (if applicable) signs and dates the IC Form, the patient is considered a subject enrolled in the study. The date the subject signed the IC Form (and data protection authorization where applicable) must be documented in the subject's medical records. Enrollment will occur ≤ 30 days of post-acute MI. Medtronic should be notified (via Enrollment eCRF) as soon as possible to aid in enrollment tracking. Once consent is obtained, report cardiac adverse events, study deviations, system modifications, and subject deaths as they occur.

The following information is required to be collected at Baseline:

- Patient Informed Consent Date (Enrollment Date)
- Eligibility Verification (Inclusion/Exclusion Assessment)
- Subject Demographics
- Acute MI information
- Medical History
- Cardiovascular Medication categories including Angiotensin-converting enzyme (ACE) Inhibitors, angiotensin receptor blocker (ARB), Beta blockers, Vasodilators, Diuretics, Aldosterone receptor antagonists, Digoxin, Anticoagulation agents, anti-platelet agents, statin, anti-arrhythmics, or any cardiovascular medication categories that will become available during the course of the study.
- LVEF measurement (≤14 days post -acute MI) and ECG done as per standard practice. For LVEF, it is recommended to measure by echocardiography (for example Simpson's method) and to use the same method when assessing the same subject at Baseline and 3-month follow-up visit.

9.6. Follow-Up Visits

Table 3 below specifies permitted time windows for the required subject visits. Subject visit target dates and windows for each follow-up will be made available to the study site. Follow-up visit windows are based on days post-acute MI, and the follow-up visit can be performed either in person or via phone. If a subject visit fall outside the pre-specified window, a study deviation must be reported and the original follow-up schedule maintained for subsequent visits.

Data analyses will include follow-up visits, regardless of whether the visits occur within the time window. Therefore, a late visit is preferred over a missed visit but must be accompanied by a deviation.

Table 3: Follow-up windows

Study Follow-up Visit	Window (Calculated days post-acute MI)		
	Window Start (days post-MI)	Target (days post-MI)	Window End (days post-MI)
3 month	40	90	120
6 month	150	180	210
12 month	335	365	395

Complete a Subject Visit CRF for each follow-up visit.

At 3-month follow-up visit, LVEF will be assessed as per standard practice:

- As per Investigator's discretion, if the subjects have LVEF ≤ 40% or meeting one of the referral criteria (sustained VT, cardiac or unexplained syncope, clinically significant palpitations, new onset bundle branch block, conduction abnormalities, or symptomatic bradycardia), the subjects can be referred for SCD risk stratification and management (EP Referred Group). If the referral does not take place, it is not a study deviation.
- If the subjects have LVEF >40% but <50% (between 41%- 49%), the subjects will remain in the Non-Referred Group.
- If the subjects have LVEF ≥ 50%, they shall be exited from the study.

For the Non-Referred Group, a Referral Status CRF is needed for each subsequent visit unless the subject is referred to the EP Referred Group. During study follow-up visits, the Non-Referred Group subjects can be referred to the EP Referred Group if their LVEF is ≤ 40% or meets one of the referral criteria (as listed above).

9.6.1. Information Collected

The following information is required to be collected at follow-up visits:

- Referral status
- Implant status
- Cardiovascular Medication categories as listed under Enrollment/ Baseline (for 3-month visit only)

- LVEF measurement as per standard practice.
    - For 3-month visit, the LVEF measurement needs to be performed ⩾40 days post-acute MI for MI subjects without revascularization, or ⩾90 days post-revascularization for post-MI subjects with revascularization done.
- ECG as per standard practice
- Cardiovascular Adverse events, Study Deviations and System Modification.

9.6.2. Subjects with Medtronic device

Subjects who are indicated for a device and ultimately receive an implant will not be required to be implanted with a Medtronic device. However, if the subject is implanted with a Medtronic ICD or CRT-D, a device interrogation (save-to-disk) will be performed at implant and study follow-up visits, or via CareLink transmission as applicable.

It is recommended that data are not cleared during any interrogation or save-to-disk. Retain one copy at site for the subject file and submit the other copy to Medtronic via Medtronic Secure Messaging (MSM).

9.7. Study Exit

At 3-month follow-up, if a subject has an LVEF ≥ 50%, the subject will be exited from the study. Subject who remain in the study after 3-month follow-up should remain in the study until the 12-month follow-up is completed or until all data required to meet study objectives have been collected (whichever comes first). Either an in-office visit or phone call is required for study exit.

A study exit eCRF is required for all subjects. Prior to exiting a subject from the study, it is recommended to follow the subject until all AEs are resolved. Following exit, subjects will continue to receive standard medical care. Upon exiting from the study, no further study data will be collected or study visits will occur for the subject. Exited subjects will not be replaced with newly enrolled subjects.

Subjects are urged to remain in the study as long as possible, but may be exited from the study for any of the following situations:

- Study closure
- Subject lost to follow-up (refer to Section 9.11.1)
- Subject did not meet inclusion/exclusion criteria
- Subject did not provide consent or data use protection authorization
- Subject chooses to withdraw (refer to section 9.11.2 for more information)
- Investigator deems withdrawal necessary (e.g. medically justified, inclusion/exclusion criteria not met)
- Subject exited study at the 3 months visit if the 3-month LVEF is ≥ 50%
- Subject completed study after 12 months visit
- Subject Death

For study exit visits the following information is required:

- Reason for exit
- Final interrogation file (or CareLink transmission) for subjects implanted with Medtronic device
- Cardiovascular Adverse events, Study Deviations and System Modification

9.8. Assessment of Safety

This study is related to guideline-based care, using only market approved therapies, and so there are no pre-specified objectives relating to patient safety. Deaths and cardiovascular related adverse events, will be collected. See section 11 for further details.

9.9. Recording Data

The study will collect data using Oracle Clinical, an electronic data management system for clinical studies. Sites will enter data onto electronic case report forms (eCRFs), and the principal investigator or his/her authorized designee(s) will sign off the data entered.

Device interrogation files collected via electronic media at office visits will be sent to Medtronic. Device data from CareLink transmissions will be uploaded to secure servers. Upon receipt via transmissions or electronic media, device data will be maintained with databases and retrieved for analysis and reporting.

Data reported on the CRFs shall be derived from source documents, which may include worksheets, patient medical records and device interrogation/save-to-media files. These source documents must be created and maintained by the investigational site team. Further detail on data management is provided in Section 14.2.

9.10. Deviation Handling

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

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

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

All study deviations must be reported on the Case Report Form regardless of whether medically justifiable, pre-approved by Medtronic, an inadvertent occurrence, or taken to protect the subject in an

emergency. Please refer to the Case Report Form Completion Guideline for the examples of deviations. The deviation must be recorded with an explanation for the deviation and corrective/ preventative action(s).

In the event the deviation involves a failure to obtain a subject's consent, or is made to protect the life or physical wellbeing of a subject in an emergency, the deviation must be reported to the MEC/IRB (where applicable) as well as Medtronic within five (5) working days. Reporting of all other 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. Reporting of deviations must comply with IRB/ MEC policies, local laws, and or regulatory agency requirements. Refer to Investigator Reports (Table 8) for geography/country-specific deviation reporting requirements and timeframes for reporting to Medtronic and/or regulatory bodies.

Medtronic is responsible for analyzing deviations, assessing their significance, and identifying any additional corrective and/or preventive actions (e.g. amend the Clinical Investigation Plan, conduct additional training, terminate the investigation, etc.). 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 ultimately terminating the investigator's participation in the study. Medtronic will provide center-specific reports to investigators summarizing information on deviations that occurred at the investigational site on a periodic basis.

9.11.Subject Withdrawal or Discontinuation

9.11.1. Lost to Follow-Up

In the case that the subject is determined to be lost to follow-up, a minimum of two attempts to contact the subject must be documented. The recommended method of contact is one letter and one phone record or two letters. In addition, follow the regulations set forth by the governing IRB/EC.

9.11.2. Subject Withdrawal

A subject will be exited from the study in the event that he or she is unable to participate, expresses a desire to withdraw, or is unwilling to continue participation in the study. In addition, a subject may be exited from the study if an investigator feels it is necessary to withdraw the subject from the study due to a medical condition, if the inclusion/exclusion criteria are not met, or other reason. In such cases, the subject will be notified and provided an explanation regarding the reason for the study exit.
The subject should be informed that their future care or treatment will not be affected in any way as a result of choosing to not participate in this study. Furthermore, alternative treatments and medical consequences of exiting the study should be discussed with the subject. Any significant new findings related to the study that may develop, which may relate to the subject's willingness to continue participation, should be communicated to the subject.

10. Risks and Benefits

10.1. Potential Risks

While the study is characterizing the post-MI patient care pathway who may be referred and indicated for ICD therapy, there is no required study product for this study. In fact, this study does not require the administration of any pharmacological or device medical treatment, and required testing is restricted to standard LVEF measurement. Subjects are treated according to standard practice and there are no required additional procedures outside of standard of care. If the patients are indicated and receiving an ICD implant, the risks associated will be consistent with market-released ICD therapies. There may be other discomforts and risks related to the ICD and/or this study that are not foreseen at this time such as movement of the device from its original implant location, device prominence or protrusion under the skin, device requiring repositioning, wearing away of the skin in the area of device implant, awareness of device discomfort with certain types of pacing, pain when receiving a shock, the ICD batteries deplete and may require replacement of the ICD.

10.2. Potential Benefits

Participation in this study may offer no benefit. Subjects enrolled in the study may have additional contact with their physicians or other medical care staff beyond their normal standard of care visits, which may provide benefit from a patient care perspective. The information gained from this study could result in the improved management post-MI patients through bridging referral linkages, reimbursement coverage, and user adoption.

10.3. Risk-Benefit Rationale

Subjects may be identified as being indicated for ICD therapy regardless of their participation in this study. While subjects not indicated for ICD therapy may derive minimal or no benefit of participation in the study in terms of long term treatment, there is a potential for better acute care due to the protocol-required repeat diagnostic imaging and referral pathway.

11. Adverse Events

Timely, accurate, and complete reporting and analysis of safety information for clinical studies are crucial for the protection of subjects. Medtronic has established procedures in conformity with worldwide regulatory requirements to ensure appropriate reporting of safety information. The products used in the clinical trial are market approved and used within the current Indications for use as indicated in the product labeling. It is the responsibility of the Investigator to abide by any adverse event reporting requirements stipulated by local laws and regulations and the site's IRB or MEC.

User (Investigator) reporting of events to regulatory authorities related to market approved products may be required as per local law requirement.

11.1. Definitions/Classifications

Adverse Event definitions are provided in Table 4. Sites are required to report the following throughout the study duration, starting at the time the informed consent form is signed:

- Deaths
- Cardiovascular related Adverse Events including Cardiovascular related Serious Adverse Events and Major Adverse Cardiovascular and Cerebrovascular Events (MACCE)

For the purposes of the clinical report, Medtronic will classify each adverse event according to ISO14155:2011 definitions. The term "investigational medical device" is part of ISO14155 definitions. This study is not using any devices that are considered to be investigational. Where the definition indicates "device", it refers to any device used in the study.

Table 4 Adverse Event Definitions

Event Type	Definition
Cardiovascular Related AE	An AE relating to the heart and the blood vessels or the circulation. This includes but is not limited to syncope, stroke/TIA (Transient Ischemic Attack), myocardial infarction, heart failure, atrial or ventricular arrhythmia, and peripheral vascular disease.
Adverse Event (AE)	Any untoward medical occurrence, unintended disease or injury, or untoward clinical signs (including abnormal laboratory findings) in subjects, users or other persons, whether or not related to the investigational medical device. *NOTE 1: This definition includes events related to the investigational medical device or the comparator.* *NOTE 2: This definition includes events related to the procedures involved.* *NOTE 3: For users or other persons, this definition is restricted to events related to investigational medical devices.* *(ISO 14155:2011 section 3.2)*
Adverse Device Effect (ADE)	Adverse event related to the use of an investigational medical device. NOTE 1: This definition includes adverse events resulting from insufficient or inadequate instructions for use, deployment, implantation, installation, or operation, or any malfunction of the investigational medical device. NOTE 2: This definition includes any event resulting from an error use or from intentional misuse of the investigational medical device. (ISO 14155:2011, 3.1)
Serious Adverse Event (SAE)	Adverse event that a) led to death, b) led to serious deterioration in the health of the subject, that either resulted in 1) a life-threatening illness or injury, or 2) a permanent impairment of a body structure or a body function, or 3) in-patient or prolonged hospitalization, or

Event Type	Definition
	4) medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function, c) led to fetal distress, fetal death or a congenital abnormality or birth defect. *NOTE: Planned hospitalization for a pre-existing condition, or a procedure required by the CIP, without serious deterioration in health, is not considered a serious adverse event.* *(ISO 14155:2011 section 3.37)*
Serious Adverse Device Effect (SADE)	Adverse device effect that has resulted in any of the consequences characteristic of a serious adverse event. (ISO 14155:2011, 3.36)

11.2. Reporting of Adverse Events

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

Upon receipt of an Adverse Event at Medtronic, a Medtronic representative will review the Adverse Event for completeness and accuracy and when necessary will request clarification and/or additional information from the Investigator. Medtronic will utilize MedDRA, the Medical Dictionary for Regulatory Activities, to assign a MedDRA term for each adverse event based on the information provided by the Investigator.

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

Table 5 Adverse Event Classification Definition Responsibilities

What is classified	Who classifies?	Classification Parameters
Relatedness	Investigator	Device, Right Atrial (RA) Lead, Right Ventricular (RV) Lead, LV Lead
	Sponsor	Device, RA Lead, RV Lead, LV Lead
Seriousness	Investigator	SAE
	Sponsor	SAE
Diagnosis	Investigator	Based on presenting signs and symptoms and other supporting data
	Sponsor	MedDRA term assigned based on the data provided by Investigator

11.2.1. Adverse Events Reporting Requirements

Regulatory reporting of AEs will be recorded and reported according to local regulatory requirements. It is the responsibility of the Investigator to abide by any additional adverse event reporting requirements

stipulated by local law and the site's IRB/EC. Please refer to Appendix E for the investigator reporting requirements for countries where there are specific requirements.

Table 6 Reporting Requirements

All Cardiovascular related Adverse Events	
Investigator submit to:	
Medtronic	Submit in a timely manner after the investigator first learns of the event.
Regulatory authorities	Submit to regulatory authority per local reporting requirement.
Ethics Committee	Submit to Ethics Committee per local reporting requirement.

11.3.Subject Death

11.3.1. Death Data Collection

All subject deaths must be reported by the investigator to Medtronic on an AE (AE with the outcome of fatal) and Death CRFs as soon as possible after the investigator first learns of the death. Exit CRF also needs to be completed.

If any Medtronic system component is returned to Medtronic, internal return product reporting systems may be used to gather additional information about the returned device/component.

A copy of the death certificate, if available and allowed by state/local law, should be sent to the Medtronic study team. When a death occurs in a hospital, a copy of the death summary report and all relevant hospital records should be sent to the Medtronic study team, if available. If an autopsy is conducted, the autopsy report should also be sent to the Medtronic study team if available and allowed by state/local law. When the death occurs at a remote site, it is the investigative site's responsibility to attempt retrieval of information about the death. Additionally, device disposition information should be updated. In summary, the following data will be collected:

- Date of death
- Detailed description of death
- Cause of death
- Device interrogation (or CareLink transmission) for subjects implanted with Medtronic device
- Death summary/hospital records (if available and allowed by state/local law)
- Autopsy report (if available and allowed by state/local law)
- Death certificate (if available and allowed by state/local law)

11.3.2. Death Classification and Reporting

Sufficient information will be required in order to properly classify the subject's death. The Investigator shall classify each subject death per the following definitions:

- Sudden Cardiac Death (SCD): Natural death due to cardiac causes, indicated by abrupt loss of consciousness within one hour of the onset of acute symptoms; preexisting heart disease may have been known to be present, but the time and mode of death are unexpected. If the time of onset cannot be determined, SCD will alternatively be defined as any unexpected cardiac death occurring out of the hospital or in the emergency room as dead on arrival.
- Non-sudden Cardiac Death: All cardiac deaths that are not classified as sudden deaths, including all cardiac deaths of hospitalized subjects on inotropic support.
- Non-cardiac Death: A death not classified as a cardiac death.
- Unknown Classification: Unknown death classification is intended for use only when there is insufficient or inadequate information to classify the death.

Table 7 Subject Death Classification Responsibilities

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

Regulatory reporting of subject deaths will be completed according to local regulatory requirements.

11.4. Product Complaint Handling

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

Product Complaint: Any written, electronic or oral communication that alleges deficiencies related to the identity, quality, durability, reliability, safety, effectiveness or performance of a medical device that has been placed on the market.
It is the responsibility of the investigator to report all product complaint(s) associated with a medical device distributed by Medtronic, regardless whether they are related to intended use, misuse or abuse of the product. Reporting must be done immediately and via the regular channels for market-released products. Medtronic will notify the regulatory authorities, as applicable for the following incidents immediately upon learning of them:

- Any malfunction or deterioration in the characteristics and/or performance of a device, as well as any inadequacy in the labeling or instructions for use which led or might have led to the death or serious deterioration in the state of health of a patient, user, or other person.
- Any technical or medical reason resulting in the withdrawal of a device from the market by the manufacturer.
- A serious deterioration in the state of heath includes:
- Life-threatening illness or injury, or
- Permanent impairment of a body structure function or a body function, or
- In-patient or prolonged hospitalization, or

- Medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function.

12. Statistical Design and Methods

12.1. General Considerations

Medtronic statisticians or designee will conduct all statistical analyses. The purpose of the study is to characterize treatment patterns in different geographies for this population, and so descriptive statistics will primarily be used, and reported by geography. A separate Statistical Analysis Plan (SAP) will be developed and include a comprehensive description of the statistical methods to be included in the final study report. Any change to the data analysis methods described in the protocol will require an amendment only if it changes a principal feature of the protocol. Any other change to the data analysis methods described in the protocol or the SAP, and the justification for making the change, will be described in the clinical study report.

12.2. Primary Objective

Characterize the proportion of post-acute MI patients who are referred for sudden cardiac death risk (SCD) stratification and management.

12.2.1. Hypothesis

This is a characterization study, and so there are no hypotheses for this objective.

12.2.2. Endpoint definitions

The endpoint will be defined as the clinician's determination to refer the subject for SCD risk stratification and management. The pre-defined reasons for this referral are:

- Subject's LVEF at 3 months determined to be up to 40%
- Subject experiences unexplained syncope, ventricular arrhythmia, AV block, clinically significant palpitations, new onset bundle branch block, conduction abnormalities, or symptomatic bradycardia.

12.2.3. Analysis Methods

Subjects will be evaluated during their chronic phase (≥40-90 days after MI) for determination of the need for SCD risk stratification and management. As of this visit, subjects may be partitioned into several groups: died of cardiovascular causes prior to reaching the 3 months visit, exited or died of non-cardiovascular causes prior to reaching 3 months visit, reached the 3 months visit and were not referred for SCD risk stratification and management, reached the 3 months visit and were referred for SCD risk stratification and management. Descriptive statistics will be used to summarize these groups. Among

the subjects with a reason for referral during their chronic phase (≥40-90 days after MI) as described in Section 12.2.2, the proportions and Wilson score 95% CI of those who were referred will be computed. A subject not referred for SCD risk stratification and management during their chronic phase (≥40-90 days after MI) may later be referred. Thus, similar descriptive statistics may be generated at 6 and 12 months post-baseline visits. The analyses will be performed separately for each geography/country.

12.2.4. Determination of Patients/Data for Analysis

All subjects enrolled will be included in the analysis.

12.2.5. Sample Size

The sample size calculation was based on the width of the 95% confidence interval for the proportion of subjects that is referred for SCD risk stratification and management among subjects who have a reason for referral at the 3 months visit (see Section 12.2.2). The following assumptions were made:

- Drop-out and mortality rate combined from enrollment to 3 months visit of 10%,
- At the 3 months visit, 30% of subjects will have a reason for referral.

Under these assumptions, enrollment of approximately 200 patients per geography is needed, to have at least 80% power to achieve a 95% confidence interval width of 25% when 70% of patients is referred for SCD risk stratification and management.

12.3. Secondary Objectives

12.3.1. Proportion of post-acute MI patients who are indicated for an ICD/CRT-D

Characterize the proportion of post-acute MI patients who are known to be indicated for an ICD/CRT-D within 12 months post-MI.

12.3.1.1. Hypothesis

There are no hypotheses for this objective, as this is a characterization objective.

12.3.1.2. Endpoint definitions

The endpoint will be defined as whether a subject was indicated for an ICD/CRT-D device during follow-up.

12.3.1.3. Analysis methods

The proportion and Wilson score 95% CI of subjects recommended for ICD/CRT-D during their chronic phase (≥40-90 days after MI), at the 6 months and at the 12 months visits will be computed. Further, in

case any subject will be indicated for ICD/CRT-D at the 6 months or the 12 months visits, a competing risk analysis with accompanying 95% confidence bounds and mortality accounted for, will be produced to assess a subject's time to recommendation of ICD/CRT-D therapy, in months from date of enrollment to date of recommendation. Results will be determined separately for each relevant geography/country.

12.3.1.4. Determination of Patients/Data for Analysis

All subjects enrolled will be included in the analysis.

12.3.2. Proportion of post-acute patients who receive an ICD/CRT-D

Characterize the proportion of post-acute MI patients who receive an ICD/CRT-D within 12 months post-MI.

12.3.2.1. Hypothesis

There are no hypotheses for this objective, as this is a characterization objective.

12.3.2.2. Endpoint definitions

The endpoint will be defined as whether a subject received an ICD/CRT-D device during follow-up.

12.3.2.3. Analysis methods

The proportion of subjects who received an ICD/CRT-D during each of their follow-up visits will be computed. Further, a competing risk event curve with accompanying 95% confidence bounds and mortality accounted for, will be produced, to assess a subject's time to receiving ICD/CRT-D therapy. Results will be determined separately for each relevant geography/country.

12.3.2.4. Determination of Patients/Data for Analysis

All subjects enrolled will be included in the analysis.

12.3.3. Referral and implant refusal rationale

Summarize the referral and refusal implant rationale.

12.3.3.1. Hypothesis

There are no hypotheses for this objective, as this is a characterization objective.

12.3.3.2. Endpoint definitions

The outcome measure will be the proportion of patients with ICD indication, who were not referred, refused referral or refused implant. The denominator will count all patients with at least one of the below:

a. a reduced ejection fraction, as measured by the Left Ventricular Ejection Fraction (LVEF) being lower or equal than 40%.
b. ventricular arrhythmia, AV block, new onset bundle branch block, or conduction abnormalities as measured by ECGs.
c. unexplained syncope, clinically significant palpitations or symptomatic bradycardia as assessed by the physician

The numerator will count the patients included in the denominator who were not referred, refused referral or refused implant of an ICD/CRT-D.

12.3.3.3. Analysis methods

Descriptive statistics will be used to summarize the proportion of subjects who meet any of the referral criteria but are not referred for SCD risk stratification and management and the proportion of subjects refusing an ICD/CRT-D implant. The reasons for not having referred to subject for SCD stratification and for refusal of implant will also be summarized. All summary statistics will be produced overall and by geography.

12.3.3.4. Determination of Patients/Data for Analysis

All subjects enrolled will be included in the analysis at that time point.

12.3.4. Incidence of CV Mortality

Characterize the proportion of post-acute MI patients who experience cardiovascular mortality.

12.3.4.1. Hypothesis

There are no hypotheses for this objective, as this is a characterization objective.

12.3.4.2. Endpoint definitions

The endpoint will be defined as cardiovascular mortality.

12.3.4.3. Analysis methods

At each follow-up visit, the cumulative proportion of subjects who experienced cardiovascular mortality between each visit will be computed.

Further, for subjects who experience cardiovascular mortality, a subject's time to death will be computed in months from enrollment to date of death. If a subject does not meet the endpoint, the subject will be censored at the later of their last follow-up visit or exit. A competing risks event curve will be generated with accompanying 95% confidence bounds and non-cardiovascular mortality accounted for.

Results will be determined separately for each relevant geography/country.

12.3.4.4. Determination of Patients/Data for Analysis

All subjects enrolled will be included in the analysis.

12.3.5. Change in LVEF Over Time

Determine how the ejection fraction evolves over the immediate period of post MI.

12.3.5.1. Hypothesis

There are no hypotheses for this objective, as this is a characterization objective.

12.3.5.2. Endpoint definitions

The Left Ventricular Ejection Fraction (LVEF) will be measured acutely post MI (≤14 days after MI onset) and chronically (40-90 days). The endpoint will be the change between the acute and the chronic measurement.

12.3.5.3. Analysis methods

Descriptive statistics (e.g.: mean, standard deviation, median, range) will be used to summarize the LVEF during the acute phase and the chronic phase post-MI. Similar statistics will be provided for subjects with LVEF measured at the 6 months and at the 12 months visits. Additionally, the proportion and associated 95% CI of subjects whose LVEF measurement was at most 40% will also be computed, in both the acute and chronic phases. The average change in LVEF between the acute phase and the chronic phase, will be estimated using the ANCOVA method. The model will contain LVEF measurement as an outcome and visit (acute phase and chronic phase) and baseline LVEF as covariates, the latter to adjust the estimated difference by the effect of their baseline measure (eg regression to the mean).

Results will be determined separately for each relevant geography/country.

12.3.5.4. Determination of Patients/Data for Analysis

All subjects enrolled and for whom LVEF will be available will be used in the analysis at that time point.

12.4. Interim analysis

No interim analysis is planned for this study. However, drop out, mortality rates and reason for referral at the chronic phase visit will be monitored on an ongoing basis to account for possible heterogeneity in drop-out rate, mortality rate and reason for referral across geographies, which may require a different number of patients than expected to be enrolled in certain geographies.

In geographies where the drop-out and mortality rates and the reasons for referral are different than expected, enrollment may continue beyond 200 subjects to account for their specific drop-out rate, mortality rates and reasons for referral, while it may be stopped at approximately 200 subjects in other geographies.

12.5.Missing data

Missing data will not be imputed. For survival endpoints, subjects who do not meet the endpoint and exit or die prior to completing follow-up will be censored at the date of death or exit for endpoints that do not include the type of death the subject experienced (e.g. cardiovascular death).

12.6. Subgroup analysis

The following pre-defined subgroup will be investigated: clinic types (Interventional Cardiologist and Electrophysiologist are the same physician versus Interventional Cardiologist and Electrophysiologist are different physicians), PCI versus non-PCI, all objectives stratified by LVEF at baseline, STEMI vs non-STEMI. Details of their analysis will be described in the SAP.

13. Ethics

13.1.Statement(s) of Compliance

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

The study will be conducted according to national and local laws, regulations, standards, and requirements where the study is being conducted. The principles of the Declaration of Helsinki version 2013 or the most updated version have been implemented through the patient informed consent process, IRB/EC approval, study training, clinical trial registration, risk-benefit assessment, and publication policy.

The study will be publicly registered prior to first enrollment in accordance with Declaration of Helsinki on http://www.clinicaltrials.gov.

- In China, applicable local regulations will be followed.

- In Taiwan, applicable local regulations will be followed.
- In Middle East and Africa, local regulations will be followed.
- In India Subcontinent, applicable local regulations will be followed
- In Korea, Standards for Management of Clinical Trials for Medical Devices (KGCP) (Attachment 2-2 of Enforcement Regulations of the Medical Device Act, Ministerial Decree No.1512) and other applicable Korean regulations will be followed.
- In Singapore, Health Products (Medical Devices) Regulations 2010 and other local applicable regulations will be followed.
- In Malaysia, National Medical Research Register (NMRR) requirements are applicable although the medical device is not regulated in Malaysia. In addition, applicable local regulations will be followed.
- In Indonesia, MoH Decree No. 63 2017 and other local regulations will be followed

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

- Medtronic
- PIs (where required by local law/regulations)
- Geography-specific regulatory authorities (if regulatory approval is required)
- An Independent Ethics Committee

14. Study Administration

14.1. Monitoring

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

The Principal Investigator and site personnel will provide the Medtronic monitor(s) with complete access to primary source data (e.g., paper and electronic hospital/clinical charts, appointment books, laboratory records) that support the data on the eCRFs as well as other documentation supporting the conduct of the study. The monitor will perform source data verification and routine reviews of study related regulatory documents during scheduled monitoring visits, and work to secure compliance. Planned extent of source data verification will be performed in accordance to the study- specific monitoring plan. Frequency of monitoring visits may be based upon subject enrollment, duration of the study, study compliance, number of deviations, findings from previous monitoring visits and any suspected inconsistency in data that requires investigation. Regulatory documents (e.g., Ethics Committee approval letters, Clinical Trial Agreements) may be reviewed at each study site. Monitoring

for the study, including site qualification visits, site initiation visits, interim monitoring visits, and closeout visits, will be done in accordance to the study-specific monitoring plan.

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

Further details of monitoring will be given in the study monitoring plan.

14.2. Data Management

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

Only authorized persons can complete eCRFs. eCRFs shall be signed by the Principal Investigator. The Principal Investigator can delegate the CRF sign off task to Sub-Investigators only. Delegation of authority will be specified on the appropriate documentation.

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

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

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. The eCRF may be considered the source for the following data collection elements:

- Enrollment Notification
    - Site assigned patient reference
- Baseline
    - Administrative information
- Adverse Event
    - Date study site became aware of event
    - Relatedness of adverse event
- Deviations

- Reason for deviation

14.3. Direct Access to Source Data/Documents

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

14.4. Confidentiality

All records and other information about subjects participating in this study will be treated as confidential.

14.5. Liability

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

14.6. CIP Amendments

Approval of subsequent revisions to the CIP is required at each study site from the following groups prior to implementation of the revised CIP at the site:

- Medtronic
- PIs (where required by local law)
- Regulatory authorities (where required by local law)
- IRB/EC

If a CIP amendment occurs, site personnel will need to be re-trained as necessary and will need to submit any changes to their IRB/EC.

14.7. Record Retention

14.7.1 Investigator Records

The Investigator is responsible for the preparation and retention of the records including, but not limited to, those cited below. All of the below records, with the exception of case history records and case report forms, should be kept in the Investigator Site File (i.e., the study binder provided to the Investigator) or Subject Study Binder. eCRFs must be maintained and signed electronically by an Investigator within the electronic data capture system during the study. Medtronic will provide electronic copies of CRFs (i.e. Patient Data Report) from the database upon request following study closure.

The following records are subject to inspection and must be retained for a period of two years (or longer as local law/regulation or hospital administration requires) after study conclusion. Measures shall be taken to avoid loss or premature destruction.

- Essential correspondence between the IRB/EC, sponsor, monitor, and/or the Investigator that pertains to the investigation, including required reports.
- Subject's case history records, including:
  - Signed and dated Informed Consent Form, in accordance with local requirements
  - Observations of adverse events
  - Medical history
  - Baseline and follow-up data (if applicable)
  - Documentation of the dates and rationale for any deviation from the protocol
- Subject identification records
- Electronically signed and dated eCRFs and a blank set of eCRFs where required by local law
- All approved versions of the CIP and IC Form
- Signed and dated CTA
- IRB/EC approval documentation. Written information that the Investigator or other study staff, when a member of the IRB/EC, did not participate in the approval process. Approval documentation must include the IRB/EC composition, where required per local law.
- Regulatory authority notification, correspondence and approval, where required per local law.
- Current curriculum vitae of PIs and key members of investigation site team
- Documentation of delegated tasks
- Study training records for site staff
- Study reports including Final Study Report

14.7.2 Investigator Reports

The Investigator is responsible for preparing and submitting the following complete, accurate, and timely reports as listed in the following tables (as applicable per geography).

Table 8: Investigator Reports applicable for all geographies per Medtronic requirements

Report	Submit to	Description/ Constraints
Withdrawal of Ethics Committee approval	Sponsor and Regulatory Authority (as per local law)	The investigator must report a withdrawal of approval by the reviewing Ethics Committee of the investigator's part of the investigation within 5 working days.
Study Deviations	Sponsor, Ethics Committee and Regulatory Authority (as per local law)	Any deviation from the Clinical Investigation Plan shall be reported together with the explanation of the deviation as soon as

		possible upon the center becoming aware of the deviation. Notice of deviations from the CIP involving 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 shall be given within 5 working days, or sooner if required by local requirements. Except in such emergency, prior approval is required for changes in the plan or deviations.
Progress Report	Ethics Committee	Provide if required by local Ethics Committee
Final Report	Ethics Committee and Regulatory Authority (as per local law)	This report must be submitted within 3 months of study completion or termination, or as per local requirement.

Reports are subject to inspection and to the retention requirements as described above for Investigator records. Investigator reporting requirements for safety data are listed in Section 11.

14.7.3 Sponsor Records

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

- Essential correspondence which pertains to the clinical study
- Executed Clinical Trial Agreement
- Current curriculum vitae of PIs and key member of investigation site team
- Electronically signed and dated eCRFs
- All approved informed consent versions, and other information provided to the subjects and advertisements, including translations
- Copies of all IRB/EC approval letters and relevant IRB/EC correspondence and IRB/EC voting list/roster/letter of assurance
- List of names, addresses, and professional position of the clinical investigators and coordinating clinical investigators if appointed.
- Names, addresses and contact information of the institutions in which the clinical study will be conducted
- Regulatory authority notification, correspondence and approval, if applicable.
- Insurance Certificates
- Names/contact addresses of monitors
- Monitoring reports (interim monitoring visit reports, follow-up letters, and close-out visit reports)

- Site qualification visit reports
- Statistical analyses and underlying supporting data
- Final report of the clinical study
- The approved Clinical Investigation Plan, study related reports, and revisions
- Documentation of delegated tasks
- Study training records for site personnel and Medtronic personnel involved in the study
- Sample of CRFs
- Any other records that local regulatory agencies require to be maintained

14.7.4 Sponsor Reports

Medtronic shall prepare and submit the following complete, accurate, and timely reports listed in the tables below. In addition to the reports listed below, Medtronic shall, upon request of reviewing IRB/EC or regulatory authorities, provide accurate, complete and current information about any aspect of the clinical study. Medtronic reporting requirements for safety are listed in 11.2.1.

Table 9 Sponsor Reports for all geographies

Report	Submit to	Description/Constraints
Premature termination or suspension of the clinical study	Investigators, Ethics Committee and Regulatory Authorities	Provide prompt notification of termination or suspension and reason(s) per Ethics Committee or per local requirement.
Withdrawal of Ethics Committee approval	Investigators, Ethics Committee and Regulatory Authorities	Investigators and other Ethics Committees will be notified only if required by the Ethics Committee or local law.
Progress Reports, if applicable	Ethics Committee and Regulatory Authorities	This will be submitted to the Ethics Committee as required by Ethics Committee or local law.
Final report	Investigators, Ethics Committee and Regulatory Authorities	This will be submitted to the Ethics Committee as required by Ethics Committee or local law
Study deviation	Investigators	Site-specific study deviations will be submitted to Investigators periodically.

Medtronic electronic records and reports will be maintained in a password-protected document management system. After the closure of the study, Medtronic will archive records and reports in accordance with local laws and current standard operating procedures.

14.8. Publication and Use of Information

Results may be submitted for publication. Additional analyses may be published in relation to the learnings and understanding of topics related to the objectives. If results from the Improve SCA Bridge

study will be published, they will be handled according to Medtronic Standard Operating Procedures and as indicated in the Clinical Trial Agreement.

Publications from the Improve SCA Bridge Study will be handled according to Medtronic Policies and Standard Operating Procedures and as indicated in the CTA.

The Improve SCA Bridge Study will utilize a Publication Committee which will including the Steering Committee members as well as Medtronic personnel. This committee will manage study publications with the goal of publishing findings from the data. The Publication Committee will develop the final Publication Plan as a separate document. The publication plan may include, but is not limited to, description of committee member criteria and management of publications.

14.9.Suspension or Early Termination

14.9.1 Planned study closure

Study Closure is a process initiated by the distribution of a study closure letter. Study closure is defined as closure of a clinical study that occurs when Medtronic and/or regulatory requirements have been satisfied per the Clinical Investigation Plan and/or by a decision by Medtronic or regulatory authority, whichever occurs first. The study closure process is complete upon the distribution of the Final Report or after final payments, whichever occurs last. Ongoing IRB/EC oversight is required until the overall study closure process is complete. Upon study closure, subjects should be managed and followed per physician discretion.

14.9.2 Early Termination or Suspension

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

Study-Wide Termination or Suspension

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

- Adverse events associated with the system or product under investigation which might endanger the safety or welfare of the subject
- Observed/suspected performance different from the product's design intent
- Decision by Medtronic

Investigator/Site Termination or Suspension

Possible reasons for Clinical Investigator or site termination or suspension include but are not limited to:

- Failure to obtain initial IRB/EC approval or annual renewal of the study

- Persistent non-compliance to the clinical investigation (e.g. failure to adhere to inclusion/exclusion criteria, failure to follow subjects per scheduled follow-ups)
- Lack of enrollment
- Noncompliance with regulations and the terms of the CTA or WO (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/EC suspension of the site
- Fraud or fraudulent misconduct is discovered (as defined by local law and regulations)
- Investigator request (e.g. no longer able to support the study)

14.9.3 Procedures for Termination or Suspension

Medtronic-Initiated and Regulatory Authority-Initiated

- Medtronic will promptly inform the Clinical Investigators of the (early) termination or suspension and the reasons and inform the regulatory authority(ies) where required
- In the case of study termination or suspension for reasons other than a temporary IRB/EC approval lapse, the Investigator will promptly inform the IRB/EC
- In the case of study termination, the Investigator must inform the subjects and may inform the personal physician of the subjects to ensure appropriate care and follow-up is provided
- In the case of a study suspension, subject enrollment must stop until the suspension is lifted by Medtronic
- In the case of a study suspension, enrolled subjects should continue to be followed out of consideration of their safety, rights, and welfare
- In case the suspension is lifted, the investigator should assess whether or not to continue the study at the respective site

Investigator-Initiated

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

IRB/EC-Initiated

- The Investigator will inform Medtronic and provide a detailed written explanation of the termination or suspension within 5 business days
- Subject enrollment must stop until the suspension is lifted
- Subjects already enrolled should continue to be followed in accordance with IRB/EC policy or its determination that an overriding safety concern or ethical issue is involved

- The Investigator will inform his/her institution (where required per local requirements)
- The Investigator will promptly inform the subjects, and/or the personal physician of the subjects, with the rationale for the study termination or suspension
- In case the suspension is lifted, the investigator should assess whether or not to continue the study at the respective site

15 Reference

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16 Appendices

Appendix A: Case report forms

Case report forms will be provided under separate cover upon request.

Appendix B: Informed consent template

Informed Consent form templates will be provided under separate cover.

Appendix C: Participating investigators and institutions

A complete list of participating investigators and institutions where study activities are conducted will be maintained by the Sponsor and distributed under separate cover upon request.

Appendix D: Study Sponsor Contact Information

The study sponsor contact list will be provided in the site's study documents binder/investigator site file. Sponsor will maintain this list and send update if necessary.

Appendix E: Investigator Reporting Requirements

Investigator Reporting Requirements for India		
Events to Report	**Reporting Requirement and Timeframe**	**Submit to**
Cardiovascular Related SAE/SADE/USADE		
Investigator submit to:		
All SAE, SADE, USADE	Investigator shall report all SAEs, SADEs and USADEs to the Ethics Committee, monitor and Sponsor promptly of their occurrence. (Indian GCP section 3.3.4.3) For reported deaths the investigator shall supply any additional information (e.g., autopsy report and terminal medical reports.) (Indian GCP section 3.3.4.5) It is recommended for investigator to report all SAEs, SADEs and USADEs to the sponsor within 24 hours. It is recommended for investigator to report all SAEs, SADEs and USADEs to EC within 7 working days unless the stricter timeline is required by the EC.	Medtronic Monitor EC
New information that may adversely affect safety of the subjects or the conduct of the study	Investigator shall promptly report new information that may adversely affect safety of the subject or the conduct of the study. (Indian GCP section 3.3.4.4)	EC Medtronic Monitor

Investigator Reporting Requirements for Korea		
Events to Report	**Reporting Requirement and Timeframe**	**Submit to**
Cardiovascular Related SAE/SADE/USADE		
Investigator submit to:		
All SAE	The investigator shall create and submit relevant document for all SAEs (excluding what classified in the protocol or the IB as ones not requiring immediate report) to the sponsor within the period provided in the protocol. (KGCP Article 7 item 11)	Medtronic
SADEs, USADEs causing death or life threatening	Within 7 calendar days from the date when the investigator had relevant effects reported or informed. In this case, the investigator shall make a detailed report of the SADEs, USADEs causing death or life threatening within 8 calendar days from the initial report. For Death, investigator shall submit additional information, such as	IRB

	an autopsy report (only if an autopsy was performed) and a death certificate.	
Other SADEs, USADEs excluding death or life threatening	Within 15 calendar days from the date when the investigator had relevant effects reported or informed.	IRB

Investigator Reporting Requirements for Taiwan		
Events to Report	**Reporting Requirement and Timeframe**	**Submit to**
Cardiovascular Related SAE		
Investigator submit to:		
SAE	The investigator should report SAEs to the sponsor immediately. A detailed written report should be provided to the sponsor as soon as possible. (Medical Device GCP Guidance (2016-01-01) Article 67) It is recommended for investigator to report all SAEs to the sponsor within 48 hours.	Medtronic
SAE	Report within 7 calendar days of first acknowledged of death and life-threatening SAEs, SADEs and USADEs, make a report and submit to TFDA and ADR center, submit a copy to the sponsor. If the information of the report mentioned in the preceding paragraph is not complete, it should be supplied within 15 calendar days. If the information of the report mentioned in the preceding paragraph requires the sponsor to provide information relevant to the products, the sponsor should not refuse. Note: The requirement is not applicable if MDT is not the product license holder. (Procedure for Reporting Severe Adverse Reactions to Medicines (2004-8-31) Article 5) It is recommended to report all non-fatal or non-life- threatening SADEs and USADEs following the same requirements mentioned above.	TFDA