Improve SCA Bridge Study
Statistical Analysis Plan Version 1.0
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Medtronic

Statistical Analysis Plan

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1. Version History

Version	Summary of Changes	Author(s)/Title
1.0	Not applicable, new version	Francesca Lemme, Senior Statistician

2. List of Abbreviations and Definitions of Terms

Abbreviation	Definition
AE	Adverse Event
AV block	Atrioventricular block
CRF	Case Report Form
eCRF	Electronic Case Report Form
CRT-D	Cardiac Resynchronization Therapy with Defibrillator
ECG	Electrocardiogram
EF	Ejection Fraction
EP	Electrophysiologist
ICD	Implantable Cardioverter Defibrillator
LVEF	Left Ventricular Ejection Fraction
MDT	Medtronic
MEACAT	Middle East, Africa, Central Asia & Turkey
MI	Myocardial Infarction
PCI	Percutaneous Coronary Intervention
SCA	Sudden Cardiac Arrest
SCD	Sudden Cardiac Death
SEA	South East Asia
STEMI	ST-elevation Myocardial Infarction
VT	Ventricular Tachycardia

3. Introduction

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. Left ventricular dysfunction following an acute MI identifies patients at higher risk of sudden cardiac arrest (SCA) and death (SCD).

It is well established that the use of Implantable Cardioverter Defibrillators (ICDs) reduces the risk of mortality in patients with reduced left ventricular ejection fraction (LVEF) who are at risk of SCA or sustained ventricular tachycardia (VT). However, low ICD utilization in ICD-indicated patients worldwide (ranging from 30 to 50% in USA, 24% in Europe, 12% in Asia) and persistent high post-PCI mortality rates suggest that barriers in this patient care pathway exist.

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. 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.

Efforts have been made to improve and align guidelines-based clinical practice for prevention of sudden death post-MI. For example, the ACC/AHA/HRS guidelines for post-MI care 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". These guidelines detail post-MI care and emphasize 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 more than 40 days after a MI identifies patients at higher risk of SCD.

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.

The Improve SCA Bridge study will assess the care pathway for post-acute MI patients through standard assessment of LVEF and implementation of an educational strategy to bridge the treatment pathway for patients who are indicated for an ICD/CRT-D as per the AHA/ACC/HRS guideline.

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.

This Statistical Analysis Plan (SAP) will be used to support the final report and analysis of the Improve SCA Bridge study. The Statistical Analysis Plan has been designed to document, before data is analyzed, the planned analyses for the final report. This SAP does not limit the analysis in reports, and additional analyses of the study data beyond this plan might be conducted. However, this document provides the basis for the statistical sections of the final report. Analyses not planned in the SAP and incorporated into the final report will be referred to as "Additional Analysis". Further, in case any analyses will be

done differently than planned in the CIP or SAP and explanation will be provided in the final report. The following document was used to create this Statistical Analysis Plan (SAP): CIP Improve SCA Bridge Version 2, dated 1 MAY 2019.

4. Study Objectives

4.1 Primary Objective

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

4.2 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

4.3 Endpoints

4.3.1 Primary Endpoint

The primary 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 40% or less
- Subject experiences unexplained syncope, ventricular arrhythmia, AV block, clinically significant palpitations, new onset bundle branch block, conduction abnormalities, or symptomatic bradycardia.

4.3.2 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" 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.

5. Investigation Plan

5.1. Study Design

This study is a prospective, non-randomized, single-arm, multi-site, global, post-market study. There is no investigational device and there is no control group; 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 regions are: China, India, 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 regions. Each region is expected to enroll approximately 200 subjects. The study is expected to enroll approximately 1,200 subjects.

Prior to study site initiation, current referral information will be collected from sites, and investigators and other site clinical personnel will be trained using educational materials (available under a separate cover) that address the importance of EF measurement and care pathway for post-MI patients. Apart from the educational material, there is no intervention and there are no requirements for treatment of

the patients. Referral of patients to SCD risk stratification and management is at the discretion of the physicians.

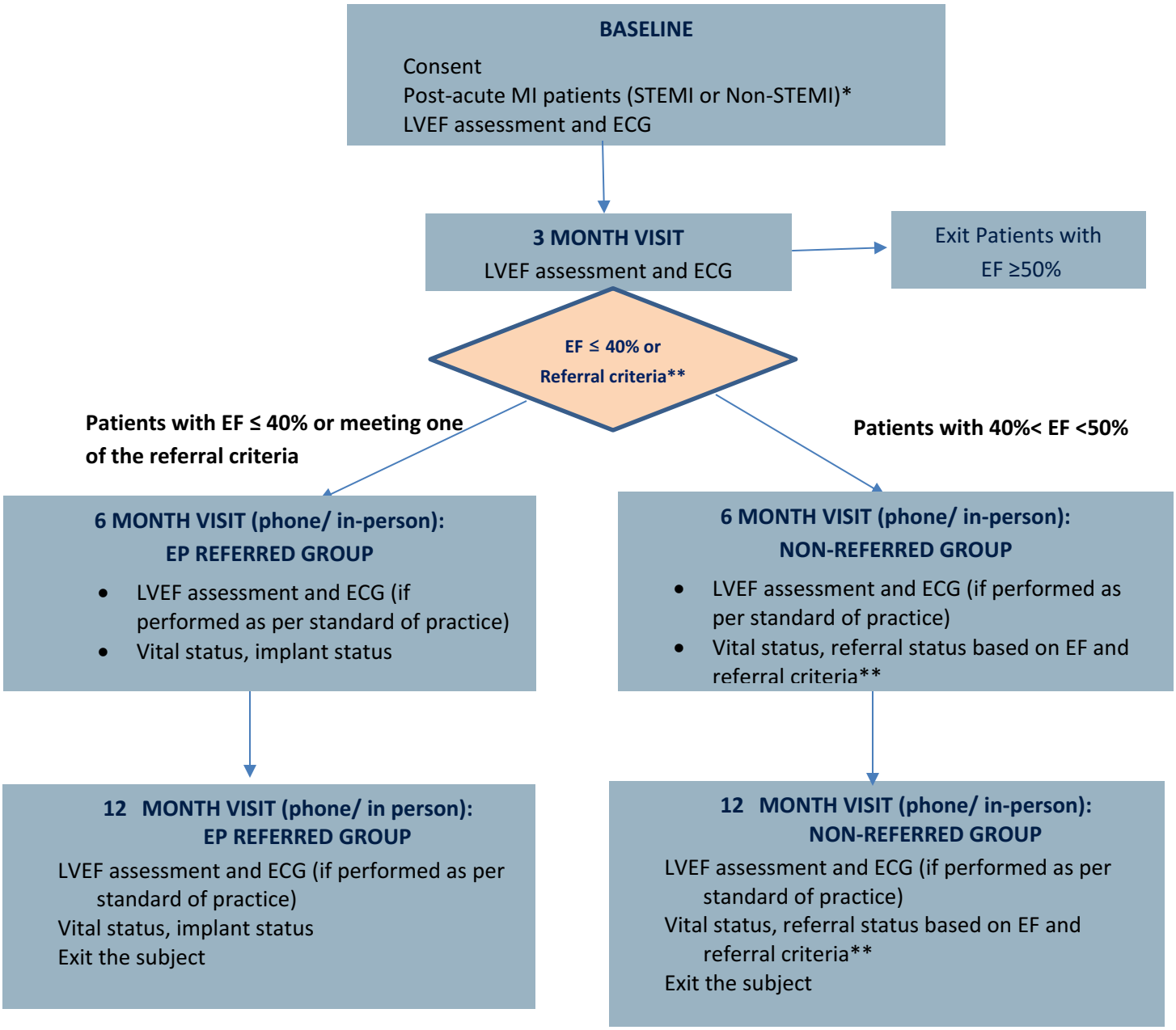
Methods incorporated in the study design to minimize potential bias include (but are not limited to):

- 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 region is expected to enroll approximately 200 subjects to have at least 80% power to achieve a sufficient number of patients referred for SCD risk stratification and management.
- For each region, sites where the same physician acts both as an interventional cardiologist and as an electrophysiologist will be limited to a maximum of 20% of all sites.

No interim analysis is planned, but a sample size re-assessment for each region may be produced, as described in Section 6.2.

See Figure 1 for further detail on study procedures.

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.

Table 1 below specifies the time windows for the required subject visits, which are based on days post-acute MI. If a subject visit falls outside the pre-specified window, a study deviation will 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. If a subject has an out of window visit, referral will be counted at the consecutive visit, while non-referral will be counted at the previous visit. For example, if a subject has a 3 months visit at 140 days post MI and is referred, he'll be considered as having been referred at the 6 months visit. On the contrary, if a subject has a 3 months visit at 140 days post MI and is not referred, he'll be considered as not having been referred at the 3 months visit. Rationale of this is:

1. When the late visit does not have the event (e.g. no referral yet), the event also had not happened yet in the window of the previous visit, but it may occur at the consecutive visit.
2. When the late visit has the event (e.g. referral), the status at the next visit is referred, but it is unsure whether the referral would have already happened in the window of the previous visit.

Table 1: 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

5.2. Duration

The study duration is expected to be approximately 24 months. The first enrollment occurred in Nov 2018. The 24 months study duration 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.

5.3. Rationale

This study is characterizing 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.

5.4. 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 have had an EP referral in the last 12 months will not be approached for this study.

5.5. Eligibility

5.5.1. 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 for acute MI definition.

5.5.2. 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.*

6. Determination of Sample Size

6.1 Sample Size Assessment

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. 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 region is needed, to have at least 80% power to achieve a 95% confidence interval width of 25% when 70% of patients with a reason for referral at the 3 months visit is referred for SCD risk stratification and management.

The sample size has been computed as follows.
First, the number of subjects needed in each region with a reason for referral at the 3 months visit ($N_{reason\_referral}$) was computed using the SAS procedure below:

```
proc power;
 onesamplefreq
  ci = wilson
  halfwidth = 0.125
  probwidth = .
  proportion = 0.70
  ntotal = 40 to 70 by 1;
run;
```

where proportion = 0.70 is the proportion of subjects to be referred among those with a reason for referral and halfwidth =0.125 is half of the 95% confidence interval around this proportion. As a result of the above SAS procedure, the needed number of subjects that will give at least 80% power to achieve a 95% confidence interval of halfwidth =0.125 around a proportion of 70% of subjects with a reason for referral that will be referred is $N_{reason\_referral}$ = 54.
Secondly, the number of subjects expected at the 3 months visit was computed as the ratio between the required number of subjects with a reason for referral at the three months visit ($N_{reason\_referral} = 54$) and the assumed proportion of subjects with a reason for referral at the three months visit ($prop_{referral\_assumed} = 0.30$) :

$$N_{3months} = \frac{N_{reason\_referral}}{prop_{referral\_assumed}} = \frac{54}{0.30} = 180$$

The number of subjects to be enrolled was then computed as the expected number of subjects that will complete the three months visit (($N_{3months} = 180$) and the assumed proportion of subjects that will not drop-out or die between enrollment and the 3 months visit ($1 - rate_{exit\_assumed} = 0.90$):

$$N_{enrolled\_planned} = \frac{N_{3months}}{1 - rate_{exit\_assumed}} = \frac{180}{0.90} = 200$$

Therefore, assuming a drop-out and mortality rate of 10% and a proportion of subjects with a reason for referral of 30%, approximately 200 subjects needs to be enrolled in each region to ensure at least a 80% power to achieve a 95% confidence interval width of 25% when 70% of patients with a reason for referral at the three months visit will be referred.

6.2 Sample Size Re-assessment

Drop out and mortality rates from enrollment to the 3 months visit and the proportion of subjects with a reason for referral at the 3 months visit will be monitored on an ongoing basis to account for possible heterogeneity in the drop-out and mortality rate and in the proportion of subjects with a reason for referral across geographies. A sample size re-assessment may be performed in regions with mortality

and drop-our rates different than 10% or with a proportion of subjects with reasons for referral different than 30%. The sample size reassessment will be produced as explained below.

The data gathered from each region at the time of the sample size re-assessment from enrollment to the 3 months visit will be used to compute the observed mortality and drop-out rate at the 3 months visit ($rate_{exit\_observed}$) and the proportion of subjects with a reason for referral at the 3 months visit ($prop_{referral\_reason}$) as follows:

$$rate_{exit\_observed}=\frac{Number\ of\ deaths\ and\ drop\ out\ before\ the\ 3\ months\ visit}{Number\ of\ subjects\ enrolled}$$

$$prop_{referral\_reason}=\frac{Number\ of\ subjects\ with\ a\ reason\ for\ referral\ at\ the\ 3\ months\ visit}{Number\ of\ subjects\ with\ a\ 3\ months\ visit\ completed}$$

In regions where the drop-out and mortality rate ($rate_{exit\_observed}$) will differ from 10% or the proportion of subjects with a reason for referral ($prop_{referral\_reason}$) will differ from 30%, the total number of subjects to be enrolled ($N_{enrolled}$) will be computed following the below two steps:

Step 1: the number of subjects expected at the 3 months visit, given $prop_{referral\_reason}$ will be computed as the ratio between the required number of subjects with a reason for referral at the three months visit ($N_{reason\_referral} = 54$) and the observed proportion of subjects with a reason for referral at the three months visit ($prop_{referral\_reason}$) :

$$N_{3months} = \frac{54}{prop_{referral\_reason}}$$

Step 2: the number of subjects to be enrolled, given $rate_{exit\_observed}$ will be computed as the expected number of subjects that will complete the three months visit and the observed proportion of subjects that did not drop-out or die between enrollment and the 3 months visit ($1 - rate_{exit\_observed}$):

$$N_{enrolled\_update} = \frac{N_{3months}}{1 - rate_{exit\_observed}}$$

Therefore, in regions where the drop-out and mortality rate will differ from 10% or the proportion of subjects with a reason for referral will differ from 30%, the number of subjects to be enrolled will change from the assumed approximately 200 to $N_{enrolled\_update}$, to ensure at least a 80% power to achieve a 95% confidence interval width of 25% when 70% of patients with a reason for referral at the three months visit will be referred.

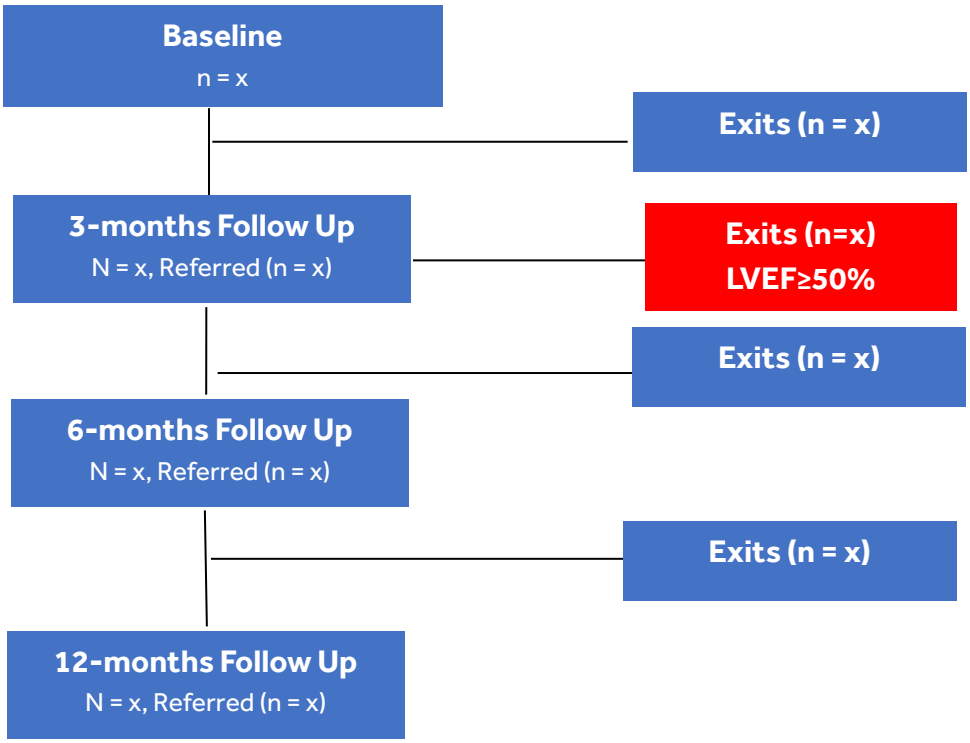
7. Statistical Methods

7.1 Study Subjects

7.1.1 Disposition of Subjects

A subject is enrolled in the study when he/she signs and dates the Patient Informed Consent. The study is expected to be conducted at approximately 50 sites worldwide in the regions listed in Section 5. Each region is expected to enroll approximately 200 subjects, with a total of approximately 1,200 subjects.
A flow chart similar to figure 2 will be created to describe patient disposition.

Figure 2: patient disposition flow chart



Study exits will be summarized according to exit reason. Violation of inclusion and exclusion criteria at baseline will be summarized for all enrolled patients.

7.1.2 Clinical Investigation Plan (CIP) Deviations

Deviations from the clinical investigation plan will be collected as deviations on the Study Deviation eCRF. Deviations will be summarized in the final report in a table by coded category. Deviation coding will be performed by Medtronic, and the coding will be collected on the MDT Deviation eCRF. The

number of deviations per category, the number and percentage of subjects with a deviation in this category will be reported.

7.1.3 Analysis Sets

Study manager, data manager and statistician will determine the visit cut-off date and received data cut-off date for the final data base lock as suitable.

Data from all patients who signed the informed consent document, are enrolled and have no inclusion or exclusion criteria violation will be analyzed. This set of patients will be referred to as the Enrolled Population. Depending on the analysis objective, statistical analyses based on subsets of the Enrolled Population will also be produced, as defined in the "Determination of Patients/Data for Analysis" of each of the analysis objectives described in Section 7.9.

7.2 General Methodology

Data summaries for categorical data will include count, e.g., number of patients, and/or number of events, and a percentage relative to the total number of patients/events. The denominator will be explicitly identified when not clear from the context. Continuous variables will be represented by mean and standard deviation, except when the distribution of the variable is highly skewed in which case median and quartiles will be reported.

P-values for hypothesis testing will be evaluated based on two-sided testing using significance level of 0.05. Confidence intervals will be reported as two-sided 95% confidence intervals.

7.3 Center Pooling

The study is expected to be conducted at approximately 50 sites worldwide, within 6 regions (see details of regions in Section 5). Data will be pooled across centers within the same region and analyses will be presented by region. Within each region, heterogeneity in the primary endpoint across centers will be evaluated using the Fisher Exact test. If this test is significant at the 0.05 level, further investigation of the data may occur to determine the source of the heterogeneity.

7.4 Handling of Missing, Unused, and Spurious Data and Dropouts

Because this is a feasibility study and no hypothesis testing is involved in any of the study objectives, the main analysis for each objective will not account for missing data. All available data will be used for analyses. In the unlikely presence of any unused or spurious data, such data will be listed or summarized in a dedicated table and the reasons for not using it will be explained. Drop outs between each study visit will also be summarized by region and overall.

7.5 Adjustments for Multiple Comparisons

No adjustment for multiple comparisons is planned due to the exploratory nature of the study.

7.6 Demographic and Other Baseline Characteristics

Standard baseline and relevant medical history will be collected on the e-CRFs for all enrolled subjects. Baseline and medical history variables to be summarized include, but are not limited to: age, sex, region of enrollment, cardiovascular history, arrhythmia history, and cardiovascular medications.

For continuous variables, mean, standard deviation, median, and range will be reported. For categorical variables, frequency and percentage will be reported. Baseline information will be summarized overall and by region for all enrolled subjects.

7.7 Treatment Characteristics

Subjects are treated per standard of care, there are no treatment requirements and there is no investigational device. Any treatment information that will be collected will be summarized, including devices and medications.

7.8 Interim Analyses

No interim analysis is planned for this study. A sample size re-estimation may be performed instead, as described in Section 6.2.

7.9 Evaluation of Objectives

7.9.1 Primary Objective

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

7.9.1.1 Hypothesis

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

7.9.1.2 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.

7.9.1.3 Analysis Methods

Subjects will be evaluated during their three months visit (chronic phase, ≥40-90 days after MI) for determination of the need for SCD risk stratification and management. As of this visit, subjects will be partitioned into several groups: died of cardiovascular causes prior to reaching the 3 months visit, exited or died of non-cardiovascular or unknown causes prior to reaching 3 months visit, reached the 3 months visit and exited because of LVEF≥50%, reached the 3 months visit and had at least one reason for referral for SCD risk stratification and management, reached the 3 months visit and had no reason for referral for SCD risk stratification and management.

Subjects classified as "died of cardiovascular causes" will be all subjects with subject status "death" within the exit CRF and with primary cause of death "non-sudden cardiac death" or "sudden cardiac death" within the death CRF.

Subjects classified as "exited or died of non-cardiovascular or unknown causes" will be all subjects with subject status "death" within the exit CRF and with primary cause of death "non-cardiovascular death" or "unknown classification" within the death CRF and all subjects with subject status "adverse event, lost to follow-up, physician decision, sponsor request or withdrawal by subject" in the exit CRF.

Subjects classified as "reached the 3 months visit and exited because of LVEF>50%" will be all subjects that will have completed the three months visit and will have subject status "other" within the exit CRF and will have a result of LVEF measurement higher or equal than 50% within the LVEF CRF.

Subjects classified as "reached the 3 months visit and had at least one reason for referral" will be all subjects that will have completed the three months visit and that in the referral CRF will have answer "yes" to the question "does the subject meet referral criteria" and will have at least one reason for referral selected underneath the question "if yes, indicate referral criteria met".

Subjects classified as "reached the 3 months visit and had no reason for referral" will be all subjects that will have completed the three months visit and that will have answer "no" to the question "does the subject meet referral criteria" in the referral CRF.

Descriptive statistics will be used to summarize these groups and displayed as shown in the example Table 2 below.

Table 2: Number (%) of subject in each group between enrollment and the 3 months visit

		Enrolled Population
Region 1	Died of cardiovascular causes	XX/XX (XX.XX%)
	Exited or died of non-cardiovascular or unknown causes	XX/XX (XX.XX%)
	Reached the 3 months visit and exited because of LVEF≥50%	XX/XX (XX.XX%)
	Reached the 3 months visit and had reasons for referral	XX/XX (XX.XX%)
	Reached the 3 months visit and had no reasons for referral	XX/XX (XX.XX%)
Region 2	Died of cardiovascular causes	XX/XX (XX.XX%)
	Exited or died of non-cardiovascular or unknown causes	XX/XX (XX.XX%)
	Reached the 3 months visit and exited because of LVEF≥50%	XX/XX (XX.XX%)
	Reached the 3 months visit and had reasons for referral	XX/XX (XX.XX%)
	Reached the 3 months visit and had no reasons for referral	XX/XX (XX.XX%)
…	…	…
Overall	Died of cardiovascular causes	XX/XX (XX.XX%)
	Exited or died of non-cardiovascular or unknown causes	XX/XX (XX.XX%)
	Reached the 3 months visit and exited because of LVEF≥50%	XX/XX (XX.XX%)
	Reached the 3 months visit and had reasons for referral	XX/XX (XX.XX%)
	Reached the 3 months visit and had no reasons for referral	XX/XX (XX.XX%)

The same summary statistics will be computed at the 6 months and at the 12 months visits and displayed in tables similar to Table 1, except for the group "exited because of LVEF≥50%" as patients are exited from the study for this reason at the 3 months visit only.

Note that at the three months visit, subjects with a LVEF≥50% will be exited from the study regardless of other reasons for referral. The proportion of those subjects that had a reason for referral other than LVEF will be computed by region and overall.

Among the subjects with a reason for referral during their three months visit, the proportions and Wilson score 95% CI of those who were referred for sudden cardiac death risk (SCD) stratification and management will be computed.

The subjects with a reason for referral (denominator) will be all subjects that at the three months visit will have at least one referral criterion met in the referral CRF. The subjects referred (numerator) will be

all subjects that will have completed the three months visit and that will have answer “yes” to the question “has the subject been referred or invited for SCD risk stratification” in the referral CRF.

An example SAS code for the computation of the proportions for each region is provided below:

```
proc freq data = referral;
 by region;
 table referred/binomial (cl = wilson) alpha = 0.05 out = perc;
 ods output binomialCLs=percConf;
run;
```

The results will be shown for each region and overall in a table similar to the example table below:

Table 3: percentage (95% CI) of subjects referred for sudden cardiac death risk (SCD) stratification and management, among the subjects with at least one reason for referral at the 3 months visit (chronic phase)

Region	Proportion Referred	95% CI
Region 1	XX/XX (XX.XX%)	(XX.XX% - XX.XX%)
Region 2	XX/XX (XX.XX%)	(XX.XX% - XX.XX%)
…	…	…
Overall	XX/XX (XX.XX%)	(XX.XX% - XX.XX%)

A subject not referred for SCD risk stratification and management during their three months visit may later be referred. Thus, similar descriptive statistics may be generated at the 6 and at the 12 months post-baseline visits and displayed in a table similar to table 2 above.
Further, as part of an attempt to continually train the physicians on referring subjects with a reason for referral, periodic feedbacks on referral rates will be provided. Whether these periodic feedbacks will have an impact on referral rate will be investigated by producing, for each region and overall and over time, a penalized B spline plot. A SAS code similar to the below will be used:

```
ods graphics on / attrpriority=none;
proc sgplot data=referral noautolegend;
   title 'Penalized B-Spline for each region';
   styleattrs datalinepatterns=(solid);
   pbspline y=prop x=time/group=region;
run;
```

Additional analyses may be provided and described in the final report.

Additionally to the analyses described above, logistic regression models might be used overall and by region, to estimate the odds ratios of referring patients for SCD stratification and management

depending on different factors, such as age, gender, LVEF≤40% versus any other reason for referral, physician's specialty, PCI versus non-PCI patients, STEMI versus non-STEMI patients. An example SAS code similar to the below will be used:

```
proc logistic data = referral;
 by region;
 class factor/descending;
 model referred (event = '1') = factor/expb;
 oddsratio factor;
 ods output ParameterEstimates = ParEstim;
 ods output OddsRatiosWald = OREstim;
run;
```

where referred is the outcome and is equal to 1 if the subject has been referred and 0 otherwise, factor is the independent factor of interest (eg: reason for referral, physician's specialty). Results of the logistic regression model will be displayed by means of either tables or plots.

7.9.1.4 Determination of Patients/Data for Analysis

The Enrolled Population will be included in the descriptive statistics shown in Table 1.

At each FU visit, the subset of subjects of the Enrolled Population that at that visit will have a reason for referral will be used to compute the descriptive statistics shown in Table 2 and the odds ratios of referral.

7.9.2 Secondary objective 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

7.9.2.1 Hypothesis

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

7.9.2.2 Endpoint definitions

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

7.9.2.3 Analysis methods

Among all subjects referred, the proportion of subjects that had an SCD risk stratification visit will firstly be computed, followed by the proportion of subjects that were indicated for ICD/CRT-D implant. Details of the computations are described below.

First, at each follow-up visit, among all patients who were referred for SCD risk stratification, the proportion of those who had an SCD risk stratification visit will be computed.

For any given follow-up visit (3 months, 6 months, 12 months), the denominator will be patients referred for SCD risk stratification up to the given visit and the numerator will be all patients that, among the patients included in the denominator, will have an SCD risk stratification visit

In the referral CRF, the patients included in the denominator will be a composite of the below:

(a) ***all patients that were referred but did not have any ICD risk stratification visit at any previous follow-up visit.*** That is, within the referral CRF form, all subject that at any of the previous visits will have answer "yes" to the question "has the subject been referred or invited for SCD risk stratification?" and answer "no" to the question "was the SCD visit performed?".

(b) ***all patients being referred at the given visit***. That is, within the referral CRF form, all subject that at a given visits will have answer "yes" to the question "has the subject been referred or invited for SCD risk stratification?".

The subjects included in the numerator will be all subjects part of the denominator that will have answer "yes" to the question "was the SCD visit performed?".

For example, at the 6 months visit, the numerator will be all patients that had their SCD risk stratification visit at the 6 months visit and the denominator will be all patients who were referred but did not have their SCD risk stratification visit within the 3 months visit window and of all patients that were referred at the 6 months visit.

The results will be shown in a table similar to table 4 below:

Table 4: Number (%) of subject that had their SCD risk stratification visit

	3 months visit	**6 months visit**	**12 months visit**
Region 1	XX/XX (XX.XX%)	XX/XX (XX.XX%)	XX/XX (XX.XX%)
Region 2	XX/XX (XX.XX%)	XX/XX (XX.XX%)	XX/XX (XX.XX%)
…	…	…	…
Overall	XX/XX (XX.XX%)	XX/XX (XX.XX%)	XX/XX (XX.XX%)

It may also happen that a patient might have an SCD risk stratification visit without having been referred, for example, patients who had an SCD risk stratification visit for secondary prevention. An additional table will then be created to show, for each visit, the number of subjects that were not referred but had an SCD risk stratification visit and among those, the proportion of subjects that had a reason for referral.

Second, the proportion and Wilson score 95% CI of subjects recommended for ICD/CRT-D at the three months visit, at the 6 months and at the 12 months visits will be computed overall and by region, for the Enrolled Population and for the subjects in the numerator in table 3 above, that is, all subjects that have had an SCD risk stratification visit (called in table 4 below "SCD risk stratification Population"").

A SAS code similar to the example SAS code shown in Section 7.9.1.3 will be used. For each follow up visit, the results will be shown in a table similar to Table 5 below.

Table 5: Proportion (95% CI) of subjects indicated to receive ICD/CRT-D, at visit X

	Enrolled Population		SCD risk stratification population	
Region	**n/N (%)**	**95% CI**	**n/N (%)**	**95% CI**
Region 1	XX/XX (XX.XX%)	(XX.XX% - XX.XX%)	XX/XX (XX.XX%)	(XX.XX% - XX.XX%)
…	…	…	…	…
Overall	XX/XX (XX.XX%)	(XX.XX% - XX.XX%)	XX/XX (XX.XX%)	(XX.XX% - XX.XX%)

Where n is number of the subjects "recommended for ICD/CRT-D" and N is either the Enrolled Population or the SCD risk stratification population.

In addition to the above analyses, logistic regression models similar to the example model in Section 7.9.1.3 might be fitted overall and by region, to estimate the odds ratios of being indicated for an ICD/CRT-D, depending on different factors, such as sex, age, specialty of physician who performed the ICD/CRT-D risk stratification, type of device received – ICD or CRT-D, PCI versus non-PCI patients, STEMI versus non-STEMI patients . Results will be displayed either by means of either tables or of plots.

7.9.2.4 Determination of Patients/Data for Analysis

The Enrolled Population and, at each FU visit, the subset of subjects part of the Enrolled Population that were referred for sudden cardiac death risk (SCD) stratification and management will be included in the analysis.

7.9.3 Secondary objective 2: Proportion of post-acute patients who received an ICD/CRT-D

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

7.9.3.1 Hypothesis

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

7.9.3.2 Endpoint definitions

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

7.9.3.3 Analysis methods

At each follow-up visit (3 months, 6 months, 12 months), the proportion of subjects who received an ICD/CRT-D will be computed.

The numerator will be the number of subjects who were implanted at a given follow up visit. In the Implant CRF, these subjects will have answer "yes" to the question "Has the subject received an ICD or CRT-D?".

The denominator will be either the Enrolled Population or a composite of the below:

- ***(a) all patients meeting an indication for implant and not having been implanted at the previous visits***. That is, within the Implant CRF form, all subject that at any previous visits will have answer "yes" to the question "did the subject meet an indication for an ICD or CRT-D?", and at all previous visits will have answer "no" to the question "has the subject received an ICD or CRT-D?"
- ***(b) all patients meeting an indication for implant at the given visit***. That is, within the referral CRF form, all subject that at a given visit will have answer "yes" to the question "did the subject meet an indication for an ICD or CRT-D?"

A SAS code similar to the example SAS code shown in Section 7.9.1.3 will be used. Separately for each follow up visit, the results will be shown in a table similar to Table 6 below, where "Indicated for an ICD/CRT-D" is the denominator above.

Table 6: Proportion (95% CI) of subjects who receive ICD/CRT-D at visit X

	Enrolled Population		**Indicated for an ICD/CRT-D Population**	
Region	**n/N (%)**	**95% CI**	**n/N (%)**	**95% CI**
Region 1	XX/XX (XX.XX%)	(XX.XX% - XX.XX%)	XX/XX (XX.XX%)	(XX.XX% - XX.XX%)
Region 2	XX/XX (XX.XX%)	(XX.XX% - XX.XX%)	XX/XX (XX.XX%)	(XX.XX% - XX.XX%)
…	…	…	…	…
Overall	XX/XX (XX.XX%)	(XX.XX% - XX.XX%)	XX/XX (XX.XX%)	(XX.XX% - XX.XX%)

In addition to the above analyses, logistic regression models similar to the example model in Section 7.9.1.3 might be fitted overall and by region, to estimate the odds ratios of being implanted, depending on different factors, such as age, gender, specialty of physician who implanted, type of device received – ICD or CRT-D, PCI versus non-PCI, STEMI versus non-STEMI. Results will be displayed either by means of either tables or of plots.

Additional analysis:

A competing risk event curve with accompanying 95% confidence bounds and mortality accounted for, will be produced for each region, to assess a subject's time from enrollment to:

(a) Having met the referral criteria;
(b) Having been referred;
(c) Having had an SCD stratification visit;
(d) Having been indicated an ICD/CRT-D implant
(e) Having received an ICD/CRT-D.

An SAS code for the competing risk analysis similar to the below will be used:

```
proc lifetest data=KM plots=cif(test) timelist=0 1 2 3 4 5 6 7 8 9 10 11 12;
   by region;
   time T*Status(0)/eventcode=1;
   strata Event / order=internal;
run;
```

where Event is a categorical variable with categories the event of interest (meeting the referral criteria, having been referred, having had an SCD risk stratification visit, having been indicated for an ICD/SCD-D implanted, having received an ICD/CRT-D), T is the time in months from enrollment to the date of the event of interest and Status is an indicator variable with 3 values: 0 for censored observations, 1 observations related to the event of interest and 2 observations related to subjects who died. Note that the dataset to be used will contain one row for each event per subject (e.g.: if a subject will have all events, from having met the referral criteria to having received the ICD/CRT-D, the dataset will contain 5 rows for that subject).

7.9.3.4 Determination of Patients/Data for Analysis

The Enrolled Population and, at each FU visit, the subset of subjects that were indicated for an ICD/CRT-D will be included in the analysis as described in Section 7.9.3.3.

7.9.4 Secondary objective 3: Incidence of CV Mortality

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

7.9.4.1 Hypothesis

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

7.9.4.2 Endpoint definitions

The endpoint will be defined as cardiovascular mortality.

7.9.4.3 Analysis methods

At each follow-up visit, the cumulative proportion of subjects who experienced cardiovascular mortality between each visit will be computed. A SAS code similar to the example SAS code shown in Section 7.9.1.3 will be used and the results will be shown in a table similar to Table 7 below.

Table 7: Proportion of post-acute MI patients who experienced cardiovascular mortality

Region	3 months visit	6 months visit	12 months visit
China	XX/XX (XX.XX%)	XX/XX (XX.XX%)	XX/XX (XX.XX%)
Taiwan	XX/XX (XX.XX%)	XX/XX (XX.XX%)	XX/XX (XX.XX%)
India	XX/XX (XX.XX%)	XX/XX (XX.XX%)	XX/XX (XX.XX%)
Korea	XX/XX (XX.XX%)	XX/XX (XX.XX%)	XX/XX (XX.XX%)
South East Asia	XX/XX (XX.XX%)	XX/XX (XX.XX%)	XX/XX (XX.XX%)
Middle East, Africa, Central Asia and Turkey	XX/XX (XX.XX%)	XX/XX (XX.XX%)	XX/XX (XX.XX%)
Overall	XX/XX (XX.XX%)	XX/XX (XX.XX%)	XX/XX (XX.XX%)

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. A SAS code similar to the example code below will be used.

```
proc lifetest data=KM plots=cif(test) timelist=0 1 2 3 4 5 6 7 8 9 10 11 12;
   by region;
   time T*Status(0)/eventcode=1;
run;
```

where T will be the time in months from enrollment to date of cardiovascular death and Status will be an indicator variable with 3 values: 0 for censored observations, 1 for patients who died for cardiovascular death and 2 for subjects who died for non-cardiovascular death. Results will be determined separately for each region and overall.

7.9.4.4 Determination of Patients/Data for Analysis

The Enrolled Population will be included in the analysis.

7.9.5 Secondary objective 4: Referral and implant refusal rationale

Summarize the referral and refusal implant rationale.

7.9.5.1 Hypothesis

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

7.9.5.2 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.

7.9.5.3 Analysis methods

At each visit, the reasons for refusing referral ("reasons the subject has not been referred at this visit" in the referral CRF) at each visit will be summarized as displayed in table 8.

Table 8: Reason of referral

Region	Reason for refusal referral	3 months visit	6 months visit	12 months visit
Region 1	Reason 1	XX/XX (XX.XX%)	XX/XX (XX.XX%)	XX/XX (XX.XX%)
	Reason 2	XX/XX (XX.XX%)	XX/XX (XX.XX%)	XX/XX (XX.XX%)
	…	…	…	…
	Reason n	XX/XX (XX.XX%)	XX/XX (XX.XX%)	XX/XX (XX.XX%)
…	Reason 1	…	…	…
	Reason 2	…	…	…
	…	…	…	…
	Reason n	…	…	…
Overall	Reason 1	XX/XX (XX.XX%)	XX/XX (XX.XX%)	XX/XX (XX.XX%)

	Reason 2	XX/XX (XX.XX%)	XX/XX (XX.XX%)	XX/XX (XX.XX%)
	…	…	…	…
	Reason n	XX/XX (XX.XX%)	XX/XX (XX.XX%)	XX/XX (XX.XX%)

Further, at each visit, among all subjects that were recommended for ICD/CRT-D (ie: answer "yes" to question "did the subject meet an indication for an ICD or CRT-D" in the implant CRF), the proportion of those who refused implant (answer "yes" to the question "did the subject refuse the implant") will be computed and displayed. The reasons for implant refusal ("reason for implant refusal" in implant CRF) will then be computed and displayed in a table similar to Table 7 above.

7.9.5.4 Determination of Patients/Data for Analysis

The subset of subjects of the Enrolled Population that had a reason for referral as described in Section 7.9.5.2 will be included in the analysis.

7.9.6 Secondary objective 5: Change in LVEF Over Time

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

7.9.6.1 Hypothesis

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

7.9.6.2 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.

7.9.6.3 Analysis methods

Descriptive statistics (e.g.: mean, standard deviation, median, range) will be used to summarize the LVEF during the acute phase and the 3 months visit (chronic phase) post-MI and displayed as shown in Table 9 below and graphically with the use of a scatter plot.

Table 9: LVEF at the Acute and Chronic phases

Region	Acute phase	Chronic phase
Region 1		
Mean ± Standard Deviation	XX.X±XX.X	XX.X±XX.X
Median	XX.X	XX.X
25th Percentile - 75th Percentile	XX.X – XX-X	XX.X – XX-X
Minimum - Maximum	XX-X – XX.X	XX-X – XX.X
Subjects With Measure Available (N,%)	XX (XX.X%)	XX (XX.X%)
Region 2		
Mean ± Standard Deviation	XX.X±XX.X	XX.X±XX.X
Median	XX.X	XX.X
25th Percentile - 75th Percentile	XX.X – XX-X	XX.X – XX-X
Minimum - Maximum	XX-X – XX.X	XX-X – XX.X
Subjects With Measure Available (N,%)	XX (XX.X%)	XX (XX.X%)
…	…	…
Overall		
Mean ± Standard Deviation	XX.X±XX.X	XX.X±XX.X
Median	XX.X	XX.X
25th Percentile - 75th Percentile	XX.X – XX-X	XX.X – XX-X
Minimum - Maximum	XX-X – XX.X	XX-X – XX.X
Subjects With Measure Available (N,%)	XX (XX.X%)	XX (XX.X%)

Similar statistics will be provided for subjects with LVEF measured at the 6 months and at the 12 months visits.

Additionally, the proportion of subjects whose LVEF measurement was at most 40% will be computed, in both the acute and chronic phases and shown as displayed in Table 10 below.

Table 10: proportion of subjects with a LVEF≤40% at the Acute and Chronic phases, among all subjects with a LVEF measurement at that visit

Region	Acute phase	Chronic phase
Region 1	XX/XX (XX.XX%)	XX/XX (XX.XX%)
Region 2	XX/XX (XX.XX%)	XX/XX (XX.XX%)
…	…	…
Overall	XX/XX (XX.XX%)	XX/XX (XX.XX%)

The average change in LVEF between the acute phase and the chronic phase will be estimated using an ANCOVA method. The model will contain the difference of LVEF between the acute phase and the chronic phase as an outcome and baseline LVEF as covariate, to adjust the estimated difference in LVEF between the two visits by the effect of their baseline measure (eg regression to the mean). A SAS code similar to the example below will be used:

```
ods listing close;
proc glm data = lvef;
by region;
model lvef_diff = lvef_base /solution;
run;
ods listing;
```

Results will be determined separately for each region and will be shown by means of either tables or graphs.

In case there will be enough LVEF data at the 6 months and the 12 months follow-up visits, the ANCOVA model above will be used to investigate the average change in LVEF between the chronic phase and the 6 months visit and between the 6 months visit and the 12 months visit.

7.9.6.4 Determination of Patients/Data for Analysis

At each visit, the subset of subjects part of the Enrolled Population with a LVEF measurement available at baseline and at the 3 months visit will be included in the analysis.

8. Safety Evaluation

Relatedness of adverse events using the CEC adjudication will be summarized using counts and percentages. Seriousness of adverse events using the Medtronic classification will be summarized using counts and percentages. Details of individual adverse events will be listed.

9. Changes to Planned Analysis

Any deviation from the analyses described in the statistical analysis plan and a justification for making the change, will be described in the clinical study report. Further, spurious data will be detected and fixed by data management, unused data will be reported in listings, missing data will be reported as count/percentage.

10. Validation Requirements

To ensure the quality of the statistical results and datasets created for the study, the following validation requirements will be implemented.

Programs that contribute directly or indirectly to results pertaining to the primary objective will be validated level I or level II by a statistician or a statistical programmer. Level II or Level III validation (self-validation) will be acceptable for programs, which do not pertain to the primary objective. The table below specifies the validation requirements for data extraction, mapped datasets, analysis datasets, TLGs (Tables, Listings, and Graphs) and study objectives. Mapped datasets are considered as datasets that map case report forms. Analysis datasets are considered to be datasets that contain derived variables relevant for the statistical analysis.

Table 11: Validation requirements

Program type	Level	Description
Extracts or creates datasets, e.g., mapped datasets	II	peer review
Generates analysis datasets	II	peer review
Generates Tables, Listings and/or Graphs (primary objective)	I or II	independent programming or peer review
Generates Tables, Listings and/or Graphs (non-primary objective)	II or III	peer review or self-validation
Implements statistical procedure	II or III	peer review or self-validation
Any other program	II or III	peer review or self-validation
Program previously validated with minor changes	III	self-validation

Summary of Changes

Version	Effective Date	Summary of Changes	Change Author
1.0	06-06-19	Initial Release	