Multicenter Automatic Defibrillator Implantation Trial with Subcutaneous Implantable Cardioverter Defibrillator

(MADIT S-ICD)

CLINICAL PROTOCOL

Version **AB**
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Sponsored By

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2. Protocol Synopsis

Objective(s)	The primary objective is to test the hypothesis that post-MI diabetic patients with relatively preserved ejection fraction of 36-50% will have a survival benefit from a subcutaneous implantable cardioverter defibrillator (S-ICD).
Planned Indication(s) for Use	The EMBLEM S-ICD System is intended to provide defibrillation therapy for the treatment of life-threatening ventricular tachyarrhythmias in patients who do not have symptomatic bradycardia, incessant ventricular tachycardia, or spontaneous, frequently recurring ventricular tachycardia that is reliably terminated with anti-tachycardia pacing.
Test Device System	• EMBLEM™ S-ICD Pulse Generator (Model A209) or later generation commercially available BSC S-ICD pulse generator[1] • EMBLEM™ S-ICD Subcutaneous Electrode (Model 3401), Q-TRAK Electrode (Model 3010) or later generation market approved BSC S-ICD electrode[1] • EMBLEM™ S-ICD Electrode Insertion Tool, (Model 4711), Q-GUIDE Electrode Insertion Tool Model (Model 4010), or later generation market approved BSC electrode insertion tool[1] • EMBLEM™ S-ICD Programmer, (Model 3200) or other market approved programmer capable of interrogating BSC S-ICD Systems[1] • Additional implant accessories used in the implant procedure will be considered to be part of the device system.
Control	Conventional medical therapy (CMT).
Study Design	Prospective, multicenter, international, randomized, controlled trial.
Planned Number of Subjects	1800 subjects to be enrolled according to the sample size assumptions.

[1] Over the course of this study, new model numbers of each device may be introduced. The intention of this protocol is to allow the use of newer Boston Scientific subcutaneous implantable cardioverter defibrillator (S-ICD) system components that are market approved by the regulatory authorities in the country of the investigative site.

Planned Number of Sites/Countries	Approximately 100 sites in the US, EU and Israel with a maximum of 150.
Primary Endpoint	The primary endpoint is all-cause mortality.
Additional Objectives	In all randomized subjects the following analyses will be performed: • All-cause mortality and sudden cardiac death in various subgroups including sex, race, age continuous and dichotomized at 75 years, duration of diabetes, presence vs. absence of insulin therapy, HbA1c dichotomized at 8%, LVEF continuous and dichotomized at 40%, and other relevant subgroups • Healthcare utilization assessed through adverse event reporting
Additional Pre-Specified Analyses	In subjects randomized to S-ICD the following analyses will be performed: • Frequency and outcomes of S-ICD Inappropriate Shocks • Frequency and outcomes of S-ICD treated ventricular tachycardia (VT) and ventricular fibrillation (VF) • Frequency and outcomes of S-ICD device complications, including but not limited to: infection, device malfunction and electrode movement
Method of Assigning Patients to Treatment	Subjects will be randomized 2:1 (S-ICD:CMT). Randomization will occur electronically using the clinical data collection system.

Follow-up Schedule	• **Screening and Consent**
	• **Baseline data collection**
	• **Implant procedure** (device subjects only)
	• **1 month visit** (in-clinic visit for S-ICD subjects and phone contact for CMT subjects)
	• **6 month phone contact** (conduct annually thereafter at months 18, 30, 42, etc.)
	• **12 month visit** (conduct annually thereafter at months 24, 36, 48, etc.)
	  ○ S-ICD Arm 12 Month in-clinic follow-up
	  ○ CMT Arm 12 Month phone follow-up

Study Duration	The study is expected to enroll over a 48 month period with an average of 2.6 years of follow-up. Note: the length of the study is based on the accumulation of endpoint events and the hazard ratio.
Eligibility Criteria	Note: The most recent evaluations, measurements or test results in the medical record must be used to assess inclusion and exclusion criteria.

Key Inclusion Criteria	• Age ≥ 65 years on date of consent • Diabetes mellitus treated with oral hypoglycemic agents, non-insulin injectable and/or insulin for the past 3 calendar months or longer prior to consent date • LV ejection fraction (LVEF) of 36-50% documented by imaging (preferably by MRI or echocardiographic methods), within 12 calendar months before consent date and at least 3 calendar months after most recent MI, PCI or CABG • One or more clinically documented, enzyme-positive myocardial infarctions, more than 3 calendar months prior to consent date*. o If enzyme information and clinical documentation is not available, there must be a clear evidence of prior silent myocardial infarction identified as either new pathologic Q waves on ECG or imaging documentation of an infarcted area (left ventricular angiography/ nuclear scan/ MRI)* * MI qualification based on the Universal Definition of MI[1] • Qualifying 12-lead ECG within 6 calendar months before consent date and at least 3 calendar months after most recent MI, PCI or CABG * The qualifying ECG can be sinus rhythm or atrial fibrillation (patients with persistent or permanent atrial fibrillation should have a controlled ventricular response <100 bpm on consent date) *QRS duration on the qualifying ECG ≥90 msec • Passing S-ICD Screening ECG performed per applicable user's manual on or after the consent date that identifies one or more qualifying S-ICD sensing vectors
Key Exclusion Criteria	• Ejection fraction >50% or <36% within 12 calendar months prior to consent date and at least 3 calendar months after the most recent MI, PCI or CABG • Existing guideline based indication for an ICD, pacemaker, CRT, or CRT-D therapy • Existing or previously implanted ICD, CRT, CRT-D, or pacemaker device system • Active infection at the time of consent • Contraindication for S-ICD implantation according to the S-ICD pulse generator (PG) User's Manual • Hemodialysis and/or peritoneal dialysis at the time of enrollment • New York Heart Association Class IV in the past 3 calendar months prior to or at the time of consent date • Coronary artery bypass graft surgery or percutaneous coronary intervention (balloon and/or stent angioplasty) within 3 calendar months prior to the consent date • Enzyme-positive myocardial infarction or silent myocardial infarction diagnosed within 3 calendar months prior to the consent date

	• Unstable angina with need for outpatient treatment or hospitalization (change/addition of anti-anginal medication and/or coronary revascularization), within 3 calendar months prior to the consent date • Angiographic evidence of coronary disease in a patient that is a candidate for coronary revascularization and is likely to undergo CABG or PCI in the next 3 calendar months • High risk for arterial embolism (e.g. presence of mobile left ventricular • thrombus) • Hemodynamically significant congenital heart disease, aortic valvular heart disease, or amyloid heart disease • Baseline body mass index > 45 kg/m^2 • On a heart transplant list or likely to undergo heart transplant within one calendar year • Presence of any other disease, other than the subject's cardiac disease, that in the opinion of the investigator is likely to significantly reduce the patient's likelihood of survival for the duration of the trial (e.g. cancer, liver failure). • Unwillingness or inability to cooperate with the protocol • Resides at such a distance from the enrolling site so travel to follow-up visits would be unusually difficult • Reversible causes of heart disease (e.g. viral myocarditis or tachycardia induced cardiomyopathy) • Participation in other clinical trials (observational registries are allowed with approval from the CDC) • Does not anticipate residing in the vicinity of the enrolling site for the duration of the trial • Unwillingness to sign the consent for participation
Statistical Methods	
Primary Statistical Hypothesis	Post-MI diabetes patients with a relatively preserved left ventricular ejection fraction will have reduced mortality from S-ICD as compared to CMT.
Statistical Test Method	Wang-Tsiatis group sequential design based on monitoring the log-rank statistic for time-to-death, with stochastic curtailment based on conditional power and sample size re-estimation based on overall recruitment, withdrawal, and event rates.
Sample Size Parameters	1800 patients are expected to yield a maximum of 454 deaths, which provides 80% power at a two-sided significance level of 5% to detect a HR of 0.75.

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4. Introduction

Implantable cardioverter defibrillators (ICD)[2] and more recently the subcutaneous ICD (S-ICD)[3-6] have been shown to be effective in preventing sudden cardiac death in high-risk cardiac patients. The MADIT II trial previously demonstrated a significant reduction in all-cause mortality with an ICD implantation compared to optimal medical therapy (hazard ratio 0.69; 95% CI 0.51 to 0.93; two-sided P=0.016) in high-risk cardiac patients with prior myocardial infarction and severely impaired left ventricular ejection fraction (LVEF $\leq$ 30%).[2]

However, patients with severely impaired LVEF represent only a minority of patients at risk for sudden cardiac death (SCD)[7]. Other cohorts at high risk for SCD who could potentially benefit from an ICD include patients following a coronary event, especially those with other clinical risk factors, such as age or diabetes mellitus (DM).

Diabetes mellitus has been shown to be associated with increased risk for SCD following a myocardial infarction, independent of the infarct size and LVEF, but is not currently used in the indication for ICD implantation[8]. Data from a substudy of the VALIANT trial[9], which enrolled 11,000 subjects (3, 095 diabetics), indicate that diabetes was associated with a 37% higher risk of all-cause mortality, independent of LVEF, (adjusted hazard ratio of 1.37, 95% CI 1.25-1.51) compared to non-diabetics. The mortality risk in diabetic patients with LVEF >39% was similar to the mortality risk in non-diabetic patients with LVEF in the 30% range.[10] This observation was further supported by another large clinical study, the Candesartan in Heart Failure – Assessment of Reduction in Mortality and Morbidity (CHARM) program[11], and by smaller single and multicenter studies[12, 13]. The large multi-center study assessing 3276 post infarction patients from Germany and Finland showed that the incidence of SCD was significantly higher in diabetic versus non-diabetic patients with an LVEF >35% (HR 3.8 (95% CI 2.4-5.8; p<0.001), and the incidence of SCD in diabetic patients with LVEF >35% was similar to the incidence in non-diabetic patients with an LVEF $\leq$ 35% (4.1% vs 4.9%, respectively)[13].

These data indicate that post-MI diabetic patients have a significant risk for SCD even with a relatively preserved LVEF, and present a population with a significant unmet need that could potentially be addressed with an expanded ICD indication. This may have an important global health impact and clinical implications. Diabetes is currently one of the most prevalent, major health issues in the United States and throughout the world. It is estimated that DM affects nearly 29 million people in the United States alone and claims more than 250,000 lives annually, with higher mortality risk in those older than 60 years of age; furthermore, the prevalence of diabetes is expected to increase dramatically in the US and worldwide in the near future. [14, 15]

Therefore, the MADIT S-ICD study was designed to prospectively test the hypothesis that post-MI diabetic patients with a relatively preserved left ventricular ejection fraction (LVEF 36-50%) will demonstrate a lower rate of all-cause mortality with an S-ICD than in those who do not receive an S-ICD. The S-ICD was chosen for this study design due to device system characteristics that could potentially provide advantages in diabetic patients who may otherwise be at a higher risk for device-related infections[16-18].

5. Test Device Description (Treatment Arm Only)

5.1. *Device Description*

The following information is a brief summary of the EMBLEM S-ICD System and its principle of operation. Refer to the applicable User's Manuals for additional information.

The EMBLEM S-ICD System is an implantable defibrillator system that treats ventricular tachyarrhythmias using a subcutaneous pulse generator and a subcutaneous electrode. The full EMBLEM S-ICD System consists of four devices that comprise the study device system:

- EMBLEM™ S-ICD Pulse Generator (Model A209) or later generation market approved BSC S-ICD pulse generator
- EMBLEM™ S-ICD Subcutaneous Electrode (Model 3401), Q-TRAK Electrode (Model 3010) or later generation market approved BSC S-ICD electrode
- EMBLEM™ S-ICD Electrode Insertion Tool, (Model 4711), Q-GUIDE Electrode Insertion Tool Model (Model 4010), or later generation market approved BSC electrode insertion tool
- EMBLEM™ S-ICD Programmer, (Model 3200) or other market approved programmer capable of interrogating BSC S-ICD Systems

Note: Additional commercially available implant accessories used in the implant procedure are considered to be part of the test device system.

Over the course of this study, new model numbers of each device may become approved for use. The intention of this protocol is to allow the use of newer Boston Scientific subcutaneous implantable cardioverter defibrillator (S-ICD) system components that are market approved by the regulatory authorities in the country of the study center.

The EMBLEM S-ICD System is designed to work with the following accessories:

- Programmer telemetry wand;
- Magnet;
- Suture sleeve;
- Torque wrench;
- SD memory card

The EMBLEM S-ICD System also involves the use of a surface ECG screening tool, which is used to determine the adequacy of sensing in potential candidates for an S-ICD. Any new screening tools or methods that are market approved by the regulatory authorities in the country of the study center may be used.

5.1.1. *EMBLEM S-ICD Pulse Generator*

The EMBLEM S-ICD pulse generator comprises an inner structure of discrete electrical components, interconnected hybrid assemblies, batteries, and high energy capacitors. The inner assembly is enclosed in a hermetically sealed can with a pre-molded polyurethane header for electrode connection. The header contains a single port for connection of the subcutaneous electrode to accommodate sensing, pacing, and defibrillation. The EMBLEM S-ICD pulse generator is designed to provide high energy defibrillation shocks using a constant tilt biphasic waveform and is capable of delivering bradycardia demand pacing for a period up to thirty seconds following defibrillation therapy. Future generations of the BSC S-ICD pulse generator market approved by the appropriate regulatory bodies may be included in the study.

5.1.2. *EMBLEM S-ICD Subcutaneous Electrode*

The EMBLEM S-ICD subcutaneous electrode features one high voltage defibrillation coil for the purpose of providing defibrillation energy. It is constructed using multifilars of metallic wire formed into a coil. Two sense electrodes (proximal and distal) are used for sensing. These sense electrodes are electrically insulated from the shock electrode by a multi-lumen polymeric tube.

Electrical connectivity to the pulse generator is provided using multiple strands of insulated metallic cable inserted into the same multi-lumen polymeric tube. This tube comprises the body of the subcutaneous electrode and is subcutaneously implanted from the device pocket along the rib margin to the sternum. The proximal termination comprises a multi-pole connector to plug into the header of the BSC S-ICD pulse generator. The connector is designed to be compatible with the BSC S-ICD pulse generators only. Future generations of the BSC subcutaneous electrode market approved by the appropriate regulatory authorities may be included in the study.

5.1.3. *EMBLEM S-ICD Electrode Insertion Tool (EIT)*

The EMBLEM S-ICD EIT is a single use, disposable subcutaneous tunneling tool that is used to facilitate predictable placement of the subcutaneous electrode. The EIT is designed to create an appropriately sized subcutaneous sinus for the subcutaneous electrode such that the electrode will fit securely and not loosely in the subcutaneous sinus. The tip of the EIT and the tip of the subcutaneous electrode are equipped with suture holes which enable the two devices to be temporarily sutured together during the implant procedure. Once the two devices are sutured together, the EIT can be used to pull the subcutaneous electrode through a subcutaneous sinus. Future generations of the BSC subcutaneous electrode insertion tool market approved by the appropriate regulatory bodies may be included in the study.

5.1.4. *EMBLEM S-ICD Programmer*

The programmer is a completely self-contained, non-sterile, non-implantable, lightweight, easily portable computer that does not allow general purpose computing. It implements a graphical user interface (GUI) design which gathers user input via touch screen and/or keyboard. Communication between the pulse generator and the programmer is accomplished through an RF telemetry wand. The radio link operates in the Medical Implant Communication Service band specified in EN 301 839-1:2002 and complies with applicable FCC regulations. The programmer is capable of recognizing multiple pulse generators, but active communication is permitted with only one pulse generator at a time. Communication between the programmer and a printer is based on a standard Bluetooth piconet.

The programmer application consists of multiple screens from which online (active communication with the pulse generator) and offline modes may be commanded. Programmer functionality includes:

- Scan for devices, resulting in a display of pick list of pulse generators
- Establishment and termination of communication link
- Display of a real-time S-ECG
- Selection of programmable parameters
- Review of subject event history
- Induction ECG capability

Future generations of the BSC programmer market approved by the appropriate regulatory bodies may be included in the study.

5.1.5. *S-ICD System Indication*

For US clinical sites, the S-ICD Device system indications for the MADIT S-ICD study are consistent with the indications documented in current and future S-ICD User's Manuals that are market approved by the FDA. For clinical sites in countries accepting devices with CE Mark, the study protocol will follow the CE-marked instructions for use.

6. Objectives

6.1. *Primary Study Objective*

The primary objective is to test the hypothesis that post-MI diabetic patients with relatively preserved ejection fraction of 36-50% will have a survival benefit from a subcutaneous implantable cardioverter defibrillator (S-ICD).

6.2. *Secondary Study Objective*

The secondary objective of the study is to evaluate the effects of the S-ICD on all-cause mortality in various subgroups and on sudden cardiac death.

The pre-specified subgroups include but are not limited to: gender, race, age continuous and dichotomized at 75 years, duration of diabetes, presence versus absence of insulin therapy, HbA1c dichotomized at 8%, LVEF continuous and dichotomized at 40% and MADIT II risk score sub-groups (MADIT II risk score: New York Heart Association functional class > II, age > 70 years, BUN > 26 mg/dl, QRS duration > 120 ms, and atrial fibrillation).

6.3. *Tertiary Study Analyses*

Pre-specified tertiary analyses include the following:

- Frequency and outcomes of S-ICD treated episodes of ventricular tachycardia (VT) and ventricular fibrillation (VF),
- Frequency and outcomes of S-ICD inappropriate shocks,
- Frequency of S-ICD device complications, including but not limited to: infection, device malfunction and electrode movement and,
- Healthcare utilization assessed through adverse event reporting.

7. Endpoints

7.1. *Primary Endpoint*

The primary endpoint will be all-cause mortality. All-cause mortality is defined as death by any cause during the duration of the trial.

8. Design

MADIT S-ICD is a prospective, multicenter, international, randomized (2:1), controlled clinical trial. Subjects (n=1800) will be enrolled at approximately 100 study sites and randomized to receive conventional medical therapy plus an S-ICD or conventional medical therapy alone in a 2:1 ratio, respectively. The trial uses a group sequential design with 18 pre-specified interim analyses. The sample size was chosen to detect a hazard ratio of 0.75 with 80% power (1-β), two-sided 5% significance level (α) and accounts for an estimated dropout rate of 10%. This trial will be conducted under an investigational device exemption (IDE) in the United States and as a post-market study in Europe and Israel.

8.1. *Scale and Duration*

The investigation will be initiated in the U.S., Europe, and Israel, at approximately 100 sites with a maximum of 150 centers. Other geographies may be added over the course of the study. An average of 40-60 subjects per month, once all sites are approved to enroll, is expected to result in up to 1800 subjects enrolled within a 48 month period. The recruitment rate will be closely monitored. If the monthly recruitment rate is less than the projected average of 40-60 subjects per month, or a lower rate of events is observed, the study duration may be prolonged or additional subject enrollment beyond 1800 may be required. Subjects must be followed per this investigational protocol for the duration of the study, unless the investigator is notified by the Coordination Data Center (CDC) or sponsor to the contrary.

- Study initiation will begin approximately 3-6 months post IDE approval
- Estimated first enrollment is 6 months post IDE approval.

- The number of enrollments per month is estimated at 40-60, once all sites are approved to enroll.
- The estimated date to complete enrollment is 48 months after the first enrollment.
- The estimated date to complete follow-up is dependent on the events accumulated during the study and the hazard ratio.
- The study report will be submitted to the appropriate regulatory bodies no later than 6 months after the study has been completed.

8.2. *Treatment Assignment*

Treatment assignments are generated from a pre-determined randomization schedule and administered from the electronic data capture system when a new subject is entered and confirmed as meeting study eligibility criteria. Randomization will be blocked and stratified by enrolling site.

8.2.1. *Treatment and Control*

Subjects randomized to the control arm of the trial will continue to receive conventional medical therapy alone (CMT) and will continue to be treated per standard of care by their current physician. Follow-up data in the CMT arm will be collected by the enrolling site study team through phone follow-up and chart review. Subjects in the control arm will not receive any investigational treatments or devices as a part of their participation.

Subjects randomized to the device arm of the trial will receive conventional medical therapy (per standard of care) plus a subcutaneous implantable defibrillator (see Section 5.0) and will be followed primarily by the enrolling site study team.

It is strongly recommended that subjects in both randomized arms receive standard of care treatment consistent with the American Diabetes Association (ADA) 2015 Guidelines[19], the 2013 ACCF/AHA guideline for the management of heart failure[20], the ESC guidelines for the diagnosis and treatment of acute and chronic heart failure 2012[21]

and the ESC Guidelines on diabetes, pre-diabetes, and cardiovascular diseases from 2013[22] and other guidelines as they come into effect over the course of the study.

All subjects will be followed in the randomly assigned arm regardless of the actual medical treatments administered during the study (intention to treat).

8.3. *Justification for the Study Design*

Diabetic patients with prior myocardial infarction are at an increased risk for all-cause mortality and sudden cardiac death. There is abundant data from prior literature suggesting that the incidence of sudden cardiac death in post-infarction patients with diabetes and an LVEF >35% is similar to non-diabetic patients with an LVEF $\leq 35\%$[9], supporting the concept that a prophylactic implantable cardioverter defibrillator implantation could improve survival in post MI diabetes patients with an LVEF < 35% unless contraindicated.

Furthermore the S-ICD was chosen for this study because it utilizes a non-vascular electrode, minimizing the risks associated with device related system infections that might be especially relevant in diabetic patients who have previously shown to be at higher risk of device related infections[16-18]. Although direct comparison of infection rates with the S-ICD vs transvenous ICD are lacking, we hypothesize that the non-vascular electrode in the S-ICD system could minimize the likelihood of device-related systemic infection and endocarditis in diabetic patients, since it avoids the central cardiovascular system and the heart.

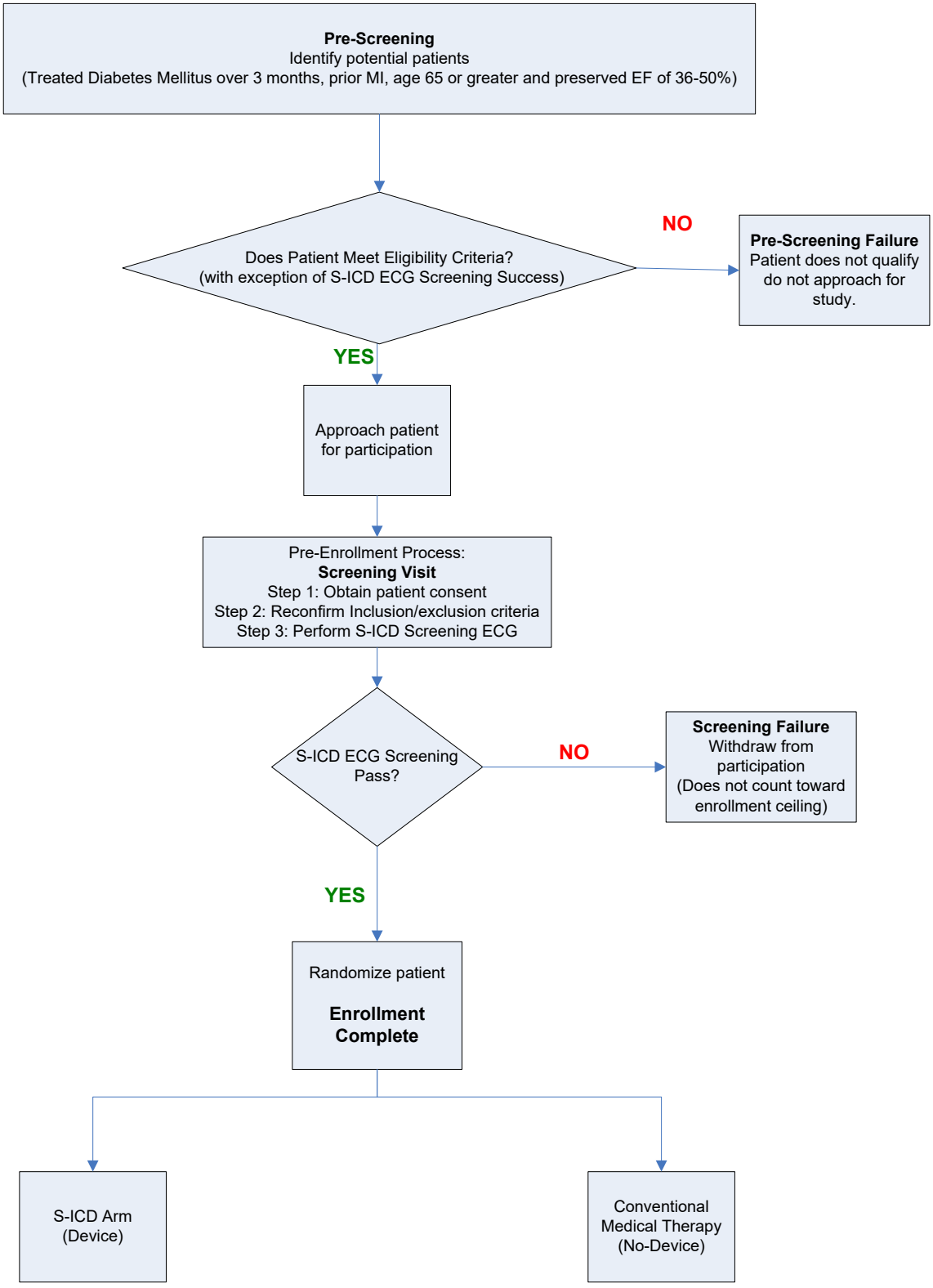
The MADIT S-ICD study was designed to assess if post-MI diabetic patients with a relatively preserved LVEF derive a survival benefit from implantation of an S-ICD in addition to conventional medical therapy.

9. Subject Selection

9.1. *Study Population and Eligibility*

Subjects will be screened for recruitment by the clinical study team within each enrolling site. Screening information will be recorded by each enrolling site on a screening log and entered into the electronic data capture system. Reasons for exclusion will also be documented. Subjects who met the criteria will be approached for participation. Figure 9-1 represents the enrollment process for the study.

Figure 9-1: Enrollment Process



9.2. *Inclusion Criteria*

Subjects who meet all of the inclusion criteria listed in Table 9.2-1 and none of the exclusion criteria listed in Table 9.3-1 may be considered for enrollment. The most recent evaluations, measurements or test results in the medical record must be used to assess inclusion criteria.

Table 9.2-1: Inclusion Criteria

Clinical Inclusion Criteria	• Age ≥ 65 years on date of consent • Diabetes mellitus treated with oral hypoglycemic agents, non-insulin injectable and/or insulin for the past 3 calendar months or longer prior to consent date • LV ejection fraction (LVEF) of 36-50% documented by imaging (preferably by MRI or echocardiographic methods), within 12 calendar months before consent date and at least 3 calendar months after most recent MI, PCI or CABG. • One or more clinically documented, enzyme-positive myocardial infarctions, more than 3 calendar months prior to consent date*. o If enzyme information and clinical documentation is not available, there must be a clear evidence of prior silent myocardial infarction identified as either new pathologic Q waves on ECG or imaging documentation of an infarcted area (left ventricular angiography/ nuclear scan/ MRI)* * MI qualification based on the Universal Definition of MI[1] • Qualifying 12-lead ECG within 6 calendar months before consent date and at least 3 calendar months after most recent MI, PCI or CABG * The qualifying ECG can be sinus rhythm or atrial fibrillation (patients with persistent or permanent atrial fibrillation should have a controlled ventricular response <100 bpm on consent date) *QRS duration on the qualifying ECG ≥90 msec • Passing S-ICD Screening ECG performed per applicable user's manual on or after the consent date that identifies one or more qualifying S-ICD sensing vectors.

Abbreviations: MRI=Magnetic Resonance Imaging; MI=Myocardial Infarction; PCI=Percutaneous Coronary Intervention; CABG=Coronary Artery Bypass Graft; ECG=Electrocardiogram; S-ICD=Subcutaneous Implantable Cardioverter Defibrillator

9.3. *Exclusion Criteria*

Subjects who meet any one of the criteria listed in Table 9.3-1 will be excluded from this clinical study. The most recent evaluations, measurements or test results in the medical record must be used to assess exclusion criteria.

Table 9.3-1: Exclusion Criteria

Clinical Exclusion Criteria	• Ejection fraction >50% or <36% within 12 calendar months prior to consent date and at least 3 calendar months after the most recent MI, PCI or CABG • Existing guideline based indication for an ICD, pacemaker, CRT, or CRT-D therapy • Existing or previously implanted ICD, CRT, CRT-D, or pacemaker device system • Active infection at the time of consent • Contraindication for S-ICD implantation according to the S-ICD pulse generator (PG) User's Manual • Hemodialysis and/or peritoneal dialysis at the time of enrollment • New York Heart Association Class IV in the past 3 calendar months prior to or at the time of consent date • Coronary artery bypass graft surgery or percutaneous coronary intervention (balloon and/or stent angioplasty) within 3 calendar months prior to the consent date • Enzyme-positive myocardial infarction or silent myocardial infarction diagnosed within 3 calendar months prior to the consent date • Unstable angina with need for outpatient treatment or hospitalization (change/addition of anti-anginal medication and/or coronary revascularization), within 3 calendar months prior to the consent date • Angiographic evidence of coronary disease in a patient that is a candidate for coronary revascularization and is likely to undergo CABG or PCI in the next 3 calendar months • High risk for arterial embolism (e.g. presence of mobile left ventricular thrombus) • Hemodynamically significant congenital heart disease, aortic valvular heart disease, or amyloid heart disease • Baseline body mass index > 45 kg/m^2 • On a heart transplant list or likely to undergo heart transplant within one calendar year • Presence of any other disease, other than the subject's cardiac disease, that in the opinion of the investigator is likely to significantly reduce the patient's likelihood of survival for the duration of the trial (e.g. cancer, liver failure). • Unwillingness or inability to cooperate with the protocol • Resides at such a distance from the enrolling site so travel to follow-up visits would be unusually difficult • Reversible causes of heart disease (e.g. viral myocarditis or tachycardia induced cardiomyopathy) • Participation in other clinical trials (observational registries are allowed with approval from the CDC) • Does not anticipate residing in the vicinity of the enrolling site for the duration of the trial • Unwillingness to sign the consent for participation

Abbreviations: ICD=Implantable Cardioverter-Defibrillator; CRT=Cardiac Resynchronization Therapy; CRT-D=Cardiac Resynchronization Therapy Defibrillator; CABG=Coronary Artery Bypass Graft; PCI=Percutaneous Coronary Intervention, CDC=Coordination Data Center, S-ICD=Subcutaneous ICD, MI=Myocardial Infarction

10. Subject Accountability

10.1. *Pre-Enrollment Screening*

All subjects will be screened prior to enrollment, any subjects who sign the consent and fail to pass the screening ECG or do not meet all criteria will be considered screening failures and the reason for failure will be documented. Subjects who do not pass the pre-enrollment screening will not count toward the enrollment ceiling.

10.2. *Point of Enrollment*

Subjects will be considered enrolled in the trial once they have signed the consent **and** been randomized. Subjects who are consented but expire prior to randomization or otherwise fail to be randomized will not be considered enrolled in the trial and will not count toward the enrollment ceiling. All subjects enrolled in the clinical study (including those withdrawn from the clinical study or lost to follow-up) shall be accounted for and documented.

10.3. *Withdrawal*

If a randomized subject withdraws from the clinical investigation, the reason(s) shall be reported (refer to Section 11.11). A subject will be considered lost to follow-up and withdrawn after18 calendar months following the last point of contact (i.e. phone follow-up or in-clinic visit) and at least 3 documented attempts to contact the patient. Attempted contact should be documented in the subject's medical record.

10.4. *Subject Status and Classification*

Subject status will be defined as follows:

Screen Failure **(**Consented, not randomized**)** is defined as completing the consent process (refer to Section 21, but not receiving a randomization assignment (for reasons such as withdrawal of consent, failure to pass S-ICD screening ECG, etc.).

Enrolled is defined as completing the consent process and being randomized.

10.5. *Implant Status and Classification*

For subjects randomized to the treatment (S-ICD) arm, the following additional definitions will be applied:

Intent is defined as a subject randomized to the treatment (S-ICD) arm that does not undergo an S-ICD implant procedure.[2]

Attempted implant is defined as a subject randomized to the treatment (S-ICD) arm who undergoes an S-ICD implant procedure,[2] but does not go on to receive the full S-ICD system within 30 calendar days of the initial implant procedure.

Implant is defined as a subject randomized to the treatment (S-ICD) arm that undergoes an S-ICD implant procedure[2] and is discharged with an S-ICD system.

10.6. *Enrollment Controls*

The number of subjects meeting enrollment criteria will be managed by the CDC through randomization assignments issued through the electronic data capture (EDC) system. Once the enrollment limit has been met, the EDC will cease to issue randomization assignments and the CDC will communicate to the enrolling sites.

10.7. *End-of-Study Action Plan*

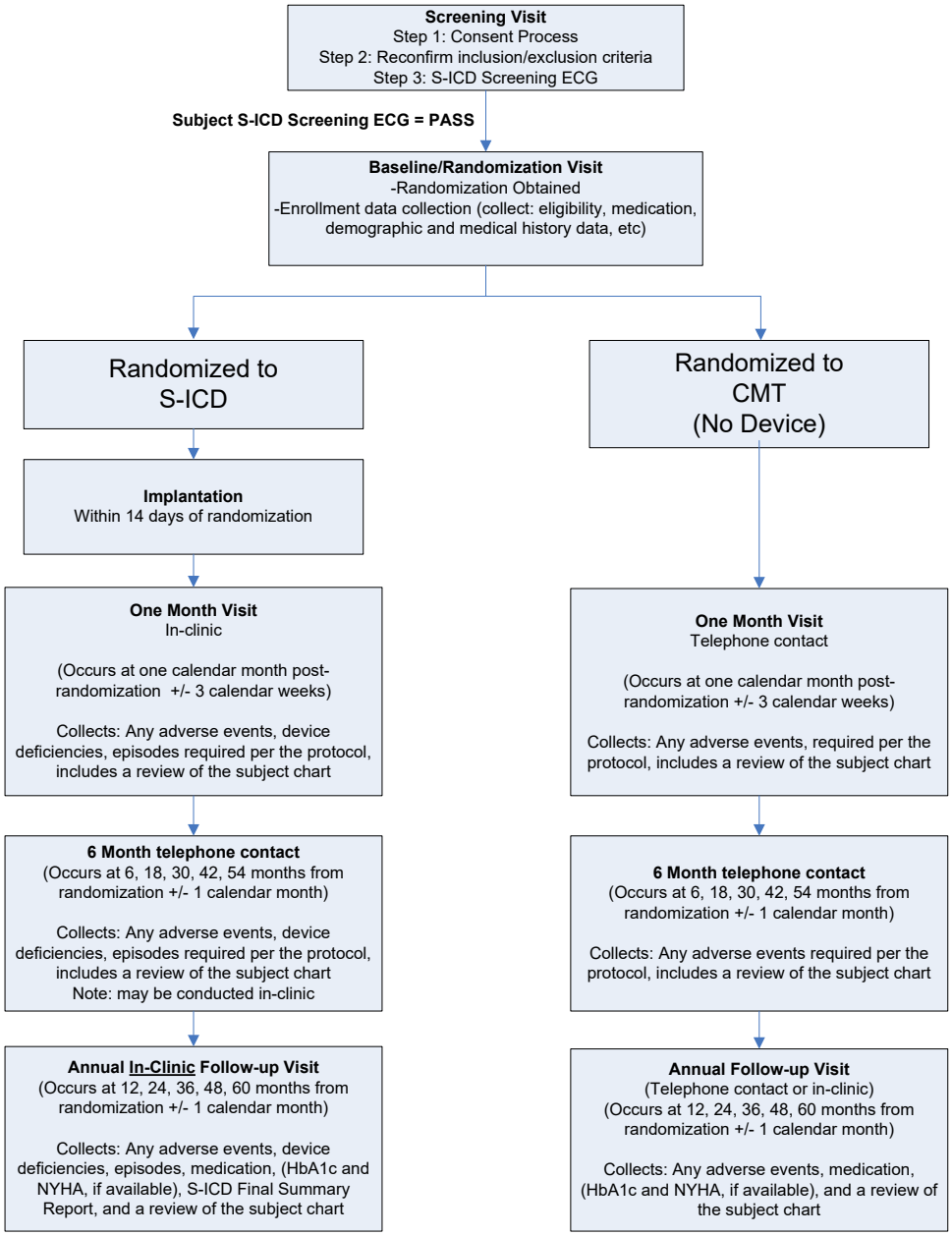
At the conclusion of the study, subjects implanted with an S-ICD system will need to continue to have the device checked at their physicians' office, in accordance with their physicians' instructions, per standard of care, as long as they remain implanted with the device. Subjects who are not implanted with an S-ICD system will continue medical treatments in consultation with his/her physician. Implantation of an S-ICD in the CMT arm is left to the discretion of the physician.

[2] A subject is considered to have undergone an S-ICD implant procedure once anaesthesia is administered in preparation for implant.

11. Study Methods

11.1. *Study Flow*

Figure 11-1: Study Visit Flow Chart



11.2. *Data Collection*

Table 11.2-1 CMT Cohort Data Collection Schedule

Procedure/Assessment	Screening	Enrollment / Randomization	One Month Follow-up (Phone contact)	6 Month Follow-up (Phone contact)	Annual Follow-up (Phone contact)	End of Study (Phone contact or in-clinic)
Consent Date	X					
Screening ECG	X					
Randomization Assignment		X				
Demographics and Medical History		X				
Diabetes and Cardiovascular Medications		X			X	
Adverse events			Y	Y	Y	Y
Vital Status			X	X	X	X

Note: The randomization date will be used as the starting point for determining the timing of all follow-up visits.
X: Data Required
Y: If Applicable

Table 11.2-2 S-ICD Cohort Data Collection Schedule

Procedure/Assessment	Screening	Enrollment / Randomization	Implant	One Month Follow-up (In-clinic)	6 Month Follow-up (Phone contact or in-clinic)	Annual Follow-up (In-clinic)	System Revision	Additional implant	End of Study (Phone or in-clinic)
Consent Date	X								
Screening ECG	X								
Randomization Assignment		X							
Demographics and Medical History		X							
Diabetes and Cardiovascular Medications		X				X			
Implant Details			X					X	
S-ICD system Parameters			X	X		X	X	X	X
Conversion Testing			X	S	S	S	S	S	
Adverse events			Y	Y	Y	Y	Y	Y	Y
Spontaneous Episodes			S	S	S	S	S	S	S

Note: The randomization date will be used as the starting point for determining the timing of all follow-up visits.
S: If applicable, S-ICD group only
X: Data Required
Y: If Applicable

11.3. *Screening Process*

Due to the nature of the trial and the patient population, it will be necessary to involve several medical disciplines for screening and enrollment as an interdisciplinary team approach. This approach may involve several of the following members: a research/study coordinator, an electrophysiologist, cardiologist, interventional cardiologist, internal medicine specialist, endocrinologist specializing in diabetes mellitus, and potentially other specialists. The role of the team is to jointly make efforts in screening and identifying potential candidates in the study who may not be otherwise routinely seen by a cardiac electrophysiologist.

A screening log must be used to document potential subjects who are evaluated for the MADIT S-ICD study. The screening log will be kept at the enrolling center and will identify subjects with a consecutive numeric value.

Each enrolling site will be responsible for a consenting process that ensures study candidates understand the risks and potential benefits of study participation. Efforts should be made to enroll subjects of all genders and ethnic backgrounds.

11.3.1. *WIN-Her Initiative*

Prior MADIT studies have increasingly enrolled women and reported on gender-specific outcomes. In the MADIT S-ICD clinical trial, we will further enhance enrollment of women by first applying the WIN-Her Initiative.[23, 24] The **W**omen Opt **In** for **He**art **R**esearch (WIN-Her) Initiative, will be conducted at sites in the United States. WIN-Her is designed to test the use of gender-specific enrollment and in-trial educational materials and training approaches. Additional methods will be employed during clinical trials to encourage enrollment of female subjects into clinical trials and to assess gender-specific adherence to trial processes, cross over rates, attitudes toward participation in the trial and ultimately, response to the WIN-Her program. Details of the WIN-Her initiative are outlined in the WIN-Her program materials.

11.4. *MADIT S-ICD Screening Data and Consent*

Those subjects who meet the criteria for the trial, with the exception of the S-ICD screening ECG and agree to participate will sign the study consent. All study candidates who undergo the consent process will be entered into the database. After the informed consent process is complete, the candidate will undergo an S-ICD screening ECG to determine if they are eligible for implantation with the S-ICD system. If the S-ICD screening ECG passes, then the candidate may go on to be randomized for the trial, completing the enrollment process. All S-ICD screening ECGs (in all leads and postures evaluated) are to be retained at the enrolling site. For candidates who fail the S-ICD screening ECG, no further data are to be collected and no randomization assignment obtained.

Table 11.4-1: Screening Source Documentation

Data Collection	Retention of Original Source Documentation
"MADIT S-ICD Consent" Form Screening log	Enrolling site
Pre-randomization S-ICD Screening ECG	Enrolling site; (if requested by CDC, this de-identified documentation would be provided)

11.5. *Randomization and Baseline Data (Enrollment)*

Subjects, who are consented, meet all the eligibility criteria (including a successful S-ICD screening ECG) and are randomized, are considered enrolled. All enrolled subjects will have baseline data collected for the study. Subjects who do not meet the definition of enrolled (see section 10.1) should not have baseline data collected. Subject demographics, medical history, current cardiovascular and diabetes medications and eligibility criteria will be collected for all enrolled subjects. The subjects randomization assignment will be documented in the electronic data capture system at baseline. Table 11.5-1 lists the data collected at baseline. Once the subject is enrolled (consented and randomized) adverse events must be collected.

Table 11.5-1: **Baseline Data Collection**

Data Collection	Retention of Original Source Documentation
Eligibility criteria Demographics, Physical and Medical History Cardiovascular and Diabetic Medications	Enrolling site
12-Lead ECG used for QRS duration inclusion criteria	Enrolling site; upload de-identified copy to EDC

11.6. *Implant Data/Visit*

11.6.1. *Implant Procedure*

Subjects randomized to receive the S-ICD must be implanted within 14 calendar days of randomization. Implantation and testing of the S-ICD system should be performed using the methods established by the enrolling site for S-ICD system implantation. Refer to the applicable S-ICD system User's Manual for detailed instructions regarding the implantation and use of the S-ICD system.

11.6.2. *Conversion Testing*

As part of the S-ICD system implant procedure, conversion testing must be performed using the process defined in Appendix 27.5. Only sustained ventricular arrhythmias that result in a shock require documentation by capturing and annotating an ECG strip. After the initial implant procedure, additional conversion testing may be performed at other times during the course of the study at the discretion of the investigator. These additional conversion tests should be documented. All documents related to conversion testing including ECG strips are to be kept at the enrolling sites unless requested by the coordination data center (CDC). Adverse events that occur during conversion testing must be reported in the electronic data capture system according to the study protocol. If the conversion testing is not able to be completed due to instability of the patient, no protocol deviation will be assessed (this must be documented in the subjects record).

11.6.3. *Implant Visit*

The implant visit collects S-ICD system procedural data such as procedure time, peri-operative medication management, product information, implant details, conversion testing outcomes, adverse events and information transcribed from a Final Summary Report obtained before discharge from the hospital. The Final Summary Report must document that the device is programmed per protocol (see Section 0). A post-implant chest x-ray is strongly recommended to document system placement. If performed, the x-ray would be retained by the enrolling site, and may be requested as source documentation if necessary. **Table 11.6.3-1** lists the data collected at the implant visit.

Table 11.6.3-1: Implant Data Collection

Data Collection	Retention of Original Source Documentation
Peri-operative medication listing (anticoagulation; antiplatelet; antibiotics; type of anesthesia) Implanted product and accessories utilized for S-ICD system (model/seria1) Medical notes/worksheets documenting implantation technique (e.g. Number and location of incisions, location of electrode and device etc…) Programmer Printouts: - Final Summary Report - Captured S-ECG in each sensing vector Conversion testing episodes (S-ICD Induced Episode Report or external ECG strips) Adverse events, device deficiencies, if applicable	Enrolling site
Programmer Printouts: - Device episodes, if applicable	Enrolling site; upload de-identified copy to EDC

11.6.4. *Protocol Required Programming*

All subjects who are randomized to the S-ICD arm of the trial will be required to have the S-ICD rate zones programmed as listed in Table 11.6.4-1 at the time of implantation. Post-shock pacing is recommended to be programmed ON. All other S-ICD programming is left to physician discretion.

Table 11.6.4-1: Required S-ICD Programming

Parameter	Value Required
Conditional Shock Zone	200 bpm
Shock Zone	250 bpm

11.7. *One Month Follow-up Visit*

The one month follow-up visit will be conducted by either an in-clinic visit for subjects randomized to S-ICD or phone contact for subjects randomized to CMT only. This visit will be conducted to ensure that any device, procedure or episode related events are collected as well as any other applicable patient related adverse events are reported per **Section 20**. The one month visit must be conducted at one calendar month +/- 3 calendar weeks post-randomization for the S-ICD arm and at one calendar month +/- 3 calendar weeks post-randomization for the CMT only arm. **Table 11.7-1** lists all the data required at one month follow-up visits.

Table 11.7-1: **One Month Follow-Up Visit Data Collection**

Data Collection	Retention of Original Source Documentation
Adverse events, device deficiencies if applicable (S-ICD only) Programmer Printouts: - Final Summary Report	Enrolling site
(S-ICD only) Programmer Printouts: - Device episodes, if applicable	Enrolling site; upload de-identified copy to the EDC system

11.8. *Six Month Follow-up Visit (Phone contact)/ Medical Record Review*

Between the annual visits a phone follow-up will be conducted by the enrolling site staff to verify survival status and ensure all adverse events are reported per **Section 20**. (This visit can be done in-clinic, but the data requirements remain the same). This visit requires a review of the subject's medical record to ensure accurate reporting of events. The six month visit must be conducted at 6 calendar months (+/- 1 calendar month) from randomization for all subjects, and annually thereafter at months 18, 30, 42, etc. If the subject is in-clinic during the visit window the visit may be completed in-clinic. Data collection and requirements would remain the same. **Table 11.8-1** lists the data required to be collected for the 6 month follow-up visit.

Table 11.8-1: **Six Month Follow-Up Visit Data Collection**

Data Collection	Retention of Original Source Documentation
Medical Record Review Adverse events, device deficiencies, if applicable	Enrolling site
(S-ICD only) Programmer Printouts: - Device episodes, if applicable and available through chart review	Enrolling site; upload de-identified copy to the EDC system

11.9. *Annual Follow-up Visit*

All subjects are required to have an annual follow-up visit. The annual visit must be conducted at 12 calendar months (+/- 1 calendar month) from randomization for all subjects, and annually thereafter at months 24, 36, 48, etc.

11.9.1. *CMT (Control) Group Annual Follow-up Requirements*

For subjects randomized to CMT only, this visit may be in-clinic or via phone contact and must be conducted by a member of the enrolling site investigative team. This visit will also require a review of the subject's medical record to ensure accurate reporting of events. Specifically this would include collection of:

- Physical history (blood pressure, heart rate, height, weight), if available documented from medical records
- NYHA Class, if available
- Record most recent hemoglobin A1c (HbA1c) test results, if available
- Protocol required adverse events that have not been previously reported (Note: hospitalization information will be collected on the adverse event form)
- Cardiac related procedures
- Record all currently prescribed diabetes and cardiovascular related medication

11.9.2. *S-ICD (Treatment) Group Annual Follow-up Requirements*

For subjects randomized to S-ICD the annual visit is required to be performed in-clinic by the enrolling site investigative team. As a part of the annual visit a review of the subject's medical record must be completed. The in-clinic visit includes collection of the following:

- Physical history (blood pressure, heart rate, height, weight)
- NYHA Class, if available
- Record most recent hemoglobin A1c (HbA1c) test results, if available
- Cardiac related procedures
- Record all currently prescribed diabetes and cardiovascular related medication
- Device interrogation (S-ICD Final Summary Report)
- Spontaneous device episodes that have not been previously reported;
- Protocol required adverse events that have not been previously reported (Note: hospitalization information will be collected on the adverse event form)
- Current S-ICD programming and changes in S-ICD programming;
- Protocol required device deficiencies that have not been previously reported.

Table 11.9.2-1 lists all the data required at annual follow-up visits.

Table 11.9.2-1: Annual Follow-Up Visit Data Collection

Data Collection	Retention of Original Source Documentation
Physical History Diabetes and Cardiovascular Medications NYHA Assessment, if available Most recent HbA1c test results, if applicable Cardiac procedures, if applicable Adverse events, device deficiencies, if applicable (S-ICD Only) Programmer Printouts: - Final Summary Reports (S-ICD only) Conversion testing episodes (ECG strips), if performed (S-ICD only) Programming changes that have not been previously reported;	Enrolling site
(S-ICD only) Programmer Printouts: - Device episodes, if applicable	Enrolling site; upload de-identified copy to EDC system

11.9.3. *Additional Non-Visit Related Data Collection*

Protocol required adverse events, treated episodes; suspected device deficiency or device programming change must be recorded on the appropriate case report form. These items must be documented in the EDC system within the required timelines.

11.10. *Device Status Change (S-ICD treatment group)*

11.10.1. *System Revision*

In the event that the electrode or PG is surgically revised, but not explanted, the system revision form must be completed. **Table 11.10.1-1. System Revision Data Collection** lists all the data required for system revisions.

Table 11.10.1-1. System Revision Data Collection

Data Collection	Retention of Original Source Documentation
Programmer Printouts: - Final Summary Reports Conversion testing episodes (ECG strips), if performed Adverse events, device deficiencies, if applicable	Enrolling site;
Programmer Printouts: - Episode Report printout, if applicable	Enrolling site; Upload de-identified copy to EDC system

11.10.2. *PG/Electrode Replacement*

If the PG or electrode is replaced, the new device(s) will be recorded on an additional implant form, and the electrode or PG removed from service must have an out-of-service device(s) form completed (see section11.10.4). It is expected, that due to the duration of the study, that the subject may need to receive a replacement device for normal battery depletion. If this occurs the subject shall remain in the study and continue study follow-up from the original enrollment time point. **Table** 11.10.2-1 lists all the data required for PG/Electrode Replacements.

Table 11.10.2-1 PG/Electrode Replacement Data Collection

Data Collection	Retention of Original Source Documentation
Peri-operative medication listing (anticoagulation, antiplatelet, antibiotics, type of anesthesia) Implanted product and accessories utilized for S-ICD system (model/serial) Medical notes/worksheets documenting implantation technique (e.g. Number and location of incisions, location of electrode and device etc.) Programmer Printouts (Newly implanted device): - Final Summary Reports Conversion testing episodes (ECG strips), if performed Adverse events, device deficiencies if applicable	Enrolling site
Programmer Printouts: - Episode Report printout, if applicable	Enrolling site: Upload de-identified copy to EDC system

11.10.3. *PG/Electrode Explant without Replacement*

If the PG or electrode is explanted without replacement, an out-of-service device(s) form must be completed documenting details and rationale for explant (see section 11.10.4). Due to the intention to treat nature of the study, these subjects should still be followed to study completion.

11.10.4. *Out of Service Device(s)*

For the S-ICD treatment group, if the PG or electrode is explanted for any reason or in the case of death, interred with the subject, an out-of-service device(s) form must be completed (see section 11.10.4). **Table 11.10.4-1** lists all the data required for out of service device(s).

Table 11.10.4-1 Out of Service Data Collection

Data Collection	Retention of Original Source Documentation
Programmer Printouts, if available: - Final Summary Reports Adverse events, device deficiencies, if applicable	Enrolling site
Programmer Printouts: - Episode Report printout, if applicable	Enrolling site; upload a de-identified copy to EDC system

11.10.5. *Cardiac Implantable Electronic Device Information (Non-study device implantation)*

If the subject receives a non-study device in the duration of the trial, this information will be collected on a non-study device implant form. If the subject experiences an adverse event related to the implantation of the non-study related device, the adverse event will be classified as subject condition. This includes any device or procedure related events they may experience.

11.11. *Study Completion Visit*

The study completion visit will take place at the subjects' participation completion. This includes the conclusion or termination of the study for any rationale and documented on the study status form.

11.11.1. *Subject Withdrawal Prior to Study Completion or Study Termination*

Subjects may be withdrawn prior to the study completion visit or study termination for a variety of reasons including:

- Subject withdraws consent for any reason;
- Subject is lost to follow-up despite best efforts to locate the subject;

- Subject is withdrawn at study investigator discretion;
- The subject expires.

The study status form documents withdrawal of any subject from the study. As this study is intention to treat, subjects should remain in the study and continue to be followed per the protocol unless this is unavoidable. Study data is collected per the assigned treatment arm schedule up until the date of withdrawal.

If a subject must be withdrawn for reasons other than death, study completion or lost to follow-up, the following level of withdrawal should be assessed and documented on the study status form and in the subject record. Written documentation with signature of the subject must be completed and kept on file at the enrolling site documenting any of the withdrawal levels described below.

- Subject declines to have further in-person follow-up, but agrees to phone follow-up per the schedule noted in the protocol, they should not be withdrawn.
- Subject declines further follow-up visits, but agrees to a phone call at the conclusion of the study to verify vital status, or Subject declines further direct contact of any kind, but agrees to: 1) study staff contacting their primary care provider and/or 2) reviewing their medical record, at the conclusion of the study, the subject should be withdrawn.
- Subject declines further direct contact of any kind, and does not provide permission to allow vital status verification.

There are no additional follow-up requirements once a subject has been fully withdrawn from the study. All applicable case report forms must be completed at study exit. Subjects who are “lost-to-follow-up” must have three documented contact attempts prior to completion of the study status form. Data collected up to the point of subject withdrawal may be used for study analysis, unless local regulations prohibit its use.

At the point of study completion and/or withdrawal, all open adverse events must be assessed by the investigator. These events must be closed or documented as chronic. Additionally, the sponsor may ask that withdrawn subjects be followed for information

related to the safety of the device if available. If such withdrawal is due to problems related to device safety or performance, the investigator shall ask for the subject's permission to follow his/her status/condition outside of the clinical study.

Table 11.11.1-1 lists all the data that are required for study completion.

Table 11.11.1-1 Study Completion Data Collection

Data Collection	Retention of Original Source Documentation
(S-ICD only) Programmer Printouts: - Final Summary Reports Adverse events, device deficiencies, if applicable	Enrolling site
(S-ICD only) Programmer Printouts: - Device episodes, if applicable For the withdrawal reason of death: • Death Narrative • All medical records/hospitalization records pertaining to death • Death certificate, if available • Autopsy report, if available • S-ICD device interrogation after terminal event, if available (S-ICD only)	Enrolling site; upload a de-identified copy to EDC system

11.12. *Source Documents*

Where copies of the original source document as well as printouts of original electronic source documents are retained, these shall be signed and dated by a member of the enrolling site team. All source documentation that is provided to the CDC must have personal health identifiers redacted and labeled with the subjects study identifier.

11.13. *Overall Study Completion Requirements*

This study will continue to follow subjects until the sequential stopping boundary is crossed. This is estimated to include an average follow-up time of approximately 2.6 years. Once the stopping boundary has been crossed the study will be assessed to ensure adequate data has been collected. If the data safety monitoring board determines that it is appropriate to stop the trial, sites will be notified. Each subject will have a final follow-up contact and a withdrawal form to conclude their participation. For subjects withdrawn during the study, if permitted the site will contact the subjects to obtain vital status.

12. Statistical Considerations

12.1. *Endpoints*

Primary Endpoint

All-cause mortality

12.1.1.1. Hypotheses

This study is being conducted to test the hypothesis that post-MI diabetes patients with a relatively preserved ejection fraction will have a lifesaving benefit from an implanted defibrillator.

12.1.1.2. Sample Size

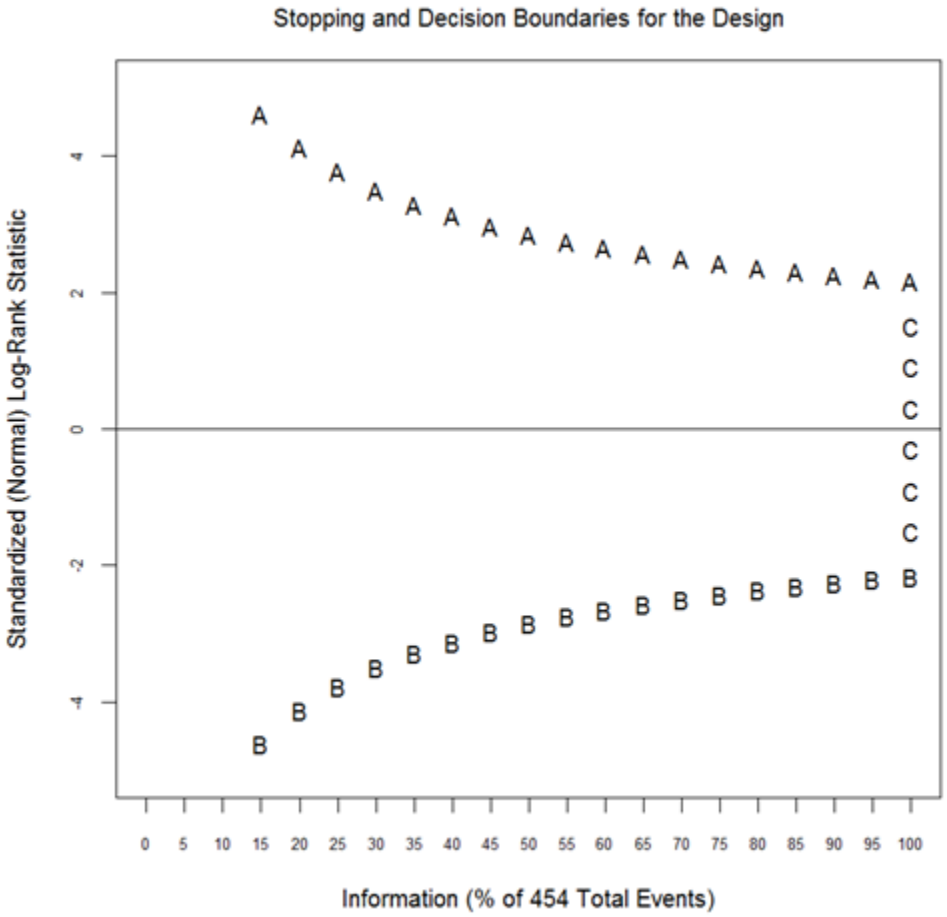
1800 men and women from the U.S., Europe, and Israel will be enrolled based on the following assumptions:

- **Wang-Tsiatis (Δ=0.1) Design with K=18 Possible Analyses**
- ***2:1 randomization (S-ICD:CMT)***
- ***α = 5% (two-sided)***
- ***Power = 80%***
- ***Hazard ratio of 0.75***
- ***Attrition rate of 10%***

12.1.1.3. Statistical Methods

A plot of the log-rank statistic versus its variance ('information') will be carried out periodically. At 18 pre-specified information times the log-rank statistic will be compared with pre-specified stopping boundaries, as indicated in Figure 12-1. If the boundary of A or B is reached prior to the final (18^{th}) analysis, the trial will be terminated at that time. Otherwise, it will be continued until either (1) the maximum information level is reached, or (2) continuing the trial is determined to be futile based on current estimates of conditional power and projected trial termination (as discussed below).

Figure 12-1: Stopping and Decision Boundaries for the Design



AAA: S-ICD more effective **BBB:** Med Rx more effective **CCC:** no difference

Reaching the upper boundary (A) leads to a decision in favor of the S-ICD, reaching the lower boundary (B) in favor of the medical treatment, and reaching the central part (C) of the vertical boundary results in a 'no difference' conclusion. Hence, a no-difference conclusion is only possible at the final analysis.

Numerical values of the boundaries, derived using SAS version 9.4, are in **Table 12.1-1**, along with the schedule of cumulative α-spending and cumulative power for hazard ratios (HR's) of 0.70 and 0.75. The cumulative power reaches 80% at analysis 18 for a HR of 0.75. For a HR of 0.70, the cumulative power exceeds 80% by analysis 14 and reaches 94% at the final analysis. Although this design could require as many as 454 events to

get to the final (18th) analysis, the trial would be expected to terminate at the 13th analysis if the HR is 0.75 and at the 10th analysis if the HR is 0.70.

Table 12.1-1: Coordinates of the Upper and Lower Stopping Boundaries and the Associated α-Spending and Cumulative Power

Analysis (Info %)	Variance	Events	Standardized Boundaries (±)	Nominal α	α-Spending	Cumulative Power HR=0.75	Cumulative Power HR=0.70
1 (15)	15.1	68.0	4.62	0.00000	0.00000	0.0002	0.0006
2 (20)	20.1	90.6	4.12	0.00004	0.00004	0.0024	0.0060
3 (25)	25.2	113.3	3.77	0.00017	0.00018	0.0106	0.0250
4 (30)	30.2	136.0	3.50	0.00046	0.00054	0.0292	0.0649
5 (35)	35.3	158.6	3.29	0.00100	0.00122	0.0611	0.1273
6 (40)	40.3	181.3	3.12	0.00181	0.00230	0.1062	0.2081
7 (45)	45.3	204.0	2.98	0.00292	0.00386	0.1626	0.3001
8 (50)	50.4	226.6	2.85	0.00433	0.00590	0.2272	0.3960
9 (55)	55.4	249.3	2.75	0.00602	0.00846	0.2966	0.4893
10 (60)	60.4	271.9	2.65	0.00799	0.01150	0.3677	0.5759
11 (65)	65.5	294.6	2.57	0.01020	0.01502	0.4377	0.6532
12 (70)	70.5	317.3	2.49	0.01263	0.01898	0.5047	0.7201
13 (75)	75.5	339.9	2.43	0.01526	0.02334	0.5675	0.7766
14 (80)	80.6	362.6	2.36	0.01806	0.02806	0.6250	0.8235
15 (85)	85.6	385.3	2.31	0.02102	0.03314	0.6770	0.8617
16 (90)	90.6	407.9	2.26	0.02410	0.03850	0.7234	0.8924
17 (95)	95.7	430.6	2.21	0.02729	0.04414	0.7643	0.9169
18 (100)	100.7	453.2	2.16	0.03058	0.05000	0.8000	0.9361

The standardized (Normal) log-rank statistic will be plotted against information at each analysis until a boundary is reached. The vertical boundary is at analysis 18, extending from –2.16 to +2.16. Alternative boundary scales are presented in **Table 12.1-2**. The Score statistic boundaries are based on the cumulative (non-standardized) log-rank statistic (and thus are simply the standardized boundaries multiplied by the square root of variance in Table 12.1-1). The boundaries based on the Maximum Likelihood Estimator (MLE) of the HR show how extreme the treatment effect would have to be in order to reach a stopping boundary early in the trial. In particular, the HR would have to be smaller than 0.31 or larger than 3.28 to stop on the first analysis. These bounds narrow considerably as the interim analyses progress, but they still represent clinically

meaningful effects at the final (18th) analysis. Specifically, the HR would have to be smaller than 0.81 or larger than 1.24 in order to be significant ($p<0.05$) at the final analysis; any HR estimate between 0.81 and 1.24 at the final analysis would result in reaching boundary C (the no-difference conclusion).

Table 12.1-2 Alternative Scales for the Upper and Lower Stopping Boundaries: Score Statistic and MLE of HR

Analysis (Info %)	Var-iance	Events	Score Statistic Boundaries (±)	HR MLE Boundaries	
				Upper (Stop on A if HR <)	Lower (Stop on B if HR >)
1 (15)	15.1	68.0	17.95	0.305	3.281
2 (20)	20.1	90.6	18.48	0.400	2.502
3 (25)	25.2	113.3	18.89	0.472	2.118
4 (30)	30.2	136.0	19.24	0.529	1.890
5 (35)	35.3	158.6	19.54	0.574	1.741
6 (40)	40.3	181.3	19.80	0.612	1.635
7 (45)	45.3	204.0	20.04	0.643	1.556
8 (50)	50.4	226.6	20.25	0.669	1.495
9 (55)	55.4	249.3	20.44	0.691	1.446
10 (60)	60.4	271.9	20.62	0.711	1.407
11 (65)	65.5	294.6	20.79	0.728	1.374
12 (70)	70.5	317.3	20.94	0.743	1.346
13 (75)	75.5	339.9	21.09	0.756	1.322
14 (80)	80.6	362.6	21.22	0.768	1.301
15 (85)	85.6	385.3	21.35	0.779	1.283
16 (90)	90.6	407.9	21.47	0.789	1.267
17 (95)	95.7	430.6	21.59	0.798	1.253
18 (100)	100.7	453.2	21.70	0.806	1.240

Any sample size that can eventually yield 454 events could be chosen, and the two-sided significance level of 5% and power of 80% at a HR of 0.75 would be maintained.

Making assumptions and choices about the recruitment period, the event rate in CMT-only patients, drop-out rates, the randomization ratio, and the desired maximum duration of the trial, an appropriate sample size can be determined.

12.1.1.3.1 Computations for Total Sample Size of 1,800 subjects

Computations show that a total sample size of n = 1,800 will meet requirements (1)-(5) below (see section 28.3 for details):

(1) Recruitment rates of 25 patients per month (ppm) in year 1, 35 ppm in year 2, and 45 ppm in years 3-4 (1800 total patients over 48 months).

(2) A 3-year cumulative event rate of 20%, 25%, or 30% in CMT-only patients.

(3) A 5-year cumulative drop-out rate of 10% in each arm.

(4) A randomization ratio of 2:1, S-ICD to CMT only.

(5) The trial should end within 6 years (2 years after recruitment ends).

12.1.1.3.2 Computations for Sample Size Expected to Generate 454 Events

Computation of a sample size that would be expected to generate 454 events depends on:

(1) The number of patients recruited each month: P_1 in month 1, P_2 in month 2, …

(2) The overall event rate. If the 3-year cumulative event rate is 25% in CMT-only patients, and the HR is 0.75, then the overall rate is a weighted average (due to 2:1 randomization) of 0.25 (weight = 1) and 1-(1-0.25)^0.75 = 0.194 (weight=2). That works out to 21.3% over 3 years, or a monthly event rate (MER) of 0.59%.

(3) The 5-year cumulative drop-out rate of 10% in each arm. That is a monthly drop-out rate (MER) of 0.17%.

In the first month, P_1 patients are enrolled, and assuming uniformly distributed enrollment times, they are expected to contribute $P_1/2$ months of follow-up. The expected numbers of events and withdrawals at the end of the first month are then $(P_1/2)$*MER and $(P_1/2)$*MDR, respectively. The expected number of patients remaining at risk entering month 2 is then P_1*(1- MER/2 - MDR/2). These monthly computations can be done sequentially, where at month j:

- R_{j-1} patients are still at-risk from month j-1
- P_j patients are enrolled uniformly in month j
- Expected follow-up time in month j: $R_{j-1} + P_j/2$
- Expected numbers of events in month j: $(R_{j-1} + P_j/2)$*MER
- Expected withdrawals in month j: $(R_{j-1} + P_j/2)$*MDR
- Expected number of patients remaining at risk entering month $_{j+1}$: R_{j-1}*(1-MER - MDR) + P_j*(1-MER/2 - MDR/2).

Setting $P_j = 25$ for j = 1, ... , 12, $P_j = 35$ for j = 13, ... , 24, $P_j = 45$ for j = 25, ... , 48, and $P_j = 0$ for j > 48, the expected counts that appear in Table 27.3-1 are obtained.

Table 27.3-1 in the Appendix provides a monthly accounting of patients with projections of events (assuming a HR of 0.75 and a 25% rate in (2)), withdrawals, and timing of analyses for this design. The 1st analysis should be performed at 15% information (69 events) and is projected to occur at month 30 with 990 patients enrolled. Further analyses would be performed at 5% increments of information (every 23 events), and these are expected to occur approximately every 3-4 months.

The trial will likely end earlier if the S-ICD is effective (even though events will accumulate more slowly). In particular, if the true HR is 0.75 and assumptions (1)-(4) hold, the trial will require 56-71 months. A HR of 0.70 would require 4-6 fewer months. The worst case scenario is a HR of 1.00 and a 20% event rate, which could require 83 months (See **Table 12.1-4)**.

Adaptive trial design elements will be used to guard against the possibility of a negative or overly lengthy trial. Stochastic curtailment based on conditional power (i.e. the chance of reaching boundary A or B under the alternative hypothesis, given the currently available data) will be used as a basis for terminating the study early due to futility. If the chance of reaching boundary C becomes so large that the no-difference conclusion is practically inevitable, then it would be futile to continue the study.

Simulations were used to determine an appropriate threshold for conditional power in declaring futility. This involved repeatedly (1 million times for each scenario) generating the sequence of 18 log-rank test statistics (according to a multivariate normal distribution that depends on the set of information levels in Table 12.1-1 and the true HR^{25}), calculating the conditional power (a function of observed log-rank test statistics, the information levels in Table 12.1-1, the overall significance level, and the true HR^{25}) under the alternative hypothesis (HR = 0.75) after interim analyses 1-17, and determining the outcome (reaching boundary A, B, or C, or declaring futility early). Simulations were conducted under a variety of true HR's in order to find a suitable conditional power threshold. Choosing a value of 0.0001% appears appropriate because (1) there is virtually no effect on the significance level or power; (2) declaring futility is practically impossible until the 15^{th} analysis; (3) there is a good chance (64%) of declaring futility early if the true HR is 1.0; and (4) there is little chance (2%) of declaring futility early if

the true HR is 0.75. Complete results of the simulation study using a conditional power threshold of 0.0001% are shown in **Table 12.1-3**. Note that the simulation size implies a standard error for percentages of at most 0.05%, and thus percentages can be assumed accurate to ±0.2% (with 99.99% confidence).

Table 12.1-3 Simulation Results Using a Conditional Power Threshold of 0.0001%

True HR	Chance (%) of Hitting Boundary A or B	Chance (%) of Hitting Boundary C (No Difference)	Chance (%) of Declaring Futility Before Analysis 18	Chance (%) of Declaring Futility at		
				Analysis 15	Analysis 16	Analysis 17
1.54	98.8	1.1	0.09	0.02	0.03	0.04
1.43	93.6	5.5	0.8	0.2	0.3	0.4
1.33	80.0	15.7	4.3	0.9	1.7	1.7
1.25	58.2	28.1	13.7	2.8	5.7	5.1
1.11	17.4	33.8	48.8	8.8	21.9	18.1
1.00	5.0	30.9	64.2	9.0	27.3	27.9
0.90	17.4	44.4	38.2	3.5	13.5	21.2
0.80	58.2	34.0	7.9	0.4	2.0	5.4
0.75	**80.0**	**18.0**	**2.1**	**0.07**	**0.4**	**1.6**
0.70	93.6	6.1	0.3	0.009	0.06	0.3
0.65	98.8	1.2	0.03	0.0003	0.004	0.02

The timing of these futility analyses will coincide with the scheduled interim analyses for efficacy, starting with Analysis 14 (projected at month 67; see Computations for Sample Size Expected to Generate 454 Events). This was selected because in none of the one million simulations was futility declared before Analysis 15.

Another adaptive design feature that will be used is sample size re-estimation. Deviations from our assumed enrollment, withdrawal, and event rates could result in an overly lengthy trial (in calendar time). Current projections are to observe 454 events in 79 months. These projections will be updated as the trial nears full enrollment (1800 patients), and enrollment may be extended if needed to complete the trial on-time. Because this is an event-driven trial, altering the total sample size is acceptable as long as 454 events could still eventually be observed. None of the other design features (total number of events, alpha-spending and power-accumulating functions) will be adaptively re-estimated or changed after the trial commences. To prevent bias, the decision to extend enrollment will be based only on overall (without regard to treatment group)

enrollment, withdrawal, and event rates. If this decision is required, it will essentially be a choice between enrolling additional patients to complete the study sooner or following 1800 patients longer.

All interim analyses (efficacy, futility, sample size re-estimation) will be performed by the unblinded statistician, who will serve as a liaison to the DSMB. The decision to terminate the trial due to efficacy or futility rests with the DSMB. It is the sponsor's decision whether to increase total enrollment.

If recruitment is faster than in (1), it should be ended before 48 months with a smaller total n, for otherwise the average follow-up may be too short. Also, a greater or lesser event rate will prolong or shorten the duration, as illustrated in **Table 12.1-4**.

Table 12.1-4: Characteristics of the Study Design

True HR	Power (in %)	Expected Trial Duration (Months)		
		20% Event Rate	25% Event Rate	30% Event Rate
1.00	5	83	71	64
0.80	58	80	69	62
0.75	**80**	**71**	**62**	**56**
0.70	94	65	57	52
0.65	99	60	53	49

Any slower rate of recruitment or lesser total recruitment will prolong the duration of the trial, about one month additionally for each two months delay in reaching target enrollment. Alternative scenarios for the estimate of the duration of the trial are demonstrated below: 1) assuming a uniform, faster enrollment rate of 45 ppm for the duration of the trial (1800 pts in 40 months), shortening the trial by 7 months (Table 12.1-5); 2) assuming a steady, slower enrollment rate of 30 ppm for the duration of the trial (1800 pts in 60 months), lengthening the trial by 3 months (Table 12.1-6).

Alternative Scenarios:

Table 12.1-5: Assuming 45 ppm throughout (1800 pts in 40 months)

True HR	Power (in %)	Expected Trial Duration (Months)		
		20% Event Rate	25% Event Rate	30% Event Rate
1.00	5	76	64	57
0.80	58	73	62	55
0.75	**80**	**64**	**55**	**49**
0.70	94	58	50	45
0.65	99	53	46	42

Table 12.1-6: Assuming 30 ppm throughout (1800 pts in 60 months)

True HR	Power (in %)	Expected Trial Duration (Months)		
		20% Event Rate	25% Event Rate	30% Event Rate
1.00	5	86	75	68
0.80	58	83	72	65
0.75	**80**	**74**	**65**	**60**
0.70	94	69	61	56
0.65	99	63	56	52

12.2. *General Statistical Methods*

12.2.1. *Analysis Sets*

All analyses will be carried out according to the intention-to-treat principle. All subjects randomized in the study will be included in the analysis.

12.2.2. *Control of Systematic Error/Bias*

Selection of subjects will be made from the Investigators' usual patient load. All patients meeting the eligibility criteria and having signed the ICF will be eligible for randomization in the study.

12.2.3. *Number of Subjects per Investigative Site*

A maximum of 10% of the total number of subjects per investigative site has been established for this trial. Any one site may not enroll more than 180 subjects without written permission from the CDC.

12.3. *Data Analyses*

Statistical tests of the difference in the primary endpoint (rate of all-cause mortality) between the randomized S-ICD and CMT groups will be computed by the unblinded statistician at periodic intervals during the trial and submitted to the Data Safety Monitoring Board (DSMB) as part of the group sequential design, and at the conclusion of the study (see section 12.1.1.3). The primary analysis will be based on statistical evaluation comparing the life-table time-to-event curves for S-ICD and CMT arms of the trial, the graphs being constructed by the method of Kaplan and Meier.[26] The stratified log-rank test[27, 28] (stratified by enrolling site) will be used to evaluate statistical significance, adjusted for the group-sequential stopping rule of the trial with maximum-likelihood ordering;[25] late-reported data will be appropriately incorporated.[29] The hazard ratio for S-ICD relative to CMT, based on Cox proportional hazards modeling,[27-29] will likewise be estimated. Also, 95% confidence limits for this hazard ratio will be determined, likewise adjusted for the sequential design.[29, 30]

12.3.1. *Other Objectives/Measurements*

The secondary objective of the study will evaluate the effects of the S-ICD on all-cause mortality in various subgroups and on sudden cardiac death. Sudden cardiac death will be analyzed using methods similar to those for all-cause mortality, except that they will be performed without adjustment for the sequential design. Sudden cardiac death events in the study will be independently adjudicated by the Mortality Events Committee using the Hinkle-Thaler criteria (see Appendix 28.4).

The pre-specified subgroups include but are not limited to: gender, race, age continuous and dichotomized at 75 years, duration of diabetes, presence versus absence of insulin therapy, HbA1c< 8% or ≥ 8%, LVEF continuous and dichotomized at 40%, MADIT II risk score subgroups. For each subgroup analysis, the Cox proportional-hazards regression analysis will be used to evaluate differences between subgroups in the hazard ratios (S-ICD vs. CMT). The baseline covariate or stratum and its interaction with treatment group will be added to the regression model and a test for significant interaction carried out. Each analysis will be stratified by enrolling site, where appropriate. These analyses will be done without

adjustment for the sequential design. Subgroup analyses are further described in section 12.3.3.

Pre-specified tertiary analyses include the following:

1. Frequency and outcomes of S-ICD treated episodes of ventricular tachycardia (VT) and ventricular fibrillation (VF).
2. Frequency and outcomes of S-ICD inappropriate shocks.
3. Frequency of S-ICD device complications, including but not limited to: infection, device malfunction and electrode movement.
4. Healthcare utilization assessed through adverse event reporting.

Tertiary analyses will be descriptive and exploratory. Detailed statistical methods for these outcomes will be presented in a Statistical Analysis Plan (SAP) prior to study termination.

12.3.2. *Interim Analyses*

Interim analyses for efficacy, futility, and sample size re-estimation are described in sections 12.1.1.3 and 12.3.

12.3.3. *Subgroup Analyses*

Interactions between treatment and important baseline variables will be investigated by including the appropriate interaction term in the statistical model and testing for its significance. The list of potential baseline variables to evaluate is listed below. Also included are dichotomous cut points if applicable (based on clinically meaningful cut point, historical use, or median value):

- Duration of diabetes > 2 years,
- Presence or absence on insulin therapy,
- Age ≥ 75 years,
- LVEF ≤ 45%,
- QRS ≥ 120 msec,
- Males vs. females,
- Caucasian (Non-Hispanic) vs other racial and ethnic categories,

- Small centers (<10 patients enrolled) vs. large centers (≥ 10 patients enrolled)

12.3.4. *Justification of Pooling*

Tests for interactions will be used to evaluate treatment differences between subgroups as described in section 12.3.3. Random effects for centers will be used to justify pooling data across investigational sites

12.3.5. *Multivariable Analyses*

Multivariate models will be constructed using the method of best subsets to select important covariates predicting the primary outcome of all-cause mortality. However data reporting in the primary analyses will include unadjusted models as appropriate in a randomized clinical trial.

12.3.6. *Other Analyses*

A table comparing baseline variables between treatment arms will be prepared. A list of potential baseline variables is categorized below. Differences between treatment groups will be evaluated by chi-square tests, Fisher's exact tests, t-tests, or Wilcoxon rank sum tests, as appropriate.

- *Demographic:* age (numeric and/or % ≥ 75 yrs), gender (%), Caucasian (non-Hispanic) (%).
- *Clinical*: NYHA, paroxysmal atrial fibrillation (%), permanent atrial fibrillation (%),QRS (numeric and/or % ≥ 120 msec), LVEF (numeric and/or % ≤ 45), SBP, DBP, BMI, heart rate, prior atrial arrhythmias.
- *Medical History*: single/multiple MI, hypertension, CABG, angioplasty, smoking.
- *Medications:* amiodarone, ACE/ARB, beta blockers, calcium-channel blockers, class I antiarrhythmic, digitalis, diuretics, lipid-lowering statins, oral hypoglycemic agents, non-insulin injectable, insulin, valsartan / sacubitril.

12.3.7. *Changes to Planned Analyses*

Any changes to the planned statistical analyses made prior to study completion will be documented in an amended Statistical Analysis Plan approved prior to implementation. Changes from the planned statistical methods after the study crossed the stopping boundary will be documented in the clinical study report along with a reason for the deviation.

13. Data Management

13.1. *Data Collection, Processing, and Review*

Subject data will be recorded in a limited access secure electronic data capture (EDC) system.

The clinical database will reside on a production server hosted by the University of Rochester. All changes made to the clinical data will be captured in an electronic audit trail and available for review by Boston Scientific Corporation (BSC) or its representative. The associated Trial Master software and database have been designed to meet regulatory compliance for deployment as part of a validated system compliant with laws and regulations applicable to the conduct of clinical studies pertaining to the use of electronic records and signatures. Database backups are performed regularly.

The enrolling site principal investigator (PI) provides his/her electronic signature on the appropriate electronic case report forms (eCRFs) in compliance with local regulations. A written signature on printouts of the eCRFs must also be provided if required by local regulation. Changes to data previously submitted to the sponsor require a new electronic signature by the PI acknowledging and approving the changes.

Visual and/or electronic data review will be performed to identify possible data discrepancies. Manual and/or automatic queries will be created in the EDC system and will be issued to the site for appropriate response. Enrolling site staff will be responsible for resolving all queries in the database, in a timely manner.

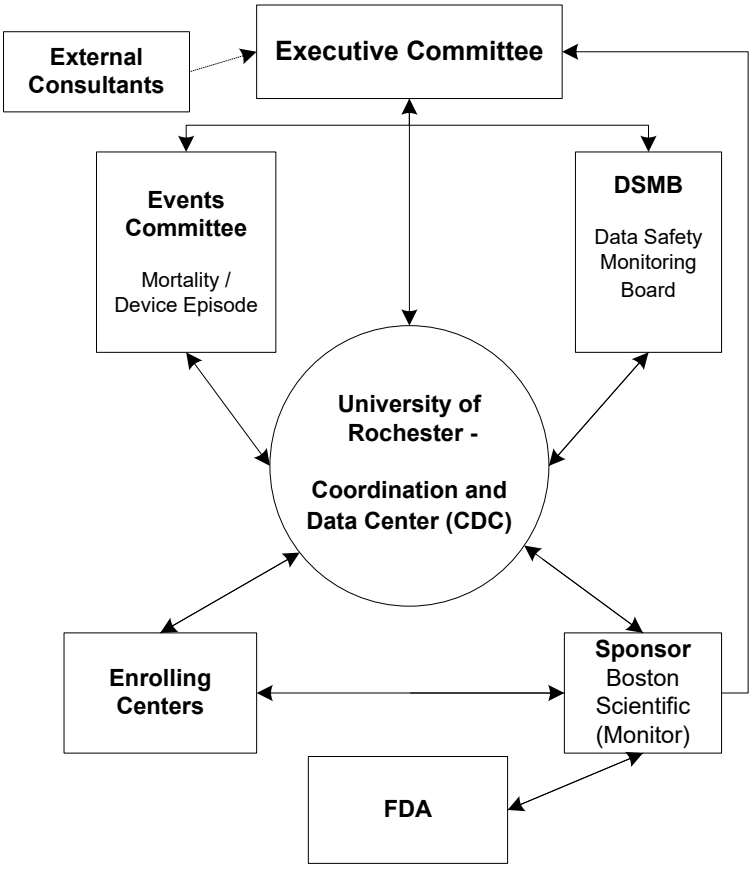
13.2. *Data Retention*

The Investigator or enrolling site will maintain, at the site, in original format all essential study documents and source documentation that support the data collected on the study subjects in compliance with ICH/GCP guidelines. Documents must be retained for at least 2 years after the last approval of a marketing application or until at least 2 years have elapsed since the formal discontinuation of the clinical investigation of the product/indication. These documents will be retained for a longer period of time by agreement with BSC or in compliance with other local regulations. The Investigator will take measures to ensure that these essential documents are not accidentally damaged or destroyed. If for any reason the Investigator withdraws responsibility for maintaining these essential documents, custody must be transferred to an individual who will assume responsibility and BSC must receive written notification of this custodial change.

14. Study Organization

The MADIT S-ICD study organization is visualized in **Figure 14-1**.

Figure 14-1: Study Organization



14.1. *University of Rochester*

Serving as the Coordination and Data Center (CDC) for the Sponsor (Boston Scientific), the University of Rochester will be responsible for overall study management, data management, data reporting and center communications for the study. The University of Rochester will also be responsible for other project management tasks.

14.2. *Data Safety and Monitoring Board*

An Independent Data Safety and Monitoring Board (DSMB) will meet periodically (as pre-specified in the DSMB charter), or as needed, to review the results of the study and to evaluate any safety or efficacy issues that may arise during the course of the study. The results will be submitted to the DSMB on a monthly basis who will then inform Boston Scientific when the sequential monitoring has reached a stopping boundary. The DSMB may recommend termination of the study at any time should prospective ethical or safety

guidelines not be met. The DSMB may also recommend increasing the sample size or lengthening the follow-up period based on the adaptive study design elements. Such recommendations will not be possible until nearing the completion of enrollment. The DSMB will also review the results of futility analyses and provide recommendations on terminating the trial early if the probability of no-difference conclusion is so large that it is practically inevitable. The DSMB consists of individuals who are not directly involved in the MADIT S-ICD study.

14.3. *Mortality Events Committee*

The Mortality Events Committee is an independent physician committee that will adjudicate all primary endpoint events that occur in the duration of the trial. Their decisions will be based on independent review of the data. Data will be provided to the Mortality Events Committee by the CDC throughout the duration of the trial.

All-Cause Mortality Events: Efforts will be made to classify cardiac deaths in terms of suddenness and arrhythmic mechanism by pre-specified Hinkle-Thaler criteria (See Appendix 27.4). Operative deaths associated with implantation of the S-ICD devices will be counted as cardiac deaths. For review of terminal events source documentation will be provided including clinical data from the hospital or out-patient record in English.

15. Amendments

If a protocol revision is necessary which affects the rights, safety or welfare of the subject or scientific integrity of the data, an amendment is required. Appropriate approvals (e.g., IRB/EC/FDA/CA) of the revised protocol must be obtained prior to implementation.

16. Deviations

An Investigator must not make any changes or deviate from this protocol, except to protect the life and physical well-being of a subject in an emergency. An investigator shall notify the CDC and the reviewing IRB/EC of any deviation from the investigational plan to protect the life or physical well-being of a subject in an emergency, and those

deviations which affect the scientific integrity of the clinical investigation. Such notice shall be given as soon as possible, but no later than 5 working days after the emergency occurred, or per prevailing local requirements, if sooner than 5 working days.

All deviations from the investigational plan, with the reason for the deviation and the date of occurrence, must be documented and reported to the CDC using the EDC system. Sites may also be required to report deviations to the IRB/EC, per local guidelines and government regulations.

Deviations will be reviewed and evaluated on an ongoing basis and, as necessary, appropriate corrective and preventive actions (including notification, center re-training, or discontinuation) will be put into place by the CDC/sponsor.

17. Compliance

17.1. *Statement of Compliance*

This study will be conducted in accordance with relevant parts of ISO14155:2011, MEDDEV 2.12/2 rev2 January 2012 (post market clinical follow-up studies), and MEDDEV 2.7/3 revision 3 May 2015 Clinical Investigations: serious adverse event reporting under directives 90/385/EEC AND 93/42/EEC. In addition, the study will be conducted in accordance with relevant parts of the ICH Guidelines for GCP, relevant parts of the Code of Federal Regulations (CFR), ethical principles that have their origins in the Declaration of Helsinki, and pertinent individual country laws and regulations. The study shall not begin until the required approval/favorable opinion from the IRB/EC and/or regulatory authority has been obtained, if appropriate. Any additional requirements imposed by the IRB/EC or regulatory authority shall be followed, where appropriate.

17.2. *Investigator Responsibilities*

The Principal Investigator of an Enrolling site is responsible for ensuring that the study is conducted in accordance with the Clinical Study Agreement, the investigational

plan/protocol, ISO 14155, ethical principles that have their origins in the Declaration of Helsinki, any conditions of approval imposed by the reviewing IRB/EC, and prevailing local and/or country laws and/or regulations, whichever affords the greater protection to the subject.

The Principal Investigator's responsibilities include, but are not limited to, the following:

- Prior to beginning the study, sign the Clinical Study Agreement and Protocol Signature page documenting his/her agreement to conduct the study in accordance with the protocol.
- Provide his/her qualifications and experience to assume responsibility for the proper conduct of the study and that of key members of the center team through up-to-date curriculum vitae or other relevant documentation and disclose potential conflicts of interest, including financial, that may interfere with the conduct of the clinical study or interpretation of results.
- Make no changes in or deviate from this protocol, except to protect the life and physical well-being of a subject in an emergency; document and explain any deviation from the approved protocol that occurred during the course of the clinical investigation.
- Create and maintain source documents throughout the clinical study and ensure their availability with direct access during monitoring visits or audits; ensure that all clinical-investigation-related records are retained per requirements.
- Ensure the accuracy, completeness, legibility, and timeliness of the data reported to the CDC in the CRFs and in all required reports. At completion of the study the Principal Investigator will be responsible for approval of the data collected via electronic signature of all CRFs.
- Record, report, and assess (seriousness and relationship to the device/procedure) every adverse event and observed device deficiency.
- Report to BSC, per the protocol requirements (Table 20.4-1), all SAEs and device deficiencies that could have led to a SADE and potential/USADE or UADE.

- Report to the IRB/EC and regulatory authorities any SAEs and device deficiencies that could have led to a SADE and potential/USADE or UADE, if required by the national regulations or this protocol or by the IRB/EC, and supply CDC/Sponsor with any additional requested information related to the safety reporting of a particular event
- Allow the sponsor to perform monitoring and auditing activities, and be accessible to the monitor and respond to questions during monitoring visits.
- Allow and support regulatory authorities and the IRB/EC when performing auditing activities.
- Ensure that informed consent is obtained in accordance with applicable laws, this protocol and local IRB/EC requirements.
- Provide adequate medical care to a subject during and after a subject's participation in a clinical study in the case of adverse events, as described in the Informed Consent Form (ICF).
- Inform the subject of the nature and possible cause of any adverse events experienced.
- Inform the subject of any new significant findings occurring during the clinical investigation, including the need for additional medical care that may be required.
- Provide the subject with well-defined procedures for possible emergency situations related to the clinical study, and make the necessary arrangements for emergency treatment, including decoding procedures for blinded/masked clinical investigations, as needed.
- Ensure that clinical medical records are clearly marked to indicate that the subject is enrolled in this clinical study.
- Ensure that, if appropriate, subjects enrolled in the clinical investigation are provided with some means of showing their participation in the clinical investigation, together with identification and compliance information for

concomitant treatment measures (contact address and telephone numbers shall be provided).

- Inform, with the subject's approval or when required by national regulations, the subject's personal physician about the subject's participation in the clinical investigation.
- Make all reasonable efforts to ascertain the reason(s) for a subject's premature withdrawal from clinical investigation while fully respecting the subject's rights.
- Ensure that an adequate investigation site team and facilities exist and are maintained and documented during the clinical investigation.
- Ensure that maintenance and calibration of the equipment relevant for the assessment of the clinical investigation is appropriately performed and documented, where applicable.

17.2.1. *Delegation of Responsibility*

When specific tasks are delegated by an investigator, including but not limited to conducting the informed consent process, the investigator is responsible for ensuring appropriate training requirements are met and adequate supervision of those to whom tasks are delegated. The investigator is accountable for regulatory violations resulting from failure to adequately supervise the conduct of the clinical study.

17.3. *Institutional Review Board/ Ethics Committee*

Prior to gaining Approval-to-Enroll status, the enrolling site will provide to the CDC documentation verifying that their IRB/EC is registered or that registration has been submitted to the appropriate agency, as applicable according to national/regulatory requirements.

A copy of the written IRB/EC and/or competent authority approval of the protocol (or permission to conduct the study) and Informed Consent Form, must be received by the CDC/Sponsor before recruitment of subjects into the study. Prior approval must also be

obtained for other materials related to subject recruitment or which will be provided to the subject.

Annual IRB/EC approval and renewals will be obtained throughout the duration of the study as required by local/country or IRB/EC requirements. Copies of the Investigator's reports and the IRB/EC continuance of approval must be provided to the CDC.

17.4. *Sponsor Responsibilities*

All information and data sent from University of Rochester or Boston Scientific (BSC) concerning subjects or their participation in this study will be considered confidential. Only authorized BSC personnel or a BSC representative including BSC's designated Contract Research Organization (CRO) will have access to these confidential records. Authorized regulatory personnel have the right to inspect and copy all records pertinent to this study. Study data collected during this study may be used by BSC for the purposes of this study, for publication, and to support future research and/or other business purposes. All data used in the analysis and reporting of this study will be without identifiable reference to specific subject name. All information received from the enrolling site will be de-identified by the enrolling site and the University of Rochester for purposes of study use.

CDC/Sponsor will keep subjects' health information confidential in accordance with all applicable laws and regulations and will comply with all applicable personal data transfer requirements in the jurisdictions in which the study will take place. CDC/Sponsor may use subjects' health information to conduct this research, as well as for additional purposes, such as overseeing and improving the performance of its device, new medical research and proposals for developing new medical products or procedures, and other business purposes. Information received during the study will not be used to market to subjects; subject names will not be placed on any mailing lists or sold to anyone for marketing purposes.

17.4.1. *Role of Boston Scientific Representatives*

Boston Scientific personnel can provide technical support to the investigator and other health care personnel (collectively HCP) as needed during implant, testing required by the protocol, and follow-ups. Support may include HCP training, addressing HCP questions, or providing clarifications to HCPs concerning the operation of BSC equipment/devices (including programmers, analyzers, and other support equipment).

At the request of the investigator , BSC personnel may operate equipment during implant or follow-up, assist with the conduct of testing specified in the protocol, and interact with the subject to accomplish requested activities. Typical tasks may include the following.

- Interrogating the device or programming device parameters to investigator-requested settings
- Performing diagnostic testing using a programmer to obtain system data (e.g. Impedance measurements)
- Clarifying device behavior, operation or diagnostic output as requested by the investigator or other health care personnel
- Assisting with the collection of study data from programmers and other equipment
- Print out programming reports directly from the programmer and provide original to clinical site as source documentation
- Provide technical expertise/support to subjects during office visits and/or during teleconference calls/electronic communications with the principal investigator or their delegated site staff and the subject

Boston Scientific personnel may perform certain activities to ensure study quality. These activities may include the following:

- Observing testing or medical procedures to provide information relevant to protocol compliance
- Reviewing collected data and study documentation for completeness and accuracy

Boston Scientific personnel will not do the following.

- Practice medicine
- Provide medical diagnosis or treatment to subjects
- Discuss a subject's condition or treatment with a subject without the approval and presence of the HCP
- Independently collect critical study data (defined as primary or secondary endpoint data)
- Enter data in electronic data capture systems or on paper case report forms

17.5. *Insurance*

Where required by local/country regulation, proof and type of insurance coverage, for subjects in the study will be obtained by Boston Scientific.

17.6 *Medicare Study Criteria (pertains to US Enrolling Sites)*

The study protocol describes the method and timing of release of results on all pre-specified outcomes, including release of negative outcomes and that the release should be hastened if the study is terminated early (see below).

Access to clinical study data provides opportunities to conduct further research that may help advance medical science and improve patient care. This helps ensure the data provided by research participants are used in the creation of knowledge and understanding. To this end, the study results on all pre-specified outcomes, including negative outcomes, will be submitted to ClinicalTrials.gov not later than one year after the study completion date, where the completion date is defined as the date that the final subject was examined or received an intervention for purposes of data collection for the primary outcome measure. Results submission could be delayed if an extension is granted to the results submission deadline; however, the release of all results on pre-specified outcomes will be hastened if the study is terminated early.

The study protocol must describe how Medicare beneficiaries may be affected by the device under investigation, and how the study results are or are not expected to be generalizable to the Medicare beneficiary population. Generalizability to populations eligible for Medicare due to age, disability, or other eligibility status must be explicitly described (see below).

Subjects in the MADIT S-ICD study include patients age ≥ 65 years old with diagnosed diabetes mellitus, documented prior MI (> 3 calendar months) and an LVEF of 36-50%. Diabetes is currently one of the most prevalent, major health issues in the United States and throughout the world. It is estimated that DM affects nearly 29 million people in the United States alone and claims more than 250,000 lives annually, with higher mortality risk in those older than 60 years of age.[14, 15] Diabetes has been shown to be associated with increased risk for SCD following a myocardial infarction, independent of the infarct size and LVEF, but is not currently used in the indication for ICD implantation[8] Thus, the device under investigation will provide Medicare beneficiaries who are post-MI diabetic patients that have a relatively preserved ejection fractions with access to potentially life-saving benefit from an implanted defibrillator. Further, the device under investigation is a market approved subcutaneous ICD (S-ICD) under investigation for a new indication for use. The S-ICD was chosen for this study design due to characteristics that could potentially provide advantages in diabetic patients who may otherwise be at a higher risk for device-related infections.[16-18] It is anticipated the study's results will be highly representative of the Medicare-aged population, as the study's key inclusion criteria includes post-infarction diabetic patients with a moderately impaired left ventricular ejection fraction (LVEF 36-50%) who are age 65 years or older. With the aging of the US population, expanding indications for ICD implantation, and growing evidence favoring device-based therapy over antiarrhythmic drugs, data on the utilization and efficacy of ICDs in older patients is becoming increasingly important.[31] Therefore, the results of this study are expected to be generalizable to the Medicare eligible population primarily due to age (e.g., 65 years or older).

18. Monitoring

Monitoring will be performed during the study to assess continued compliance with the protocol and applicable regulations. In addition, the monitor verifies that study records are adequately maintained, that data are reported in a satisfactory manner with respect to timeliness, adequacy, and accuracy, and that the Investigator continues to have sufficient staff and facilities to conduct the study safely and effectively. The Investigator/institution guarantees direct access to original source documents by BSC personnel, their designees, and appropriate regulatory authorities.

The study may also be subject to a quality assurance audit by BSC or its designees, as well as inspection by appropriate regulatory authorities. It is important that the Investigator and relevant study personnel are available during on-site monitoring visits or audits and that sufficient time is devoted to the process.

19. Potential Risks and Benefits Associated with the S-ICD System

19.1. *Anticipated Adverse Events*

The following anticipated adverse events (AE) have been identified for this study related to the S-ICD system and /or implantation procedure (See Table 19.1-1).

Table 19.1-1 Potential Adverse Events for Implantation of the S-ICD System

Potential Adverse Events for Implantation of the S-ICD System*	
Acceleration/induction of atrial or ventricular arrhythmia	Inability to defibrillate or pace
Adverse reaction to induction testing	Inappropriate post shock pacing
Allergic/adverse reaction to system or medication	Inappropriate shock delivery
Bleeding	Infection
Conductor fracture	Keloid formation
Cyst formation	Migration or dislodgement
Death	Muscle/nerve stimulation
Delayed therapy delivery	Nerve damage
Discomfort or prolonged healing of incision	Pneumothorax
Electrode deformation and/or breakage	Post-shock/post-pace discomfort
Electrode insulation failure	Premature battery depletion
Erosion/extrusion	Random component failures
Failure to deliver therapy	Stroke
Fever	Subcutaneous emphysema
Hematoma/seroma	Surgical revision or replacement of the system
Hemothorax	Syncope
Improper electrode connection to the device	Tissue redness, irritation, numbness or necrosis
Inability to communicate with the device	
Note: If any adverse events occur, invasive corrective action and/or S-ICD system modification or removal may be required. Patients who receive an S-ICD system may develop psychological disorders that include, but are not limited to, the following: • Depression/anxiety • Fear of device malfunction • Fear of shocks • Phantom shocks	

* These events are documented within the physician manual for the EMBLEM S-ICD Pulse Generator User's Manual.

19.2. *Anticipated Adverse Device Effects*

All Adverse Events mentioned in the listing in Section 19.1 are to be considered Anticipated Adverse Device Effects Risks Associated with the Study Device.

19.3. *Risks associated with Participation in the Clinical Study*

All Adverse Events mentioned in the listing in Section 19.1 are to be considered risks associated with participation in the clinical study.

19.4. *Risk Minimization Actions*

Additional risks may exist. Risks can be minimized through compliance with this protocol, performing procedures in the appropriate hospital environment, adherence to subject selection criteria, close monitoring of the subject's physiologic status during research procedures and/or follow-ups and by promptly supplying the CDC with all pertinent information required by this protocol.

19.5. *Anticipated Benefits*

Implantation of an implantable cardioverter defibrillator (ICD) has been previously demonstrated to decrease sudden cardiac death (SCD) and improve survival in post-infarction patients, both diabetic and non-diabetic who have severely reduced left ventricular ejection fraction (<35%). However, diabetic patients have been shown to exhibit a greater risk of SCD when compared to non-diabetic patients, even with a relatively preserved LVEF of 36-50%. Therefore, these post-MI diabetic patients may potentially derive survival benefit from an ICD. This hypothesis is supported by results from the VALIANT study indicating that the incidence of SCD in post-MI diabetic patients and an LVEF >35% was equal to that of non-diabetic patients with an LVEF ≤35%.[32] The MADIT S-ICD study will prospectively test the hypothesis that post-infarction diabetic patients with a relatively preserved LVEF (35-50%) will have greater survival with an S-ICD, which is indicated for the treatment of life-threatening ventricular arrhythmias, than those who do not receive an S-ICD.

19.6. *Risk to Benefit Rationale*

There are risks of complications associated with implantation of a subcutaneous implantable cardioverter defibrillator however the projected benefit of S-ICD therapy to reduce sudden cardiac death is much greater.

20. Safety Reporting

20.1. *Reportable Study Events*

Any reportable event(s), experienced by the study subject after enrollment (defined in section 10.1 as consented and randomized), must be recorded in the electronic data capture system. It is the responsibility of the investigator to determine if the event meets the criteria and report the event to the sponsor per protocol requirements.

For the purpose of this study, relevant reportable events are defined as:

- Device and/or procedure related adverse events (serious and non-serious)
- Unanticipated Adverse Device Effects/Unanticipated Serious Adverse Device Effects previously not defined in the User's manual
- Adverse events associated with cardiovascular conditions (serious and non-serious)
- Serious adverse events, regardless of cause
- Device Deficiencies

Underlying diseases are not reported as AEs unless there is an increase in severity or frequency during the course of the investigation.

Refer to **Section 19** for the known risks associated with the study device(s).

Note: Death should not be recorded as an adverse event. Death should be recorded as an outcome of only one (1) serious adverse event.

20.2. *Definitions and Classification*

In order to provide clarity, the safety reporting definitions are provided in Table 20.2-1. Administrative edits were made to combine definitions from ISO 14155-2011 and MEDDEV 2.7/3 May 2015. Events Reportable for this study are listed in section 20.1

Table 20.2-1: Safety Reporting Definitions

Term	Definition
Adverse Event (AE) *Ref: ISO 14155-2011* *Ref: MEDDEV 2.7/3 revision 3 May 2015*	Adverse Event (AE) Any untoward medical occurrence, unintended disease or injury or any untoward clinical signs (including an abnormal laboratory finding) 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 device or the comparator. NOTE 2: This definition includes events related to the procedures involved. NOTE 3: For users or other persons, this definition is restricted to events related to investigational medical devices.
Adverse Device Effect (ADE) *Ref: ISO 14155-2011* *Ref: MEDDEV 2.7/3 revision 3 May 2015*	Adverse event related to the use of an investigational medical device. NOTE 1- This includes any adverse event resulting from insufficiencies or inadequacies in the instructions for use, the deployment, the implantation, the installation, the operation, or any malfunction of the investigational medical device. NOTE 2- This includes any event that is a result of a use error or intentional abnormal use of the investigational medical device.
Serious Adverse Event (SAE) *Ref: ISO 14155-2011* *Ref: MEDDEV 2.7/3 revision 3 May 2015*	Serious Adverse Event (SAE) Adverse event that: a) led to a death, b) led to a serious deterioration in health of the subject, that either resulted in: - a life-threatening illness or injury, or - a permanent impairment of a body structure or a body function, or - in-patient hospitalization or prolongation of existing hospitalization, or - in 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 1: Planned hospitalization for pre-existing condition, or a procedure required by the Clinical Investigation Plan, without a serious deterioration in health, is not considered a serious adverse event.
Serious Adverse Device Effect (SADE) *Ref: ISO 14155-2011* *Ref: MEDDEV 2.7/3 revision 3 May 2015*	Adverse device effect that has resulted in any of the consequences characteristic of a serious adverse event.

Table 20.2-1: Safety Reporting Definitions

Term	Definition
Unanticipated Adverse Device Effect (UADE) *Ref: 21 CFR Part 812*	Any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan or application (including a supplementary plan or application), or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects.
Unanticipated Serious Adverse Device Effect (USADE) *Ref: ISO 14155-2011* *Ref: MEDDEV 2.7/3 revision 3 May 2015*	Unanticipated Serious Adverse Device Effect (USADE) Serious adverse device effect which by its nature, incidence, severity or outcome has not been identified in the current version of the risk analysis report. NOTE: Anticipated SADE (ASADE): an effect which by its nature, incidence, severity or outcome has been previously identified in the risk analysis report
Device Deficiency *Ref: ISO 14155-2011* *Ref: MEDDEV 2.7/3 revision 3 May 2015*	Inadequacy of an investigational medical device related to its identity, quality, durability, reliability, safety or performance. This may include malfunctions, use error, or inadequacy in the information supplied by the manufacturer.
For Purposes of FDA reporting, the following definitions and classifications are used: *Ref: FDA Guidance for the Submission of Research and Marketing Applications for Permanent Pacemaker Leads and for Pacemaker Lead Adaptor 510(k) Submissions*	
Clinical Observation	An adverse event that was transient or reversible and corrected with non-invasive interventions, such as reprogramming or oral medications, or else resolved with no intervention or monitoring.
Clinical Complication	An adverse event that resulted in: death, serious injury a, correction using invasive intervention, or permanent loss of device functions. a) Per 21 CFR 803.3: Serious injury means an injury or illness that: • Is life-threatening • Results in permanent impairment of a body function or permanent damage to a body structure, or • Necessitates medical or surgical intervention to preclude permanent impairment of a body function or permanent damage to a body structure Permanent means irreversible impairment or damage to a body structure or function, excluding trivial impairment or damage b) Invasive interventions are those in which treatment necessary to correct the adverse event is delivered by cutting or piercing of the skin or placing an instrument in a body cavity to provide therapy. Examples of invasive interventions (complication) include, but are not limited to: • Surgical revision of a lead

Table 20.2-1: Safety Reporting Definitions

Term	Definition
	• Electrophysiology study in which an ablation is performed • Angiogram in which angioplasty or stent placement is performed • Intravenous medications • Blood transfusions • Intubation to provide respiratory support • Chemical (pharmacologic) cardioversion with IV sedation (This is a complication due to the IV antiarrhythmic medication used for the cardioversion.) Invasive procedures that are purely diagnostic in nature should not be considered as a complication. Some examples of procedures that are invasive, but not considered to be an intervention include: • Blood draw for laboratory analysis • Cardiac catheterization in which pressures are recorded, but without therapeutic intervention • Electrophysiology study to map arrhythmias, but without therapeutic intervention • Transesophageal echo (TEE) • Electrical (external) cardioversion with IV sedation (the IV sedation used is for subject comfort and not part of the treatment)
Type I	Related to the study device, device therapy or procedure related to the implant of the study device.
Type II	Related to protocol or procedures. Specifically related to protocol testing that is not patient standard of care.
Type III	Not related to the investigational device(s), system component(s), or labeling, but would not have occurred in the absence of the investigational device(s) and/or system component(s). This includes clinical events related to commercially released devices that are used in conjunction with investigational device(s) or protocol procedures.
Type IV	Related to a change in patient's condition or to therapies other than delivered by the study device.

Abbreviations: EC=Ethics Committee; IRB=Institutional Review Board

20.3. *Relationship to Study Device(s)*

The Investigator must assess the relationship of the AE to the study device as related or unrelated. See criteria in Table 20.3-1:

Table 20.3-1: Criteria for Assessing Relationship of Study Device/Study procedure to Adverse Event

Classification	Description
Not Related	Relationship to the device or procedures can be excluded when: o the event is not a known side effect of the product category the device belongs to or of similar devices and procedures; o the event has no temporal relationship with the use of the investigational device or the procedures; o the serious event does not follow a known response pattern to the medical device (if the response pattern is previously known) and is biologically implausible; o the discontinuation of medical device application or the reduction of the level of activation/exposure - when clinically feasible – and reintroduction of its use (or increase of the level of activation/exposure), do not impact on the serious event; o the event involves a body-site or an organ not expected to be affected by the device or procedure; the serious event can be attributed to another cause (e.g. an underlying or concurrent illness/ clinical condition, an effect of another device, drug, treatment or other risk factors); o the event does not depend on a false result given by the investigational device used for diagnosis, when applicable; harms to the subject are not clearly due to use error; In order to establish the non-relatedness, not all the criteria listed above might be met at the same time, depending on the type of device/procedures and the serious event.
Unlikely Related	The relationship with the use of the device seems not relevant and/or the event can be reasonably explained by another cause, but additional information may be obtained.
Possibly Related	The relationship with the use of the investigational device is weak but cannot be ruled out completely. Alternative causes are also possible (e.g. an underlying or concurrent illness/ clinical condition or/and an effect of another device, drug or treatment). Cases were relatedness cannot be assessed or no information has been obtained should also be classified as possible.
Probably Related	The relationship with the use of the investigational device seems relevant and/or the event cannot reasonably explained by another cause, but additional information may be obtained.
Causal Relationship (Related)	The serious event is associated with the investigational device or with procedures beyond reasonable doubt when: o the event is a known side effect of the product category the device belongs to or of similar devices and procedures; o the event has a temporal relationship with investigational device use/application or procedures;

Table 20.3-1: Criteria for Assessing Relationship of Study Device/Study procedure to Adverse Event

Classification	Description
	○ the event involves a body-site or organ that: - the investigational device or procedures are applied to; - the investigational device or procedures have an effect on; ○ the serious event follows a known response pattern to the medical device (if the response pattern is previously known); ○ the discontinuation of medical device application (or reduction of the level of activation/exposure) and reintroduction of its use (or increase of the level of activation/exposure), impact on the serious event (when clinically feasible); ○ other possible causes (e.g. an underlying or concurrent illness/ clinical condition or/and an effect of another device, drug or treatment) have been adequately ruled out; ○ harm to the subject is due to error in use; ○ - the event depends on a false result given by the investigational device used for diagnosis, when applicable; In order to establish the relatedness, not all the criteria listed above might be met at the same time, depending on the type of device/procedures and the serious event.

20.4. *Investigator Reporting Requirements*

The communication requirements for reporting to CDC/BSC are as shown in Table 20.4-1.

Table 20.4-1: Investigator Reporting Requirements

Event Classification	Communication Method	Communication Timeline (MEDDEV 2.7/3 (2015)
Unanticipated Adverse Device Effect / Unanticipated Serious Adverse Device Effect **Note:** UADE is for US IDE studies only, otherwise remove UADE from the table	Complete AE eCRF page with all available new and updated information.	• Within 1 business day of first becoming aware of the event. • Terminating at the end of the study
Serious Adverse Event including Serious Adverse Device Effects	Complete AE eCRF page with all available new and updated information.	• Within 3 calendar days of first becoming aware of the event or as per local/regional regulations. • Reporting required through the end of the study
	Provide all relevant source documentation (unidentified) for reported event	• When documentation is requested by the CDC

Table 20.4-1: Investigator Reporting Requirements

Event Classification	Communication Method	Communication Timeline (MEDDEV 2.7/3 (2015)
Device Deficiencies (including but not limited to failures, malfunctions, and product nonconformities) Note: Any Investigational Device Deficiency that might have led to a serious adverse event if a) suitable action had not been taken or b) intervention had not been made or c) if circumstances had been less fortunate is considered a reportable event.	Complete a device deficiency with all available new and updated information.	• Within 3 calendar days of first becoming aware of the event and as per local/regional regulations. • Reporting required through the end of the study
Adverse Event	Complete AE eCRF page, which contains such information as date of AE, treatment of AE resolution, assessment of seriousness and relationship to the device.	• In a timely manner (e.g. Recommend within 10 calendar days) after becoming aware of the information • Reporting required through EDC

Abbreviations: AE=adverse event; eCRF=electronic case report form; EDC= electronic data capture; IDE=Investigational Device Exemption; UADE=unanticipated adverse device effect

20.5. *Boston Scientific Device Deficiencies*

All device deficiencies (including but not limited to failures, malfunctions, use errors, product nonconformities, and labeling errors) will be documented and reported to CDC/BSC. If possible, the device(s) should be returned to BSC for analysis. If it is not possible to return the device, the investigator should document why the device was not returned and the final disposition of the device. Device failures and malfunctions should also be documented in the subject's medical record.

Device deficiencies (including but not limited to failures, malfunctions, and product nonconformities) are not to be reported as adverse events. However, if there is an adverse event that results from a device failure or malfunction, that specific event would be recorded on the appropriate eCRF.

And, any Device Deficiency that could have led to a serious adverse event if a) suitable action had not been taken or b) intervention had not been made or c) if circumstances had been less fortunate is considered a reportable event.

20.6. *Reporting to Regulatory Authorities / IRBs / ECs / Investigators*

BSC is responsible for reporting adverse event information to all participating investigators and regulatory authorities, as applicable.

The Principal Investigator is responsible for informing the IRB/EC, and regulatory authorities of UADE and SAE as required by local/regional regulations.

20.7. *Subject Death Reporting*

Subject death during the investigation shall be reported to the CDC as soon as possible and in any event within three calendar days of notification to center. The center's IRB/ERC must be notified of any deaths in accordance with that center's IRB/ERC policies and procedures, even if supporting documents are not yet available. Documentation of endpoints will utilize appropriate sources of information. All death related source documentation will be provided to the Mortality Events Committee for adjudication by the CDC.

Notification of death must include a detailed narrative (death letter) of the pertinent events and be signed by the investigator or co-investigator, in addition to the required device status forms. The death narrative summary should be submitted to the CDC as soon as possible and must include the items listed in **Table 20.7-1**, if available.

Table 20.7-1 Death Narrative Summary Required Components

Date and time of death	Whether or not the death was witnessed
Rhythm at the time of death, if known (include any available documentation)	Any other circumstances surrounding the death
Whether the death was device or procedure related	Approximate time interval from the initiating event to death
Place death occurred	Device status/activity at the time of death
Immediate cause of death	

If any of the above information is not available, please state this in the death narrative summary. A copy of the death records and an autopsy report (if performed) must also be uploaded to the database as soon as possible. An Out-of-Service data form must be submitted for all implanted S-ICD system components. If device episodes have occurred and been recorded by the device since the last follow-up, this should be reported on an episode form. An attempt should be made to recover the device system post mortem. If the device is explanted it should be returned to Boston Scientific. If it is not explanted the device should be interrogated and the information reported on a final summary form.

21. Informed Consent

Subject participation in this clinical study is voluntary. Informed Consent is required from all subjects or their legally authorized representative. The Investigator is responsible for ensuring that Informed Consent is obtained prior to randomization, the use of any investigational devices, study-required procedures and/or testing, or data collection.

The obtaining and documentation of Informed Consent must be in accordance with the principles of the Declaration of Helsinki, ISO 14155, any applicable national regulations, and local Ethics Committee and/or Regulatory authority body, as applicable. The ICF must be approved by CDC or Sponsor, the center's IRB/EC, or central IRB, if applicable.

A study-specific template of the ICF will be provided to investigators participating in this study. The ICF template may be modified to meet the requirements of the enrolling site's IRB/EC. Any modification requires approval from CDC prior to use of the form. The ICF must be in a language understandable to the subject and if needed, CDC will assist the center in obtaining a written consent translation. Translated consent forms must also have IRB/EC approval prior to their use. Privacy language shall be included in the body of the form or as a separate form as applicable.

The process of obtaining Informed Consent shall at a minimum include the following steps, as well as any other steps required by applicable laws, rules, regulations and guidelines:

- be conducted by the Principal Investigator or designee authorized to conduct the process,
- include a description of all aspects of the clinical study that are relevant to the subject's decision to participate throughout the clinical study,
- avoid any coercion of or undue influence of subjects to participate,
- not waive or appear to waive subject's legal rights,
- use native language that is non-technical and understandable to the subject or his/her legal representative,
- provide ample time for the subject to consider participation and ask questions if necessary,
- ensure important new information is provided to new and existing subjects throughout the clinical study.

The ICF shall always be signed and personally dated by the subject competent to sign the ICF under the applicable laws, rules, regulations and guidelines and by the investigator and/or an authorized designee responsible for conducting the informed consent process. The original signed ICF will be retained by the enrolling site and a copy of the signed and dated document and any other written information must be given to the person signing the form.

Failure to obtain subject consent will be reported by the sponsor to the applicable regulatory authority according to their requirements (e.g., FDA requirement is within 5 working days of learning of such an event). Any violations of the informed consent process must be reported as deviations to the CDC and local regulatory authorities (e.g. IRB/EC), as appropriate.

If new information becomes available that can significantly affect a subject's future health and medical care, that information shall be provided to the affected subject(s) in written form via a revised ICF or, in some situations, enrolled subjects may be requested to sign and date an addendum to the ICF. In addition to new significant information during the

course of a study, other situations may necessitate revision of the ICF, such as if there are amendments to the applicable laws, protocol, a change in Principal Investigator, administrative changes, or following annual review by the IRB/EC. The new version of the ICF must be approved by the IRB/EC. Approval is required if changes to the revised ICF are requested by the center's IRB/EC. The IRB/EC will determine the subject population to be re-consented.

22. Additional Safety Monitoring

22.1. *Safety Monitoring Process*

To promote early detection of any potential device safety issues, Boston Scientific will evaluate safety events. Success of this program requires dynamic collection of unmonitored data as soon as the event is reported. During regularly scheduled monitoring visits, clinical research monitors will support the dynamic reporting process through their review of source document information. In addition to the DSMB, Boston Scientific will internally review on a periodic basis aggregate adverse event rates as well as specific events when necessary in order to provide additional safety oversight of the study device system. This may include obtaining subject data from internal Boston Scientific Systems (device tracking, technical services, and LATITUDE patient management systems). If required this information may be provided to MADIT S-ICD Event Committee members to ensure accurate adjudication. Any concerns found during the periodic reviews will be provided to the DSMB for evaluation.

23. Suspension or Termination

23.1 Premature Termination of the Study by the Sponsor

Boston Scientific Corporation reserves the right to terminate the study at any stage but intends to exercise this right only for valid scientific or administrative reasons and reasons related to protection of subjects. A determination to terminate prematurely will be evaluated and agreed upon by the CDC/Executive Committee/DSMB/Sponsor.

Investigators, associated IRBs/ECs, and regulatory authorities, as applicable, will be notified in writing in the event of study termination.

In the event of premature study termination a written statement as to why the premature termination has occurred will be provided to all participating centers by the CDC. The IRB/EC and regulatory authorities, as applicable, will be notified. Detailed information on how enrolled subjects will be managed thereafter will be provided.

The investigator must return all documents to the CDC/Sponsor, unless this action would jeopardize the rights, safety, or welfare of the subjects.

23.1.1 Criteria for Premature Termination of the Study by the Sponsor

Possible reasons for premature study termination include, but are not limited to, the following.

- The occurrence of unanticipated adverse device effects that present a significant or unreasonable risk to subjects enrolled in the study.
- An enrollment rate far below expectation that prejudices the conclusion of the study.

23.2 Termination of Study Participation by the Investigator or Withdrawal of IRB/ EC Approval

Any investigator, or IRB/ EC in the MADIT S-ICD Study may discontinue participation in the study or withdrawal approval of the study, respectively, with suitable written notice to the CDC/sponsor. Investigators, associated IRBs/ECs, and regulatory authorities, as applicable, will be notified in writing in the event of these occurrences.

In the event an IRB or EC terminates participation in the study, participating investigators, associated IRBs/ECs, and regulatory authorities, as applicable, will be notified in writing. Detailed information on how enrolled subjects will be managed thereafter will be provided.

In the event an investigator terminates participation in the study, study responsibility will be transferred to a co-investigator, if possible. In the event there are no opportunities to

transfer investigator responsibility; detailed information on how enrolled subjects will be managed thereafter will be provided by the CDC/Sponsor.

The investigator must return all documents to the CDC/Sponsor, unless this action would jeopardize the rights, safety, or welfare of the subjects.

23.3 Criteria for Suspending/Terminating an Individual Study Center by the CDC/Sponsor

The CDC/Sponsor reserves the right to stop the inclusion of subjects at a study center at any time after the study initiation visit if no subjects have been enrolled for a period beyond 12 months after center initiation, or if the center has multiple or severe protocol violations/noncompliance without justification and/or fails to follow remedial actions.

The IRB/EC and regulatory authorities, as applicable, will be notified. All subjects enrolled in the study at the site will continue to be followed per standard of care for their device and/or condition.

24. Publication Policy

Oversight of the publication process for the MADIT S-ICD study will be performed by the University of Rochester Coordination Data Center (CDC) with the primary oversight by the MADIT S-ICD Principal Investigator. In accordance with the Conduct of Human Subject Research policy, the study results will be submitted for publication (regardless of study outcome) following the conclusion or termination of the study in a timely manner. The MADIT S-ICD study will follow the Contributorship Criteria set forth in the Uniform Requirements of the International Committee of Medical Journal Editors (ICMJE; http://www.icmje.org).

25. Reimbursement and Compensation for Subjects

25.1. *Subject Reimbursement*

An optional stipend may be provided to participants to cover travel and other expenses incurred by subjects and specific to in-clinic visits required as a result of participation in the study. Enrolling sites will be responsible for distributing the stipend as applicable in accordance with pertinent country laws and regulations and per the site's regulations. The implementation of the subject stipend will be determined by each enrolling site and is not a requirement of the study.

25.2. *Compensation for Subject's Health Injury*

Boston Scientific Corporation will purchase an insurance policy to cover the cost of potential health injury for study subjects, as required by applicable law.

26. Abbreviations and Definitions

26.1. *Abbreviations*

Abbreviations are shown in Table 26.1-1.

Table 26.1-1: Abbreviations

Abbreviation/Acronym	Term
bpm	beats per minute
BSC	Boston Scientific Corporation
CDC	Coordination Data Center (University of Rochester)
CEC	Clinical Events Committee
CFR	Code of Federal Regulations
CRF	Case Report Form
EC	Ethics Committee
ECG	Electrocardiogram
EIT	Electrode Insertion Tool
FCC	Federal Communications Commission
ERI	Elective Replacement Indicator
GCP	Good Clinical Practice
ICD	Implantable Defibrillator
ICF	Informed Consent Form
IDE	Investigational device exemption

Abbreviation/Acronym	Term
IRB	Institutional Review Board
J	Joules
LVEF	Left Ventricular Ejection Fraction
ms	Millisecond
N/A	Not Applicable
NR	Not Required
NSR	Normal Sinus Rhythm
NYHA	New York Heart Association
OUS	Outside the United States
ppm	pulses per minute
RF	Radio Frequency
SAS	Statistical Analysis System
SVT	Supraventricular Tachycardia
EMBLEM S-ICD System	The BSC subcutaneous defibrillator, including the EMBLEM Pulse Generator, Subcutaneous Electrode, Programmer, and Electrode Insertion Tool (EIT)
TV-ICD	Transvenous ICD
US	United States
VF	Ventricular Fibrillation
VT	Ventricular Tachycardia
VT/VF Storm	3 or more treated VT/VF episodes occurring within 24 hours

26.2. *Definitions*

Terms are defined in Table 26.2-1.

Table 26.2-1: Definitions

Term	Definition
Normal Battery Depletion	A pulse generator that is not associated with a complaint and has reached its elective replacement indicator(s) with implant time that meets or exceeds the nominal (50th percentile) predicted longevity at default (labeled) programmable settings OR with implant time exceeding 75% of the expected longevity using the longevity calculation tool available at time of product introduction, calculated using the device's actual use conditions and programmable settings
Premature Battery Depletion	A pulse generator that does not meet the expected battery longevity.
Permanent Loss of Device Function	Refers to: 1) the permanent loss of shock therapy and/or post shock pacing; 2) permanent loss of appropriate sensing in all available sensing configurations (oversensing that results in persistent inappropriate shocks or undersensing that could lead to undetected arrhythmias). Loss of device function includes programming the PG permanently off or temporarily off in advance of an explant/revision.

Abbreviations are defined in Table 26.1-1.

27. Appendices

27.1. *MADIT S-ICD Executive Committee Members*

Members of the MADIT S-ICD Executive Committee include the following:

- Valentina Kutyifa, MD, PhD (Principal Investigator) - University of Rochester Heart Research Follow-up Program, Rochester, NY
- Arthur J. Moss, MD, (Co-Principal Investigator) - University of Rochester Heart Research Follow-up Program, Rochester, NY
- Christopher Beck, PhD - University of Rochester Department of Biostatistics and Computational Biology, Rochester, NY
- Mary W. Brown, MS - University of Rochester Heart Research Follow-up Program Rochester, NY
- David Cannom, MD – Good Samaritan Hospital, Los Angeles, CA
- James Daubert, MD – Duke University Health System, Chapel Hill, NC
- Mark Estes, MD - Tufts Medical Center, Boston, MA
- Henry Greenberg, MD - New York, NY
- Ilan Goldenberg, MD - Sheba Medical Center, Israel
- Stephen Hammes, MD - Strong Memorial Hospital, Rochester, NY
- David Huang, MD – University of Rochester Medical Center, Rochester, NY
- Helmut Klein, MD - Munich, Germany
- Reinoud Knops, MD - Academic Medical Center, Amsterdam, The Netherlands
- Mikhail Kosiborod, MD - St. Luke's Hospital of Kansas City, Kansas City, MO
- Jeanne Poole, MD – University of Washington, Seattle, WA
- Claudio Schuger, MD – Henry Ford Hospital, Detroit, MI
- Jagmeet Singh, MD – Massachusetts General Hospital, Boston, MA
- Scott Solomon, MD – Brigham and Women's Hospital, Boston, MA
- David Wilber, MD – Loyola University Medical Center, Maywood, IL
- Wojciech Zareba, MD - University of Rochester Heart Research Follow-up Program, Rochester, NY

27.2. *MADIT S-ICD Mortality Events Committee*

Composition and Duties

The MADIT S-ICD Mortality Events Committee will be responsible for the independent adjudication of the occurrence of mortality. The purpose of this process is to provide maximum uniformity and continuity in the review and categorization of terminal events, while still maintaining latitude for professional judgment by the investigators and committee members.

The committee will receive information regarding all deaths from the enrolling sites. This information will be first sent to the Coordination and Data Center (CDC) where the supporting documentation will be reviewed for completeness and then forwarded to the committee. The committee will review and adjudicate the events, provided that sufficient supporting documentation has been received from the enrolling site. If the supporting documentation is not sufficient or non-existent within a reasonable period of time, the enrolling site is contacted and the required documents are requested. As with all data, sometimes the enrolling site is unable to retrieve sufficient source documentation on the terminal event. If there is sufficient evidence in the form of notes from the PI or enrolling site that the requested supporting documentation is not available despite numerous attempts and these requests have been made diligently, the case is sent to the Mortality Events Committee for adjudication.

Voting Procedures

The Committee meeting will proceed as long as two of three members of the committee are present. No vote will be taken without the presence of three members, in person or by phone. All votes will be recorded, and a final classification document, indicating the committee's decision, will be completed and signed and dated by the Chair.

If there is initial agreement on the classification among the committee members, the endpoint will be classified accordingly and considered closed. However, if there is disagreement among the team members, the endpoint will go to full committee discussion. The three voting members will determine the classification of the event. In a

case where there is a split vote that cannot be resolved through discussion, the Chair reserves the right to make the final determination of the case classification.

In events initially classified as needing additional information, the Chair will request additional information from the site investigator. The request will be forwarded via the CDC to the site investigator. That decision will be tabled and placed on the agenda for review at the next committee meeting, pending the provision of the additional information requested. If with all available additional information, the committee is still unable to classify the event, the event will be adjudicated as an uncertain mortality event.

Reporting of Classification

The committee will forward a completed Event Adjudication Data Form to the CDC that will be included in the database with a confirmation report document forwarded to the DSMB by the CDC following data entry. A copy of each confirmation document will be archived by the committee and the event review will be considered closed.

27.3. *Statistical Considerations*

Computation of a sample size that would be expected to generate 454 events depends on:

(1) The number of patients recruited each month: P_1 in month 1, P_2 in month 2, ...

(2) The overall event rate. If the 3-year cumulative event rate is 25% in CMT-only patients, and the HR is 0.75, then the overall rate is a weighted average (due to 2:1 randomization) of 0.25 (weight = 1) and 1-(1-0.25)^0.75 = 0.194 (weight=2). That works out to 21.3% over 3 years, or a monthly event rate (MER) of 0.59%.

(3) The 5-year cumulative drop-out rate of 10% in each arm. That is a monthly drop-out rate (MDR) of 0.17%.

In the first month, P_1 patients are enrolled, and assuming uniformly distributed enrollment times, they are expected to contribute $P_1/2$ months of follow-up. The expected numbers of events and withdrawals at the end of the first month are then $(P_1/2)$*MER and $(P_1/2)$*MDR, respectively. The expected number of patients remaining at risk entering month 2 is then P_1*(1- MER/2 - MDR/2). These monthly computations can be done sequentially, where at month j:

- R_{j-1} patients are still at-risk from month j-1
- P_j patients are enrolled uniformly in month j
- Expected follow-up time in month j: $R_{j-1} + P_j/2$
- Expected numbers of events in month j: $(R_{j-1} + P_j/2)$*MER
- Expected withdrawals in month j: $(R_{j-1} + P_j/2)$*MDR
- Expected number of patients remaining at risk entering month j+1: R_{j-1}*(1-MER - MDR) + P_j*(1-MER/2 - MDR/2).

Setting $P_j = 25$ for j = 1, ... , 12, $P_j = 35$ for j = 13, ... , 24, $P_j = 45$ for j = 25, ... , 48, and $P_j = 0$ for j > 48, the expected counts that appear in Table 28.3-1 are obtained.

Table 27.3-1: Monthly Projections and Accounting for the Study Design

Analysis Number	Month	Newly Enrolled	Total Enrolled	New Events	Total Events	New Withdrawals	Total Withdrawals	Remaining at Risk
	1	25	25	0.07	0.07	0.02	0.02	24.91
	2	25	50	0.22	0.29	0.06	0.08	49.62
	3	25	75	0.37	0.66	0.10	0.19	74.15
	4	25	100	0.51	1.17	0.14	0.33	98.49
	5	25	125	0.66	1.83	0.18	0.52	122.65
	6	25	150	0.80	2.63	0.23	0.74	146.63
	7	25	175	0.94	3.57	0.27	1.01	170.42
	8	25	200	1.08	4.65	0.30	1.31	194.04
	9	25	225	1.22	5.87	0.34	1.66	217.47
	10	25	250	1.36	7.23	0.38	2.04	240.73

	11	25	275	1.50	8.73	0.42	2.46	263.81
	12	25	300	1.63	10.36	0.46	2.92	286.72
	13	35	335	1.80	12.16	0.51	3.43	319.42
	14	35	370	1.99	14.15	0.56	3.99	351.86
	15	35	405	2.18	16.33	0.62	4.61	384.07
	16	35	440	2.37	18.70	0.67	5.28	416.02
	17	35	475	2.56	21.26	0.72	6.00	447.74
	18	35	510	2.75	24.01	0.78	6.77	479.22
	19	35	545	2.93	26.95	0.83	7.60	510.45
	20	35	580	3.12	30.07	0.88	8.48	541.45
	21	35	615	3.30	33.37	0.93	9.41	572.22
	22	35	650	3.48	36.85	0.98	10.40	602.75
	23	35	685	3.66	40.52	1.03	11.43	633.05
	24	35	720	3.84	44.36	1.08	12.51	663.12
	25	45	765	4.05	48.41	1.14	13.66	702.93
	26	45	810	4.29	52.70	1.21	14.86	742.44
	27	45	855	4.52	57.22	1.27	16.14	781.64
	28	45	900	4.75	61.97	1.34	17.48	820.55
	29	45	945	4.98	66.95	1.41	18.89	859.16
1	30	45	990	5.21	72.16	1.47	20.35	897.48
	31	45	1035	5.44	77.60	1.53	21.89	935.51
	32	45	1080	5.66	83.26	1.60	23.48	973.26
	33	45	1125	5.88	89.14	1.66	25.14	1010.71
2	34	45	1170	6.11	95.25	1.72	26.87	1047.89
	35	45	1215	6.32	101.57	1.78	28.65	1084.78
	36	45	1260	6.54	108.11	1.85	30.50	1121.39
3	37	45	1305	6.76	114.87	1.91	32.40	1157.72
	38	45	1350	6.97	121.85	1.97	34.37	1193.78
	39	45	1395	7.19	129.03	2.03	36.40	1229.57
4	40	45	1440	7.40	136.43	2.09	38.48	1265.08
	41	45	1485	7.61	144.04	2.15	40.63	1300.33
	42	45	1530	7.82	151.86	2.20	42.83	1335.31
5	43	45	1575	8.02	159.88	2.26	45.10	1370.02
	44	45	1620	8.23	168.11	2.32	47.42	1404.47
	45	45	1665	8.43	176.54	2.38	49.80	1438.66
6	46	45	1710	8.63	185.17	2.44	52.23	1472.60
	47	45	1755	8.83	194.01	2.49	54.72	1506.27
	48	45	1800	9.03	203.04	2.55	57.27	1539.69
7	49	0	1800	9.10	212.14	2.57	59.84	1527.86
	50	0	1800	9.03	221.16	2.55	62.38	1516.28
8	51	0	1800	8.96	230.12	2.53	64.91	1504.80
	52	0	1800	8.89	239.02	2.51	67.42	1493.40

	53	0	1800	8.82	247.84	2.49	69.91	1482.08
9	54	0	1800	8.76	256.60	2.47	72.38	1470.86
	55	0	1800	8.69	265.29	2.45	74.83	1459.71
10	56	0	1800	8.63	273.91	2.43	77.26	1448.66
	57	0	1800	8.56	282.47	2.41	79.68	1437.68
	58	0	1800	8.49	290.97	2.40	82.07	1426.79
11	59	0	1800	8.43	299.40	2.38	84.45	1415.98
	60	0	1800	8.37	307.76	2.36	86.81	1405.25
	61	0	1800	8.30	316.07	2.34	89.15	1394.61
12	62	0	1800	8.24	324.31	2.32	91.48	1384.04
	63	0	1800	8.18	332.49	2.31	93.78	1373.56
13	64	0	1800	8.12	340.60	2.29	96.07	1363.15
	65	0	1800	8.05	348.66	2.27	98.34	1352.83
	66	0	1800	7.99	356.65	2.25	100.60	1342.58
14	67	0	1800	7.93	364.58	2.24	102.84	1332.41
	68	0	1800	7.87	372.46	2.22	105.06	1322.32
	69	0	1800	7.81	380.27	2.20	107.26	1312.30
15	70	0	1800	7.75	388.02	2.19	109.45	1302.36
	71	0	1800	7.70	395.72	2.17	111.62	1292.49
	72	0	1800	7.64	403.36	2.15	113.77	1282.70
16	73	0	1800	7.58	410.93	2.14	115.91	1272.98
	74	0	1800	7.52	418.46	2.12	118.03	1263.34
	75	0	1800	7.46	425.92	2.11	120.14	1253.77
17	76	0	1800	7.41	433.33	2.09	122.23	1244.27
	77	0	1800	7.35	440.68	2.07	124.30	1234.85
	78	0	1800	7.30	447.98	2.06	126.36	1225.49
18	79	0	1800	7.24	455.22	2.04	128.40	1216.21

27.4. *Hinkle- Thaler Criteria*

Clinical classification of cardiac deaths

LE Hinkle Jr. and HT Thaler

One hundred forty-two deaths among 743 men ages 50 - 65 years who had been examined and followed 5 - 10 years were investigated and classified on the basis of clinical information from medical and non- medical observers, ECGs and autopsies. A classification based on the condition of the circulation immediately before death appears to be most relevant to studies of sudden death. In 58% of the cases, the subjects collapsed abruptly and his pulse ceased without prior circulatory collapse (arrhythmic death); in 42%, the pulse ceased only after the peripheral circulation had collapsed (deaths in circulatory failure). Thirty-three percent of arrhythmic deaths and 10% of deaths in circulatory failure occurred in a setting of clinical evidence of acute ischemic heart disease (p less than 0.005). Forty-five percent of arrhythmic deaths were preceded by chronic congestive heart failure without circulatory collapse. Ninety-three percent of final illnesses that lasted less than 1 hour ended in arrhythmic deaths; 74% lasted more than 1 day ended in deaths in circulatory failure (p less than 0.001). Eighty-eight percent of deaths that occurred outside of the hospital were arrhythmic; 71% of deaths that occurred in the hospital were deaths in circulatory failure (p less than 0.001). Ninety percent of deaths in which the primary cause of the final illness was heart disease were arrhythmic; 86% of deaths in which the primary cause was other than heart disease were deaths in circulatory failure (p less than 0.001). Ninety-one percent of deaths precipitated by an acute cardiac event were arrhythmic; 98% precipitated by acute respiratory obstruction, hemorrhage, infection, stroke or other non-cardiac events were deaths in circulatory failure (p less than 0.001).

27.5. *MADIT S-ICD Conversion Testing Protocol*

Conversion (defibrillation) testing is required at S-ICD implantation.

1. Prepare for conversion testing. Prior to S-ICD implantation, external defibrillation patches should be applied to the patient and connected to an external defibrillator. External rescue shocks should be ready if the S-ICD defibrillation shock fails.
2. Implant the S-ICD (refer to the S-ICD pulse generator user's manual for guidance). Prior to defibrillation testing, carefully close the deep layers of all incisions and express any excess air or fluid along the parasternal electrode tunnel.
3. Induce VF* (refer to the S-ICD pulse generator user's manual for guidance) and allow the S-ICD to deliver a 65 J shock. (15 J safety margin)
4. If 65 J shock is successful, complete the S-ICD Implantation.

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5. If 65 J shock fails, allow the S-ICD to re-detect and deliver an 80J shock or provide an external defibrillation rescue shock to terminate the defibrillation test. This step is per physician discretion.
6. For 65 J S-ICD shock failures, check the position of the S-ICD generator and position of the electrode relative to anatomy and revise if needed. If the positions seem appropriate, consider reversing polarity.
7. Induce VF* and allow the S-ICD to deliver a 65 J shock. If 65 J shock fails, either allow the S-ICD to re-detect and deliver an 80J shock or provide external defibrillation rescue shock to terminate the defibrillation test.
8. Regardless of failure or success, complete the implantation procedure.

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*If VF cannot be induced despite 3 attempts, a dedicated shock can be delivered to identify the shock impedance.

Note: If conversion testing has to be terminated due to the instability of the patient, additional conversion testing is recommended within 30 days of S-ICD implant. Additional conversion testing can be done per the physician's discretion.

27.6. *Bibliography*

1. Thygesen K, Alpert JS, Jaffe AS, Simoons ML, Chaitman BR, White HD, Katus HA, Apple FS, Lindahl B, Morrow DA, Clemmensen PM, Johanson P, Hod H, Underwood R, Bax JJ, Bonow JJ, Pinto F, Gibbons RJ, Fox KA, Atar D, Newby LK, Galvani M, Hamm CW, Uretsky BF, Steg PG, Wijns W, Bassand JP, Menasche P, Ravkilde J, Ohman EM, Antman EM, Wallentin LC, Armstrong PW, Januzzi JL, Nieminen MS, Gheorghiade M, Filippatos G, Luepker RV, Fortmann SP, Rosamond WD, Levy D, Wood D, Smith SC, Hu D, Lopez-Sendon JL, Robertson RM, Weaver D, Tendera M, Bove AA, Parkhomenko AN, Vasilieva EJ, Mendis S, Baumgartner H, Ceconi C, Dean V, Deaton C, Fagard R, Funck-Brentano C, Hasdai D, Hoes A, Kirchhof P, Knuuti J, Kolh P, McDonagh T, Moulin C, Popescu BA, Reiner Z, Sechtem U, Sirnes PA, Torbicki A, Vahanian A, Windecker S, Morais J, Aguiar C, Almahmeed W, Arnar DO, Barili F, Bloch KD, Bolger AF, Botker HE, Bozkurt B, Bugiardini R, Cannon C, de Lemos J, Eberli FR, Escobar E, Hlatky M, James S, Kern KB, Moliterno DJ, Mueller C, Neskovic AN, Pieske BM, Schulman SP, Storey RF, Taubert KA, Vranckx P, Wagner DR. Third universal definition of myocardial infarction. *J Am Coll Cardiol*. 2012;60:1581-1598
2. Moss AJ, Zareba W, Hall WJ, Klein H, Wilber DJ, Cannom DS, Daubert JP, Higgins SL, Brown MW, Andrews ML. Prophylactic implantation of a defibrillator in patients with myocardial infarction and reduced ejection fraction. *N Engl J Med*. 2002;346:877-883
3. Olde Nordkamp LR, Dabiri Abkenari L, Boersma LV, Maass AH, de Groot JR, van Oostrom AJ, Theuns DA, Jordaens LJ, Wilde AA, Knops RE. The entirely subcutaneous implantable cardioverter-defibrillator: Initial clinical experience in a large dutch cohort. *J Am Coll Cardiol*. 2012;60:1933-1939
4. Lambiase PD, Barr C, Theuns DA, Knops R, Neuzil P, Johansen JB, Hood M, Pedersen S, Kaab S, Murgatroyd F, Reeve HL, Carter N, Boersma L. Worldwide experience with a totally subcutaneous implantable defibrillator: Early results from the effortless s-icd registry. *Eur Heart J*. 2014;35:1657-1665
5. Jarman JW, Todd DM. United kingdom national experience of entirely subcutaneous implantable cardioverter-defibrillator technology: Important lessons to learn. *Europace*. 2013;15:1158-1165
6. Bardy GH, Smith WM, Hood MA, Crozier IG, Melton IC, Jordaens L, Theuns D, Park RE, Wright DJ, Connelly DT, Fynn SP, Murgatroyd FD, Sperzel J, Neuzner J, Spitzer SG, Ardashev AV, Oduro A, Boersma L, Maass AH, Van Gelder IC, Wilde AA, van Dessel PF, Knops RE, Barr CS, Lupo P, Cappato R, Grace AA. An entirely subcutaneous implantable cardioverter-defibrillator. *N Engl J Med*. 2010;363:36-44
7. Myerburg RJ, Kessler KM, Castellanos A. Sudden cardiac death. Structure, function, and time-dependence of risk. *Circulation*. 1992;85:I2-10
8. Malmberg K, Yusuf S, Gerstein HC, Brown J, Zhao F, Hunt D, Piegas L, Calvin J, Keltai M, Budaj A. Impact of diabetes on long-term prognosis in patients with unstable angina and non-q-wave myocardial infarction: Results of the oasis (organization to assess strategies for ischemic syndromes) registry. *Circulation*. 2000;102:1014-1019

9. Pfeffer MA, McMurray JJ, Velazquez EJ, Rouleau JL, Kober L, Maggioni AP, Solomon SD, Swedberg K, Van de Werf F, White H, Leimberger JD, Henis M, Edwards S, Zelenkofske S, Sellers MA, Califf RM. Valsartan, captopril, or both in myocardial infarction complicated by heart failure, left ventricular dysfunction, or both. *N Engl J Med*. 2003;349:1893-1906
10. Shah AM, Uno H, Kober L, Velazquez EJ, Maggioni AP, MacDonald MR, Petrie MC, McMurray JJ, Califf RM, Pfeffer MA, Solomon SD. The inter-relationship of diabetes and left ventricular systolic function on outcome after high-risk myocardial infarction. *Eur J Heart Fail*. 2010;12:1229-1237
11. MacDonald MR, Petrie MC, Varyani F, Ostergren J, Michelson EL, Young JB, Solomon SD, Granger CB, Swedberg K, Yusuf S, Pfeffer MA, McMurray JJ. Impact of diabetes on outcomes in patients with low and preserved ejection fraction heart failure: An analysis of the candesartan in heart failure: Assessment of reduction in mortality and morbidity (CHARM) programme. *Eur Heart J*. 2008;29:1377-1385
12. Yeung CY, Lam KS, Li SW, Lam KF, Tse HF, Siu CW. Sudden cardiac death after myocardial infarction in type 2 diabetic patients with no residual myocardial ischemia. *Diabetes Care*. 2012;35:2564-2569
13. Junttila MJ, Barthel P, Myerburg RJ, Makikallio TH, Bauer A, Ulm K, Kiviniemi A, Tulppo M, Perkiomaki JS, Schmidt G, Huikuri HV. Sudden cardiac death after myocardial infarction in patients with type 2 diabetes. *Heart Rhythm*. 2010;7:1396-1403
14. www.cdc.gov/diabetes. 2014
15. www.professional.diabetes.org/facts. 2013
16. Puskas JD, Sadiq A, Vassiliades TA, Kilgo PD, Lattouf OM. Bilateral internal thoracic artery grafting is associated with significantly improved long-term survival, even among diabetic patients. *Ann Thorac Surg*. 2012;94:710-715; discussion 715-716
17. Greenspon AJ, Patel JD, Lau E, Ochoa JA, Frisch DR, Ho RT, Pavri BB, Kurtz SM. 16-year trends in the infection burden for pacemakers and implantable cardioverter-defibrillators in the united states 1993 to 2008. *J Am Coll Cardiol*. 2011;58:1001-1006
18. Deo SV, Shah IK, Dunlay SM, Erwin PJ, Locker C, Altarabsheh SE, Boilson BA, Park SJ, Joyce LD. Bilateral internal thoracic artery harvest and deep sternal wound infection in diabetic patients. *Ann Thorac Surg*. 2013;95:862-869
19. NDEI. 2015 american diabetes association (ADA) diabetes guidelines -summary of recommendations from ndei. 2015; 2015
20. Yancy CW, Jessup M, Bozkurt B, Butler J, Casey DE, Jr., Drazner MH, Fonarow GC, Geraci SA, Horwich T, Januzzi JL, Johnson MR, Kasper EK, Levy WC, Masoudi FA, McBride PE, McMurray JJ, Mitchell JE, Peterson PN, Riegel B, Sam F, Stevenson LW, Tang WH, Tsai EJ, Wilkoff BL. 2013 ACCF/AHA guideline for the management of heart failure: A report of the american college of cardiology foundation/american heart association task force on practice guidelines. *Circulation*. 2013;128:e240-327
21. McMurray JJ, Adamopoulos S, Anker SD, Auricchio A, Bohm M, Dickstein K, Falk V, Filippatos G, Fonseca C, Gomez-Sanchez MA, Jaarsma T, Kober L, Lip GY,

Maggioni AP, Parkhomenko A, Pieske BM, Popescu BA, Ronnevik PK, Rutten FH, Schwitter J, Seferovic P, Stepinska J, Trindade PT, Voors AA, Zannad F, Zeiher A, Bax JJ, Baumgartner H, Ceconi C, Dean V, Deaton C, Fagard R, Funck-Brentano C, Hasdai D, Hoes A, Kirchhof P, Knuuti J, Kolh P, McDonagh T, Moulin C, Reiner Z, Sechtem U, Sirnes PA, Tendera M, Torbicki A, Vahanian A, Windecker S, Bonet LA, Avraamides P, Ben Lamin HA, Brignole M, Coca A, Cowburn P, Dargie H, Elliott P, Flachskampf FA, Guida GF, Hardman S, Iung B, Merkely B, Mueller C, Nanas JN, Nielsen OW, Orn S, Parissis JT, Ponikowski P. ESC guidelines for the diagnosis and treatment of acute and chronic heart failure 2012: The task force for the diagnosis and treatment of acute and chronic heart failure 2012 of the european society of cardiology. Developed in collaboration with the heart failure association (HFA) of the ESC. *Eur J Heart Fail*. 2012;14:803-869

22. Ryden L, Grant PJ, Anker SD, Berne C, Cosentino F, Danchin N, Deaton C, Escaned J, Hammes HP, Huikuri H, Marre M, Marx N, Mellbin L, Ostergren J, Patrono C, Seferovic P, Uva MS, Taskinen MR, Tendera M, Tuomilehto J, Valensi P, Zamorano JL, Achenbach S, Baumgartner H, Bax JJ, Bueno H, Dean V, Erol C, Fagard R, Ferrari R, Hasdai D, Hoes AW, Kirchhof P, Knuuti J, Kolh P, Lancellotti P, Linhart A, Nihoyannopoulos P, Piepoli MF, Ponikowski P, Sirnes PA, Tamargo JL, Torbicki A, Wijns W, Windecker S, De Backer G, Ezquerra EA, Avogaro A, Badimon L, Baranova E, Betteridge J, Ceriello A, Funck-Brentano C, Gulba DC, Kjekshus JK, Lev E, Mueller C, Neyses L, Nilsson PM, Perk J, Reiner Z, Sattar N, Schachinger V, Scheen A, Schirmer H, Stromberg A, Sudzhaeva S, Viigimaa M, Vlachopoulos C, Xuereb RG. ESC guidelines on diabetes, pre-diabetes, and cardiovascular diseases developed in collaboration with the easd: The task force on diabetes, pre-diabetes, and cardiovascular diseases of the european society of cardiology (ESC) and developed in collaboration with the european association for the study of diabetes (easd). *Eur Heart J*. 2013;34:3035-3087
23. Moss AJ, Hall WJ, Cannom DS, Klein H, Brown MW, Daubert JP, Estes NA, 3rd, Foster E, Greenberg H, Higgins SL, Pfeffer MA, Solomon SD, Wilber D, Zareba W. Cardiac-resynchronization therapy for the prevention of heart-failure events. *N Engl J Med*. 2009;361:1329-1338
24. Arshad A, Moss AJ, Foster E, Padeletti L, Barsheshet A, Goldenberg I, Greenberg H, Hall WJ, McNitt S, Zareba W, Solomon S, Steinberg JS. Cardiac resynchronization therapy is more effective in women than in men: The MADIT-CRT (multicenter automatic defibrillator implantation trial with cardiac resynchronization therapy) trial. *J Am Coll Cardiol*. 2011;57:813-820
25. Jennison C TB. Group sequential methods with applications to clinical trials. 2000
26. Kaplan EL MP. Nonparametric estimation from incomplete observations. *J Am Stat Assoc*. 1958;53:457-481
27. Kalbfleisch P. *The statistical analysis of failure time data*. New York: John Wiley; 2004.
28. Collett D. *Modeling survival data in medical research.* London: Chapman & Hall; 1994.
29. Hall WJ LA. Sequential tests and estimates after overrunning based on maximum-likelihood ordering. *Biometrika*. 2002;89:699-707

30. D. C. Regression and life-tables. *J R Statist Soc*. 1972;34:187-220
31. Kong MH, Al-Khatib SM, Sanders GD, Hasselblad V, Peterson ED. Use of implantable cardioverter-defibrillators for primary prevention in older patients: A systematic literature review and meta-analysis. *Cardiol J*. 2011;18:503-514
32. Pfeffer MA MJ, Velazquez EJ, et al. Valsartan, captopril, or both in myocardial infarction complicated by heart failure, left ventricular dysfunction, or both. *N Engl J Med*. 2003;349:1893-1906