Improve SCA Study

Clinical Investigation Plan

Version 1.0

23 Dec 2013

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STEERING COMMITTEE

Nine steering committee members were chosen for this study and are listed below. Additional members may be added at a later date. The steering committee members are appointed by the sponsor to assist in development and execution of this investigation.

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1 INTRODUCTION

1.1 Study Purpose

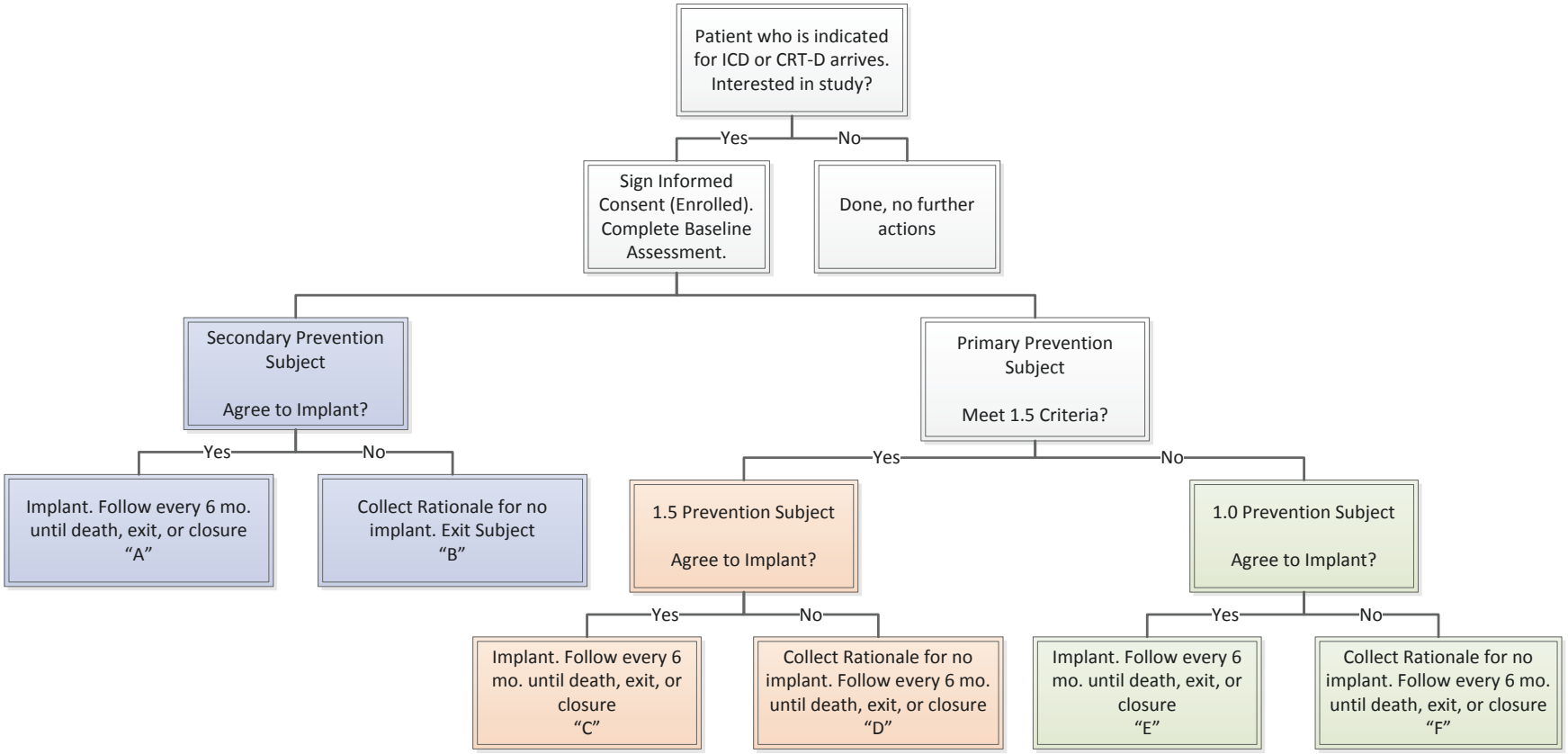
The purpose of this study is to demonstrate that primary prevention patients with one or more additional risk factors (1.5 prevention criteria: syncope/pre-syncope, non-sustained ventricular tachycardia (NSVT), frequent pre-ventricular contractions (PVCs), and low left ventricular ejection fraction (LVEF)) are at a similar risk of life-threatening ventricular arrhythmias (LTVA) when compared to secondary prevention patients, and would receive similar benefit from an implantable cardioverter defibrillator (ICD), or cardiac resynchronization therapy- defibrillator (CRT-D) implant. To assess the risk of LTVA, the primary endpoint will measure the rate of appropriate therapies delivered by an ICD (or CRT-D) following detection of ventricular tachycardia or ventricular fibrillation. Additional objectives evaluating mortality, cost effectiveness, reason for implant refusal, and Chagas disease will be analyzed.

All subjects enrolled in the study meet current AHA/ACC/HRS[1] or ESC[2] Class I guidelines for an ICD (or CRT-D) implant. For the purposes of this study, the impact of high voltage therapy on LTVAs is of primary interest, so throughout the document ICD includes devices with or without concomitant CRT therapy (CRT-D). Subjects who enroll in the study and proceed with a device implant must be implanted with a Medtronic single, dual, or triple chamber defibrillator that has received appropriate license or regulatory approval for the specific geography in which it is being implanted, and is released commercially by Medtronic. Any market-released, commercially available lead(s) can be used in this study.

1 Epstein AE, DiMarco JP, Ellenbogen KA, Estes NAM III, Freedman RA, Gettes LS, Gillinov AM, Gregoratos G, Hammill SC, Hayes DL, Hlatky MA, Newby LK, Page RL, Schoenfeld MH, Silka MJ, Stevenson LW, Sweeney MO. ACC/AHA/HRS 2008 guidelines for device-based therapy of cardiac rhythm abnormalities: executive summary: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Revise the ACC/AHA/NASPE 2002 Guideline Update for Implantation of Cardiac Pacemakers and Antiarrhythmia Devices). Circulation. 2008;117:2820–2840.

2 Zipes DP, Camm AJ, Borggrefe M, Buxton AE, Chaitman B, Fromer M, Gregoratos G, Klein G, Moss AJ, Myerburg RJ, Priori SG, Quinones MA, Roden DM, Silka MJ, Tracy C. ACC/AHA/ESC 2006 guidelines for management of patients with ventricular arrhythmias and the prevention of sudden cardiac death: a report of the American College of Cardiology/American Heart Association Task Force and the European Society of Cardiology Committee for Practice Guidelines (Writing Committee to Develop Guidelines for Management of Patients With Ventricular Arrhythmias and the Prevention of Sudden Cardiac Death). J Am Coll Cardiol 2006;48:e247–e346

Figure 1: Study Design



1.2 Study Description and Scope

Medtronic, Inc. is sponsoring the Improve SCA study, a prospective, non-randomized, non-blinded, global, interventional, multi-site post-market study. The study is expected to be conducted at approximately 100 sites worldwide, and to achieve approximately 2300 implants, the study is expected to enroll approximately 4800 subjects. However, a sample size re-estimation will occur partway through the study, so the actual sample size may be as high as 8000 subjects enrolled (see page 52). Based on input from the Improve SCA steering committee, it is estimated that sites will enroll an average of 3 subjects per site per month.

Participating geographies are expected to include, but are not limited to: Association of Southeast Asian Nations (ASEAN), Central and Eastern Europe (CEE), Greater China (including China and Taiwan), India, Latin America, Middle East and Africa (MEA), and South Korea.

There is no minimum requirement for enrollments per site for this study. To ensure a widespread distribution of data and minimize site bias in study results, the maximum number of subjects enrolled at a single site will be approximately 5% of the expected total study subjects.

It is anticipated enrollment will take approximately 2 years, beginning in April 2014; however, enrollment could take longer if there is a sample size increase as indicated above. The study will be closed approximately two years after the final subject enrollment. At approximately 22 months past the final enrollment, centers will be notified that study closure is about to occur and that they should attempt to make one final study contact with each subject to maximize overall study follow-up.

Both primary and secondary prevention subjects will be included in the study. Primary prevention subjects will be further divided into two groups, depending on whether or not they meet the 1.5 prevention criteria described above in Section 1.1. In each of these groups, there are two non-randomized arms: subjects who receive an implant, and subjects who do not receive an implant. Therefore, there are a total of six arms in the study (labeled A-F), described above in Figure 1. The primary analysis focuses on comparing arms A (secondary prevention subjects who receive an implant) and C (1.5 prevention subjects who receive an implant) for time to appropriately treated ventricular tachycardia/ventricular fibrillation (VT/VF). In order to compare arms and adjudicate VT/VF, Medtronic devices must be used.

Subjects who receive an implant of a non-Medtronic ICD/CRT-D should be exited from the study following implant, as this will impact the ability to determine the appropriateness of ICD/CRT-D therapies.

2 BACKGROUND AND JUSTIFICATION

The use of ICDs in patients who have survived an episode of sudden cardiac arrest (SCA) or sustained ventricular tachycardia (VT) is well established. However, the use of ICDs in patients without a history of SCA or sustained VT episode but at high risk of such an episode is less established in some geographies. The prevention of sudden cardiac death is an important goal, and the ICD plays a vital role by terminating sudden or unexpected arrhythmias leading to sudden cardiac arrest.

Secondary prevention refers to the use of ICDs for the prevention of sudden cardiac death in patients who have survived a prior sudden cardiac arrest or sustained VT, whereas primary prevention refers to the use of ICDs in individuals who are at risk for, but have not yet had a documented episode of sustained VT, VF, or resuscitated cardiac arrest.

The intent of the Improve SCA study is to examine four risk factors in primary prevention patients which may be associated with a higher risk of SCA, thus forming a '1.5 prevention' patient group. These 1.5 criteria are: syncope or pre-syncope, very low ejection fraction (LVEF <25%), non-sustained ventricular tachycardia (NSVT), and frequent premature ventricular contractions (PVCs). The results of this study may be beneficial in helping clinicians identify and refer the highest-risk primary prevention patients for ICDs, help local societies expand guidelines to include primary prevention of SCA utilizing ICDs, and provide additional local evidence to allow patients to make an informed decision whether to receive an ICD.

The 1.5 prevention criteria were developed in 2008 in collaboration with physicians in China to assist in the identification of primary prevention patients at highest risk of SCA. While each of these factors have been independently associated with an increased risk of LTVA and/or SCA, no prospective data have been collected to determine if one or more of these factors in a primary prevention ICD population is associated with an increased likelihood of receiving an appropriate ICD therapy. Furthermore, the geographies represented in the Improve SCA study have been underrepresented in previous primary prevention trials and, thus, there are limited local data demonstrating the benefit of ICDs in these geographies' primary prevention patients.

2.1 Syncope or pre-syncope

Pre-syncope is dizziness, lightheadedness, or feeling faint, while syncope refers to a sudden loss of consciousness with loss of postural tone with spontaneous recovery. ICD therapy is indicated for secondary prevention of SCA (Class IA) in patients with syncope of undetermined origin with clinically relevant, hemodynamically significant sustained VT or VF induced at electrophysiology study[3]. In addition, an ICD is Class IIa indicated for primary prevention of SCA in patients with unexplained syncope, significant LV dysfunction, and non-ischemic

3 Epstein AE, DiMarco JP, Ellenbogen KA, Estes NAM III, Freedman RA, Gettes LS, Gillinov AM, Gregoratos G, Hammill SC, Hayes DL, Hlatky MA, Newby LK, Page RL, Schoenfeld MH, Silka MJ, Stevenson LW, Sweeney MO 2012 ACCF/AHA/HRS focused update incorporated into the ACCF/AHA/HRS 2008 guidelines for device-based therapy of cardiac rhythm abnormalities: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines and the Heart Rhythm Society. J Am Coll Cardiol 2013;61:e6–75. Available online at: www.hrsonline.org

dilated cardiomyopathy. Thus, a history of syncope in patients with heart failure may suggest an increased risk of a future LTVA.

In SCD-HeFT, 162 (6%) patients had syncope before randomization, 356 (14%) had syncope after randomization, and 46 (2%) had syncope before and after randomization[4]. Syncope was associated with appropriate therapies in the ICD arm and across study arms and it was associated with increased mortality risk.

Sánchez et al. evaluated 102 consecutive patients from Sept. 1996 to Dec. 2000 who presented with unexplained syncope, depressed left ventricular function, regardless of etiology, and a negative electrophysiologic study (EPS).[5] The study suggested that empiric ICD therapy improved long-term outcomes in patients with unexplained syncope, ischemic or non-ischemic cardiomyopathy, and negative EPS.

Of 7814 participants in the Framingham Heart Study followed for an average of 17 years (1971-1998), 822 reported syncope.[6] Cardiac syncope doubled the risk of death from any cause and increased the risk of fatal and nonfatal cardiovascular events. Regardless of cardiovascular disease history, participants with a diagnosis of cardiac syncope were more likely to have a worse outcome than those without syncope.

A collaborative study between a cardiology and neurology department examined five years follow-up of 183 patients hospitalized for syncope. They reported the etiological diagnosis of syncope was of cardiovascular cause in 73% of patients[7] (5 % of non-cardiovascular cause, 22% of unknown cause). Syncope of cardiac causes had the highest mortality rate, of 63%. Racco et al. suggested that cardiac syncope had the worst prognosis, and therefore needed recurrent clinical examinations and prompt treatment.

The relation of syncope to sudden death was evaluated in 491 consecutive patients without a history of cardiac arrest.[8] The actuarial incidence of sudden death by 1 year was significantly greater in patients with (45%) than in those without (12%, $p < 0.00001$) syncope.

Collectively, these data suggest that a history of syncope may be an important risk factor in patients with cardiovascular disease at risk for SCA.

2.2 Low ejection fraction (low EF)

A patient's left ventricular ejection fraction, or LVEF, is the percentage of blood in the lower chamber of the heart that is pumped out from the heart with each heartbeat. A normal EF is 50% or more. An EF of ≤35% is currently considered a

4 Olshansky B, Poole JE, Johnson G, et al. Syncope Predicts the Outcome of Cardiomyopathy Patients. Analysis of the SCD-HeFT Study. JACC 2008; 51:1277-1282.
5 Sánchez JM, Katsiyiannis WT, Gage BF, et al. Implantable cardioverter-defibrillator therapy improves long-term survival in patients with unexplained syncope, cardiomyopathy, and a negative electrophysiologic study. Heart Rhythm 2005; 2:267-373.
6 Soteriades ES, Evans JC, Larson MG, et al. Incidence and Prognosis of Syncope. N Engl J Med 2002; 347:878-885.
7 Racco F, Sconocchini C, Alesi C, et al. Long-Term Follow-Up after Syncope. A Group of 183 Patients Observed for 5 Years. Minerva Cardioangiol 2000; 48:69-78.
8 Middlekauff HR, Stevenson WG, Stevenson LW, et al. Syncope in Advanced Heart Failure: High Risk of Sudden Death Regardless of Origin of Syncope. JACC 1993; 21:110-116.

primary risk factor for SCA[9], and in this study, an EF less than 25% is considered very low EF, an indication for a 1.5 prevention patient.

LVEF has been shown to significantly predict mortality. Data compiled from four randomized trials, pooled to create a cohort of 2828 patients, showed that each 10% reduction in LVEF between 15 and <40% independently conferred a 39% increase in risk for arrhythmic cardiac mortality over a 2-year period.[10] The lowest number of patients needed to prevent one death with an ICD was when an EF ≤25%.

2.3 Non-sustained ventricular tachycardia (NSVT)

Ventricular tachycardia (VT) is a rapid heartbeat originating in the ventricles. VT is potentially life-threatening because it may lead to ischemia, ventricular fibrillation (VF), asystole, and sudden cardiac death. In this study, VT is defined as three or more consecutive ventricular beats at a rate of more than 100 beats per minute. Non-sustained ventricular tachycardia (NSVT) is VT which spontaneously terminates within 30 seconds. Otherwise the VT is defined as sustained VT.

A meta-analysis of 11 studies (published from 1989 - 2007; N=4387) found NSVT to be a statistically significant predictor for arrhythmic events in patients with LV dysfunction.[11]

An analysis by Moore et al. of the SCD-HeFT trial looked at overall mortality by NSVT episode frequency. They found that in 673 patients who had NSVT, 271 had 1 NSVT and 402 had ≥1 NSVT episodes on baseline Holter Monitor. The authors concluded that the presence of ≥2 NSVT episodes conferred an increased overall mortality when compared to less frequent NSVT episodes.[12]

A Canadian trial that looked at predictors of appropriate ICD therapy in patients receiving primary prevention ICDs showed that ICD therapy occurred in 19% of 421 primary prevention patients with both ischemic and non-ischemic cardiomyopathy and was predicted most strongly by NSVT and a lack of beta blocker use.[13]

Results from 1135 primary prevention patients from the OMNI study showed a significant correlation between presence of device-detected NSVT and true VT/VF episodes.[14] The vast majority of (91.3%) patients with true VT/VF episodes also

9 Epstein AE, DiMarco JP, Ellenbogen KA, Estes NAM III, Freedman RA, Gettes LS, Gillinov AM, Gregoratos G, Hammill SC, Hayes DL, Hlatky MA, Newby LK, Page RL, Schoenfeld MH, Silka MJ, Stevenson LW, Sweeney MO 2012 ACCF/AHA/HRS focused update incorporated into the ACCF/AHA/HRS 2008 guidelines for device-based therapy of cardiac rhythm abnormalities: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines and the Heart Rhythm Society. J Am Coll Cardiol 2013;61:e6–75. Available online at: www.hrsonline.org

10 Yap YG, Duong T, Bland JM, et al. Optimising the dichotomy limit for left ventricular ejection fraction in selecting patients for defibrillator therapy after myocardial infarction. Heart. 2007 Jul;93(7):832-6. Epub 2007 Jan 19.

11 Sousa M, Morillo C, Rabelo F, et al. Non-sustained Ventricular Tachycardia as a Predictor of Sudden Cardiac Death in Patients with Left Ventricular Dysfunction: A Meta-Analysis. Eur J Heart Fail 2008; 10:1007-1014.

12 Chen J, Johnson G, Hellkamp A, et al. Rapid Rate Non-sustained Ventricular Tachycardia found on ICD Interrogation: Relationship of NSVT to Outcomes in the SCD-HeFT Trial. DOI: 10.1016/j.jacc.2013.02.046.

13 Verma A, Sarak B, Kaplan A, et al. Predictors of Appropriate Implantable Cardioverter Defibrillator (ICD) Therapy in Primary Prevention Patients with Ischemic and Nonischemic Cardiomyopathy. PACE 2010; 33:320-329.

14 Ziegler P, Zhang S, Arora V, et al. Is the Presence of Non-Sustained Ventricular Tachycardias Associated with True Ventricular Tachycardias and Ventricular Fibrillation in Primary Prevention Patients? Presented at HRS 2013.

have device-detected episodes of NSVT, and extended periods of NSVT monitoring may be useful for identifying patients who would derive a greater benefit from ICD implantation for primary prevention.

2.4 Frequent premature ventricular contractions (PVCs)

Premature ventricular contractions (PVCs), also known as premature ventricular complexes or ventricular premature contractions (VPCs), are abnormal heartbeats that begin in the ventricles. Because the beat occurs early, PVCs interrupt the normal synchrony of the heartbeat and can cause the heart to pump blood less effectively. A link between PVCs and ventricular tachycardias is well documented.

Sixty episodes of VF among 29 patients were identified in MADIT II trial (n = 724 primary prevention ICD patients randomized from 1232). A single PVC initiated 46 (77%) VF episodes whereas an SLS sequence (short-long-short; ectopic activity with a disruption of the baseline rhythm by a premature depolarization, followed by a pause, then by a short-coupled premature depolarization) accounted for 14 (23%) episodes. The study showed that VF is more commonly initiated by a PVC than by an SLS sequence among the MADIT II population.[15]

In a study by Hadhjoo et al. of 50 patients with an ICD, 182 episodes of monomorphic VT were examined. PVC-induced episodes were the most frequent pattern (58%).[16] Saeed et al. showed that patients with poor EF (<35%) had more PVCs immediately preceding VT and high frequency of extra-systolic initiation (66%) in 268 episodes of monomorphic VT identified in 52 patients.[17] Taylor et al. examined 260 episodes of polymorphic and monomorphic VT, and categorized the initiating beat of the VT; 85% were initiated by late-coupled ventricular ectopic beats, 13% by early-coupled ectopic beats, and only 2% by SLS sequences.[18]

In 69 patients implanted with ICD (21 for primary prevention), 364 episodes of VT in 40 post-infarct and 29 idiopathic dilated cardiomyopathy (IDC) patients were analyzed. Onset with variable patterns of PVC was observed in 45% and 65% and short-long-short in 29% and 14% of post MI and IDC patients, respectively.[19]

Roelke et al. evaluated 73 spontaneous monomorphic VT episodes stored in ICDs among 22 post-infarction patients.[20] VT onset was more common with a single PVC (45%) than with either 2 (22%) or more (33%) PVCs.

Finally, results from the GISSI-2 study showed that in 8676 patients followed for 6 months post-MI, ventricular arrhythmias were present in approximately 64% of the

15 Anthony, R., et al., Mechanisms of VF Initiation in MADIT II Patients with ICDs, PACE, 2008, 31: 4-10.
16 Haghjoo M, Arya A, Sadr-Ameli AS. Pattern of Initiation of Monomorphic Ventricular Tachycardia in Recorded Intracardiac Electrograms. India Pacing Electrophysiol J 2005; 5(4):263-271.
17 Saeed M, Link MS, Mahapatra S, et al. Analysis of Intracardiac Electrograms Showing Monomorphic Ventricular Tachycardia in Patients with Implantable Cardioverter-Defibrillators. Am J Cardiol 2000; 85:580-587.
18 Taylor E, Berger R, Hummel J, et al. Analysis of the Pattern of Initiation of Sustained Ventricular Arrhythmias in Patients with Implantable Defibrillators. J Cardiovasc Electrophysiol 2000; 11:719-726.
19 Grimm W, Walter M, Menz V, et al. Circadian Variation and Onset Mechanisms of Ventricular Tachyarrhythmias in Patients with Coronary Disease versus Idiopathic Dilated Cardiomyopathy. PACE 2000; 23:1939-1943.
20 Roelke M, Garan H, McGovern B, et al. Analysis of the Initiation of Spontaneous Monomorphic Ventricular Tachycardia by Stored Intracardiac Electrograms. JACC 1994; 23:117-122.

patients, and almost 20% showed frequent (more than 10 PVCs per hour). In addition, NSVT was present in 6.8% of the patients.[21]

These data suggest that PVCs are a common initiator of ventricular tachyarrhythmias and a high burden of PVCs is associated with an increased risk of LTVA.

2.5 1.5 Prevention Definition

Based on the data above, a primary prevention patient is considered to be in the 1.5 prevention subgroup if they meet one or more of the conditions in Table 4.

21 Maggioni AP, Zuanetti G, Franzosi MG, et al. Prevalence and Prognostic Significance of Ventricular Arrhythmias after Acute Myocardial Infarction in the Fibrinolytic Era: GISSI-2 Results. Circulation 1993; 87:312-322.

Table 4: 1.5 Prevention Definition

Condition	Details

Syncope or pre-syncope	Within the past 12 months:
	• Pre-syncope/ dizziness/ lightheadedness, due to suspected VT
	• Syncope, due to suspected VT
	• Unexplained Syncope or pre-syncope, after ruling out these causes:
	  • Syncope, due to carotid sinus hypersensitivity
	  • Vasovagal Syncope
	  • Syncope, due to bradycardia
	  • Syncope, due to SVT

Low LVEF	LVEF < 25% measured within 6 months of enrollment or implant. If history of MI, LVEF must be collected at least: • 40 days post-MI if there was no revascularization • 90 days post-MI if there was revascularization (e.g., percutaneous coronary intervention (PCI), coronary artery bypass graft (CABG)
NSVT	A history of NSVT since HF diagnosis in Medical Records OR A history of NSVT documented from an IPG (implantable pulse generator) on an EGM strip in the medical records, where the physician rules out SVT or ventricular artifact OR NSVT measured on an ambulatory monitor (e.g., Holter, patch) WHERE Non-sustained VT is defined as 3 or more consecutive beats at >100 beats per minute lasting less than 30 seconds.
Frequent PVCs	History of Frequent PVCs within 12 months OR Frequent PVCs on an ambulatory monitor (e.g., Holter) test lasting at least 20 hours OR A history of frequent PVCs documented from an IPG on an EGM strip in the medical records, where the physician rules out SVT or ventricular artifact. WHERE “Frequent PVCs” is defined as an average of 10 or more PVCs per hour while monitored If history of MI, PVCs must be collected at least: • 40 days post-MI if there was no revascularization • 90 days post-MI if there was revascularization (e.g., percutaneous coronary intervention (PCI), coronary artery bypass graft (CABG)

2.6 ICD and CRT-D therapy

ICD therapy terminates ventricular tachyarrhythmias and improves survival of patients at risk for sudden cardiac death.[22,23] Medtronic ICDs/CRT-Ds provide anti-tachycardia pacing (ATP) and shocks to terminate tachycardias originating in the ventricles – ventricular tachycardia (VT) and ventricular fibrillation (VF). Medtronic has engaged in over 20 years of research to establish ICD programming guidelines and develop new detection algorithms to reduce or eliminate inappropriate and unnecessary shocks that result in significant patient morbidity. The PainFree SST trial demonstrated that only about 2% of ICD/CRT-D patients will experience an inappropriate shock after one year of follow-up using the most recent Medtronic ICD/CRT-Ds and current programming recommendations[24,25]. While the Improve SCA trial does not require use of the most recent Medtronic ICD/CRT-Ds, doing so will assure the lowest possible inappropriate shock rate when using the required ICD programming described below. These requirements have been developed and proven effective in the Medtronic research studies.

The table below provides the highlights of the Improve SCA programming requirements and the study that demonstrated the value of the parameter. Older devices will not have all programming capabilities. Due to the large number of potential ICD/CRT-D devices to be implanted, tools with specifications for individual devices will be provided to investigators under separate cover as needed.

22 AVID Investigators. comparison of antiarrhythmic-drug therapy with implantable defibrillators in patients resuscitated from near-fatal ventricular arrhythmias. NEJM 1997;337:1576-1583

23 Bardy GH, Lee KL, Mark DB, et al. Amiodarone or an implantable cardioverter-defibrillator for congestive heart failure. NEJM 2005; 352:225-237.

24 Schloss EJ, Auricchio A, Kurita T, et al. PainFree SST Trial Primary Results Low Shock Rates in Patients with Dual and Triple Chamber ICDs Using Novel Detection Algorithms. Heart Rhythm Society, Denver CO, May 10, 2013.

25 Meijer A, Auricchio A, Kurita T, et al. PainFree SST Trial Primary Results Inappropriate shock rates in patients with single chamber ICDs using a novel suite of detection algorithms. EUROPACE, 25 Jun 2013.

Table 5: Improve SCA Programming Requirements

Key Programming Parameters	Evidence based Requirement	Study Source
VFDI	300 ms	PainFree SST[26,27]
VF NID	30/40	PREPARE[28], RELEVANT[29], ADVANCE III[30]
VTDI	360 ms	PainFREE II[31], MVP [32], PainFree SST
VT NID	24	PainFree SST
Wavelet	ON, 70%	WAVE[33], PainFree SST
PR Logic	ON	GEM DR[34], EMPIRIC[35]
SVT Limit	260 ms	PainFree SST
LIA	ON	PainFree SST
T Wave Rejection	ON	PainFree SST
Lead Noise Rejection	ON	PainFree SST
ATP for VT	ON, 8@88%	PainFREE II, EMPIRIC,
ATP During Charge	ON, 8@88%	EnTrust Clinical Trial

26 Schloss EJ, Auricchio A, Kurita T, et al. PainFree SST Trial Primary Results Low Shock Rates in Patients with Dual and Triple Chamber ICDs Using Novel Detection Algorithms. Heart Rhythm Society, Denver CO, May 10, 2013.
27 Meijer A, Auricchio A, Kurita T, et al. PainFree SST Trial Primary Results Inappropriate shock rates in patients with single chamber ICDs using a novel suite of detection algorithms. EUROPACE, 25 Jun 2013
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3 SYSTEM DESCRIPTION AND INTENDED USE

Subjects with an ACC/AHA/HRS or ESC Class I guideline-recommended need for an ICD (or CRT-D) implant for either primary or secondary prevention of SCA may be enrolled in the study. Subjects who enroll in the study and proceed with a device implant must be implanted with a Medtronic single, dual, or triple chamber defibrillator that has received appropriate license or regulatory approval and is commercially available by Medtronic in the geography in which the implant will take place. Any market-released, commercially available lead(s) can be used in this study.

The study will be conducted using the components described in the table below. Instructions for use of the devices used in this study are provided in their respective manuals. Additional study components which may be utilized in this study for subjects who receive an implant include Medtronic CareLink® Monitor and CareLink® Network, and Medtronic programmers. These components are described in the following sections.

Table 6: System Component Information

Model Number	Component	Investigational or Market-released
Device Components		
--	Any Medtronic single, dual, triple chamber ICD or CRT-D device	Market-released
--	Any right ventricular (RV) lead	Market-released
--	Any right atrial (RA) lead (if part of dual chamber ICD/CRT-D system)	Market-released
--	Any left ventricular (LV) lead (if part of CRT-D system)	Market-released
Accessory Components		
2090	Medtronic Programmer	Market-released
2490C	Medtronic CareLink Monitor (where applicable)	Market-released
2067 or 2067L	Medtronic RF telemetry head (where applicable)	Market-released

3.1 Market-Released Medtronic ICD or CRT-D Device

Subjects who enroll in the study and proceed with a device implant must be implanted with a Medtronic single, dual, or triple chamber defibrillator that has received appropriate license or regulatory approval and is commercially available by Medtronic in the geography in which the implant will take place. Examples from the Medtronic family of devices include but are not limited to the Medtronic InSync III Protect, Marquis, Secura, Consulta, Maximo II, Concerto, Virtuoso, Protecta, Viva, Evera, Egida, Evera, EnTrust, Brava, GEM III. Other devices may become available during the course of the clinical study and may be used if the aforementioned criteria are met. The device must not have been previously implanted in another patient.

3.1 Market-Released Lead(s)

Any market-released, commercially available lead(s) may be used in this study. Any RV lead may be used, and an RA or LV lead may be implanted if deemed necessary per the physician's medical assessment. Examples include the Medtronic Attain Ability or the Medtronic CapSureFix leads. Any lead under recall, even if not in the country of implant, should not be implanted in study patients.

3.2 Medtronic CareLink Monitor and Medtronic CareLink Network

The Medtronic CareLink Monitor and the Medtronic CareLink Network are indicated for use in the transfer of patient data from some Medtronic implantable cardiac devices based on physician instructions and as described in the product manual. These products are not a substitute for appropriate medical attention in the event of an emergency and should only be used as directed by a physician.

The Medtronic CareLink Network enables subjects to remotely transfer data from their device to the clinic. Subjects may be requested to use the Medtronic CareLink Monitor to send their device data to the clinic. Study site personnel can access the data by logging onto the CareLink website via the internet.

The use of the Medtronic CareLink Home Monitor is not required for this study and it may not be available in all participating geographies. However, if the subject uses CareLink to transmit their device data, the data may be used in the analysis of the study objectives, where allowed by local law.

3.3 Market-Released Medtronic Programmer

Medtronic's market-released Model 2090 programmer (or future models, which become market released in the geographies where this study takes place) must be available at each site to support study visits. Programmers will be used to gather lead electrical data, interrogate devices, program devices, and save device data.

3.4 Changes to the Study System

Medtronic may incorporate additional Medtronic ICD/CRT-D devices with appropriate therapies as well as Medtronic and non-Medtronic leads into this study as they receive appropriate license or regulatory approval. Likewise, future CareLink monitors, network updates, and programmers may also be incorporated into this study; study documentation will be updated if and where necessary.

4 REGULATORY COMPLIANCE

The Improve SCA study is a prospective, non-randomized, non-blinded, global, interventional, multi-site, post-market study, as specific programming and follow-up visits are required (i.e., this is not a registry study). This study is required to be in compliance with the Clinical Investigation Plan (CIP), Clinical Trial Agreement (CTA) and local laws/regulations within respective geography the study is being conducted.

The Improve SCA study was designed to reflect good clinical practice (GCP) principles including the protection of the rights, safety and well-being of human subjects, controls to ensure the scientific conduct and credibility of the clinical investigation and the definition of responsibilities of the sponsor and investigators.

The study will be conducted according to federal, national and local laws, regulations, standards, and requirements of the countries/geographies where the study is being conducted. The study will also be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki. The principles of the Declaration of Helsinki are implemented in this study by means of the Patient Informed Consent (PIC) process, MEC/IRB/HREC (all henceforth referred to as an “Ethics Committee”) approval, study training, clinical trial registration, pre-clinical testing, risk benefit assessment, and publication policy.

- In Central and Eastern Europe and Middle East and Africa, local regulations will be followed.
- In India, applicable India regulations will be followed.
- In Latin America, applicable local regulations will be followed.
- In China, applicable local regulations will be followed.
- In Taiwan, applicable local regulations will be followed.
- In Korea, Standards for Management of Clinical Trials for Medical Devices (KGCP) <Amended on March 23, 2013> (Attachment 2-2 of Enforcement Regulations of the Medical Device Act) and other applicable Korean regulations will be followed.
- In Singapore, Health Products (Medical Devices) Regulations 2010 and other local applicable regulations will be followed.
- In Malaysia, National Medical Research Register (NMRR) requirements are applicable although the medical device is not regulated in Malaysia, e.g., Guidelines for Application of Clinical Trial Import License and Clinical Trial Exemption in Malaysia. In addition, applicable local regulations will be followed.

The study will be publicly registered prior to first enrollment in accordance with the Declaration of Helsinki on http://clinicaltrials.gov (PL 110-85, Section 810(a)).

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

- Medtronic
- Principal investigators (where required by local law, e.g., Malaysia, China, India)
- Geography-specific regulatory authorities (if regulatory approval is required)
- Each site’s Ethics Committee

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

Each site's Ethics Committee will also be required to approve any subject recruitment materials, if used.

5 METHODOLOGY

5.1 Study Objectives

This prospective, non-randomized, interventional, non-blinded, multi-site global post-market study will evaluate the outcomes of ICD patients who meet 1.5 prevention criteria, as described in Section 6.7.

5.1.1 Primary objective

- Demonstrate that appropriate VT/VF therapy rates (shock and ATP) for subjects meeting 1.5 prevention criteria implanted with a Medtronic device (ICD/CRT-D) are equivalent (within 30%) to rates in subjects meeting secondary prevention criteria.

5.1.2 Secondary objective

- Compare the mortality rates for patients meeting 1.5 prevention criteria between those implanted with a device (ICD/CRT-D) and those not implanted.

[redacted]

5.2 Subject Selection Criteria

Patients of both genders who have a guideline recommendation for a single, dual, or triple chamber defibrillator will be approached regarding enrollment in the study. Subjects receiving a device implant will be required to have a Medtronic device implanted because data stored in the device will be retrieved and analyzed by Medtronic as part of the study.

Subjects currently implanted with an implantable pulse generator (IPG) are eligible for participation in the study, assuming the previous device is explanted at the time of implant.

5.2.1 Inclusion criteria

- Subject has a Class I indication for implantation of an ICD according to the ACC/AHA/HRS or ESC Guidelines
- Subject (or subject's legally authorized representative) is willing and able to sign and date the Patient Informed Consent Form.

5.2.2 Exclusion criteria

- Subject is ≤ 18 years of age
- Subject with any exclusion criteria as required by local law (e.g., age, pregnancy, breast feeding)
- Subject is enrolled in a concurrent study that has not been approved for concurrent enrollment by the Medtronic Clinical Trial Leader
- Subject has any contraindication for ICD/CRT-D

Ethics Committee approval of the Improve SCA Clinical Investigation Plan and Patient Informed Consent Form must be obtained for each site, prior to that site enrolling patients in the study. Refer to Section 6.2 for a more complete list of requirements which must be met prior to enrolling patients in the study. Enrollment of the subject must occur prior to performing any study-required testing (e.g., ambulatory monitoring for testing of 1.5 Criteria).

5.3 Minimization of Bias

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

- Subject demographics will be collected at baseline for potentially analyzing differences that may affect the endpoints.
- All study clinicians and Medtronic personnel will be trained on the corresponding aspects of the study using standardized training materials.
- All study clinicians and Medtronic personnel will be trained on, and required to follow the CIP.
- An Episode Review Committee will be formed to review and classify arrhythmia episodes based on study definitions.
- To ensure a wide distribution of data between sites, the maximum enrollments per site will be no more than 5% of the expected enrollment.

6 STUDY PROCEDURES

All clinical investigators managing the subject's heart failure must be qualified physicians, experienced in the diagnosis and treatment of subjects with heart failure. All EP/implanting physicians must be experienced and/or trained in the handling of ICD and/or CRT-D devices. Site personnel training and task delegation by the Principal Investigator will be completed prior to participation in this study.

Medtronic will provide study training relevant and pertinent to the involvement of personnel conducting study activities and investigator responsibilities.

Medtronic personnel may perform the following activities during the study, under supervision of the Principal Investigator:

- Technical support at all visits under the supervision of a study investigator, but no data entry, shall be performed by Medtronic personnel or their representatives at sites
- Monitoring and auditing activities

6.1 Investigator Selection Criteria

The following requirements were considered in the selection of sites:

- Primary Investigator has experience with the implantation of ICDs and/or CRT-Ds
- Site has the ability (high speed internet) and willingness to submit data through an internet based electronic data capture (EDC) system (Oracle Clinical)
- Site has adequate volume of patients meeting all of the inclusion/none of the exclusion criteria such that the site can target a minimum of 3 study enrollments per month, with at least 1/3 of enrollments expected to be primary prevention patients
- Site has Medtronic market-released programmer available for all study visits
- Site has sufficient staff (at least one primary investigator and study coordinator/other staff) and Medtronic support to execute and maintain compliance to the protocol, including data collection and record retention requirements
- Acknowledgement of, and agreement to, comply with applicable regulatory and local requirements governing clinical study conduct

6.2 Site Activation

During the activation process (prior to a site's involvement in study activities), Medtronic personnel or delegates will train site personnel on the clinical investigation plan, relevant standards and regulations, patient informed consent (PIC) process, written clinical trial agreements, and data collection and reporting tools. If new members join the study site team, they must receive training on the applicable clinical study requirements relevant to their role before contributing to the clinical study.

Prior to performing study-related activities, all local regulatory requirements must be fulfilled, including, but not limited, to the following:

- Ethics Committee approval (and voting list, as required by local law) of the most current version of the CIP and Patient Informed Consent form
- Regulatory authority approval or notification (as required per local law)
- Fully executed Clinical Trial Agreement (CTA) , including a description of financial aspects
- Current (within the last two years) of Principal Investigator
    - CV must be signed and dated (Central & Eastern Europe, Middle East and Africa, Latin America; best practice in all other geographies)
    - CV of other investigators prior to their activation, and CV of other key members of the investigation site team where required by local law
- Documentation of delegated tasks
- Completion and documentation of study training.

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

In addition, all participating site staff must be trained on the current version of the CIP pertinent to their role in the study and must be delegated by the Principal Investigator to perform study-related activities.

Medtronic will provide each study site with written documentation of study site/investigator readiness in the form of a Site Activation Letter; this letter must be received by the site prior to subject enrollment. If additional investigators are added, they will be notified of readiness once all requirements are met.

6.3 Equipment Requirements

The following equipment must be available at each site to support study activities (to be verified before site activation):

- Access to equipment to measure ejection fraction, including but not limited to an echocardiography machine, Cardiac Magnetic Resonance Imaging (MRI), or Multi Gated Acquisition Scan (MUGA).
- Ambulatory method of measuring PVC burden and NSVT for at least 24 hours at baseline (e.g., Holter, CardioNet™ Mobile Cardiac Outpatient Telemetry (MCOT)™).

Calibration and maintenance of equipment listed above will be done by the site (documented proof of said activities should be available upon request by Medtronic).

6.4 Data Collection

Clinical data is collected at designated time points throughout the study. Data will be collected using an electronic data management system for clinical studies. Anonymized data will be collected, and data will be stored in a secure, password-protected database which will be backed up each day. Data will be reviewed using programmed and manual data checks. Data queries will be made available to study sites for resolution. Study management reports may be generated by

Medtronic to monitor data quality and study progress. At the end of the study, the data will be frozen and retained indefinitely by Medtronic. Data collection requirements are summarized in Table 7 below.

Table 7: Data collection and study procedure requirements at subject visits

Study Procedure	Baseline	Implant/ Implant Refusal	Contact Visits (scheduled and unscheduled)	Device Change	Study Exit/ Death
Patient informed consent	x				
Eligibility Verification (Inclusion/ exclusion assessment)	x				
Baseline assessment (e.g., Demographics, NYHA assessment, indication for implant)	x				
Medical History	x				
Cardiovascular Medications	x		x (Amiodarone only)		
1.5 Criteria Assessment	x		(6 month visit)	x***	
QoL Assessment (EQ-5D)	x**		x** (6 month visit)		
Implant/Implant Refusal		x			
Device Interrogation File (.pdd) or CareLink Transmission		x*	x*	x (before & after)	x*‡
Vital status			x		x
Study Deviations	As they occur				
Subject Exit					
Subject Death					

*if subject receives device implant
**1.5 subjects only
*** if new implant of an ICD/CRT-D
‡if possible

6.5 Patient Informed Consent Process

Patient informed consent (PIC) is defined as legally effective, documented confirmation of a subject's (or their legally authorized representative or guardian) voluntary agreement to participate in a particular clinical study after sufficient information has been given to the subject on all aspects of the clinical study that are relevant to the subject's decision to participate. This process includes obtaining a PIC and other privacy language as required by law that has been approved by the study site's Ethics Committee and personally signed and dated by the subject (or their legally authorized representative or guardian). A subject may only give his/her consent after information has been given to the subject on all aspects of the clinical investigation that are relevant to the subject's decision to

participate. Consent may be given by the legally authorized representative only if a subject is unable to make the decision to participate in a clinical investigation by him/herself. In such cases, the subject shall also be informed about the clinical investigation within his/her ability to understand.

Prior to enrolling subjects, each site's Ethics Committee will be required to approve the PIC Form, and other privacy language as required by law. The document(s) must be controlled (i.e., versioned and dated) to ensure it is clear which version(s) were approved by the Ethics Committee. Any adaptation of the sample Consent Form must be reviewed and approved by Medtronic and the Ethics Committee reviewing the application prior to enrolling subjects.

Prior to initiation of any study-specific procedures, Informed Consent (as documented in the PIC form) must be obtained from the subject (or their legally authorized representative or guardian). Likewise, privacy or health information protection regulation may require subjects to sign additional forms to authorize sites to submit subject information to the study sponsor. The Informed Consent process must be conducted by the Principal Investigator or an authorized designee, and the Consent Form and other privacy language as required by law must be given to the subject (or their legally authorized representative or guardian) in a language he/she is able to read and understand. The process of Informed Consent must be conducted without using coercion or undue improper influence on or inducement of the subject to participate by the investigator or other site personnel.

The process of obtaining Informed Consent shall:

- Ensure that the Principal Investigator or his/her authorized designee conducts the Informed Consent process
- Not waive or appear to waive subject's legal rights
- Use language that is non-technical and understandable to the subject
- Provide ample time for the subject to read and understand the informed consent form and to ask questions, receive answers and consider participation
- Include a personally dated signature of the subject(or legally authorized representative) acknowledging that their participation in the study is voluntary
- Include a personally dated signature by the Principal Investigator or his/her authorized designee responsible for conducting the Informed Consent process, where required by local law (e.g., Central & Eastern Europe, Middle East & Africa)

If the PIC is obtained the same day the subject begins participating in study-related procedures, it must be documented in the subject's case history that consent was obtained prior to participation in any study-related procedures (e.g., Holter monitor data collection solely for 1.5 Prevention evaluation). It is best practice for the Informed Consent process to be documented in the subject's case history, regardless of circumstance.

In the event the subject cannot read and/or write, witnessed (impartial third party) Informed Consent will be allowed, provided detailed documentation of the process is recorded in the subject's case history and the witness signs and dates the PIC form. Informed Consent shall be obtained through a supervised oral process, with

an independent witness present. The PIC as well as any other relevant information must be read aloud and explained to the prospective subject or his/her legally authorized representative. The subject should “make his mark” (sign or otherwise physically mark the document so as to indicate consent) on the PIC form as well, attesting that the information was accurately explained and that informed consent was freely given. The PIC Form should document the method used for communication with the prospective subject and the specific means by which the prospective subject communicated agreement to participate in the study.

The original of the signed PIC form must be filed in the hospital/clinical chart and/or with the subject’s study documents. A copy of the signed and dated PIC form, as well as and other privacy language as required by law, shall be provided to the subject.

The PIC form and other privacy language as required by law must be available for monitoring and auditing. Any Medtronic Field (or delegate) personnel who support the implant must be able to review the subject’s signed and dated PIC form and verify its completeness prior to proceeding with the implant. In the event the Medtronic Field (or delegate) personnel identify a PIC form as being incomplete, the implant must not be allowed to occur until the consent of the subject can be adequately and appropriately obtained.

Any changes to a previously approved PIC form throughout the course of the study must be approved by Medtronic and the Ethics Committee reviewing the application before being used to consent a prospective study subject. The document(s) must be controlled (i.e., versioned and dated) to ensure it is clear which version(s) were approved by the Ethics Committee. All important new information should be provided to new and existing subjects throughout the study.

Confidentiality of data must be observed by all parties involved at all times throughout the clinical investigation. Privacy of each subject and confidentiality of his/her information must be preserved in reports and when publishing any data. All data shall be secured against unauthorized access.

6.6 Enrollment and Baseline

At the point in time when a patient or legally authorized representative and investigator or authorized designee have signed and dated the Patient Informed Consent Form, the patient is considered a subject enrolled in the study. The date the subject signed the PIC form must be documented in the subject’s medical records.

Enrollment/baseline data will be collected for all enrolled subjects. The following information is required to be collected at the baseline visit:

- Patient Informed Consent Date (Enrollment Date)
- Demographics
- NYHA classification
- Indication for Implant
- Medications
- Eligibility Verification (Inclusion/Exclusion Criteria)
- Medical History

- 1.5 Criteria Assessment (Syncope, LVEF, NSVT, and PVC burden)
- Quality of Life Questionnaire (EQ-5D[36]) (for 1.5 subjects only)

6.6.1 Indication Classification

At baseline, document the subject's classification of primary or secondary prevention at the time of enrollment into the Improve SCA study using the following definitions:

Primary prevention subjects: subjects who are at risk for lethal arrhythmias but who have not yet experienced a spontaneous documented sustained symptomatic ventricular arrhythmic event; primary prevention subjects with non-spontaneous sustained ventricular arrhythmias only induced during an electrophysiology study will still be classified as primary prevention.

Secondary prevention subjects: subjects who have survived an arrhythmic sudden cardiac death event due to VF, or sustained VT, or who have syncope of undetermined origin with clinically relevant hemodynamically significant sustained VT or VF induced at an EP study.

With the exception of secondary prevention subjects, in the event a subject refuses an implant at baseline, but later changes their mind, a device change CRF should be completed and that subject will be included in the primary objective as an implanted subject. Secondary prevention subjects should remain exited from the study.

6.7 The 1.5 Prevention Criteria Testing

At the baseline visit, all subjects who have been identified as primary prevention indication subjects will be assessed to see if they further meet 1.5 Prevention Criteria; secondary prevention subjects do not need to undergo 1.5 Criteria testing. If one or more criteria are met, this subject will be classified as a 1.5 Subject. All criteria should be assessed, even if it is known that the subject already meets one of the four criteria. Patients should complete 1.5 testing prior to being asked if they want to have a device implanted.

The four criteria which will be assessed include:

- Pre-syncope/syncope
- Low left ventricular ejection fraction (low LVEF)
- Frequent premature ventricular contractions (PVCs)
- Non-sustained ventricular tachycardia (NSVT)

These criteria are described in Table 4 as well as below.

6.7.1 Pre-syncope/Syncope

History of recent pre-syncope/syncope will be collected from medical records, where recent is considered 12 months prior to subject enrollment (signing informed consent). In instances where no patient medical records are available, it is

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permissible for the investigator to rely on patient memory. This should be documented in the medical records.

In this study, a history of syncope classifies a subject as a 1.5 subject when the syncope is due to suspected VT. Unexplained syncope or pre-syncope will also classify a subject as a 1.5 subject, after ruling out vasovagal syncope, syncope related to bradycardia, and syncope related to supraventricular tachycardia (SVT).

6.7.2 Low left ventricular ejection fraction (low LVEF)

In this study, a low LVEF is defined as a left ventricular ejection fraction (LVEF) of <25%. The measurement must be recent, that is, measured within 6 months prior to subject enrollment (signing informed consent) or implant. However, if no recent measurement is available, the measurement should be taken at baseline during the 1.5 Criteria assessment. There are no pre-specified requirements for how the LVEF must be measured. Examples include: radionuclide cardiography/MUGA, echocardiography, or MRI.

If the subject has a history of myocardial infarction (MI), LVEF must be collected at least:

- 40 days post-MI if there was no revascularization
- 90 days post-MI if there was revascularization, e.g., percutaneous coronary intervention (PCI), coronary artery bypass graft (CAGB)

6.7.3 Frequent premature ventricular contractions (PVCs)

In this study, frequent PVCs are defined as a subject having a PVC burden of 10 or more per hour (average) while monitored. The measurement must be recent, that is, measured within 12 months prior to subject enrollment (signing informed consent) or implant. If no recent measurement is available, or previous monitoring showed no PVCs, the investigator should test for PVC burden at baseline visit, using at least a 24 hour ambulatory test method (e.g., 24-hour Holter Monitor). Testing for longer than 24 hours is encouraged where available, but should be for at least 20 hours.

If the subject has a history of myocardial infarction (MI), PVC burden must be collected at least:

- 40 days post-MI if there was no revascularization
- 90 days post-MI if there was revascularization, e.g., percutaneous coronary intervention (PCI), coronary artery bypass graft (CAGB)

6.7.4 Non-sustained ventricular tachycardia (NSVT)

In this study, NSVT is defined as 3 or more consecutive beats at >100 beats per minute lasting less than 30 seconds. If no recent measurement is available, or previous monitoring showed no NSVTs, the investigator should test for NSVT at the baseline visit using at least a 24 hour ambulatory test method (e.g., 24-hour Holter Monitor). Testing for longer than 24 hours is encouraged where available (e.g., Corventis Patch).

If the subject has an implantable pulse generator (IPG) at enrollment, NSVT may be identified via IPG reading but must be confirmed either via 24-hour ambulatory test method, or via documentation on EGM strip in order to rule out SVT or

ventricular artifact. If NSVT cannot be confirmed, it should conservatively be assumed that subject does not meet the 1.5 Prevention Criteria for NSVT.

6.8 Quality of Life (QoL) EQ-5D Assessment

The EQ-5D questionnaire will be completed at the baseline visit and at the 6 month follow-up visit for all 1.5 prevention subjects; it is not required for secondary prevention subjects or for subjects that do not meet any of the 1.5 criteria. For this reason, at baseline the EQ-5D questionnaire should be completed after the 1.5 criteria are evaluated. If the EQ-5D questionnaire is skipped, a Study Deviation is required.

This quality of life assessment has five dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Questionnaires will be provided in a language understood by the patient along with instructions for proper administration.

6.9 Implant

All subjects enrolled are required to meet primary or secondary guidelines for implant. It is not ethical to randomize subjects to not receive an implant when they are indicated to receive one. Thus, subjects will not be randomized; instead, they will be asked if they choose to receive an ICD/CRT-D. If the subject agrees to implant they must receive a Medtronic device, as the primary endpoint evaluates appropriate therapy rates which must be retrieved and reviewed from the ICD/CRT-D. If a non-Medtronic device is implanted, the subject should be exited from the study.

A successful implant is defined as the subject having received an ICD/CRT-D and at least an RV lead. If a non-Medtronic device is implanted, the subject can still have a ‘successful’ implant; however, the subject should be exited from the study. Non-Medtronic leads are allowed as long as they are not under regulatory recall.

6.9.1 Implant Refusal

Subjects that choose not to receive a device implant will be asked the reason for refusal, which will be documented on the ‘Implant/Implant Refusal’ Case Report Form. Following refusal, primary indication subjects will be followed every 6 months until study closure or exit. These subjects will contribute to the study’s secondary endpoint of mortality (see Section 12.3). Secondary indication subjects will exit the study upon refusal of implant.

With the exception of secondary prevention subjects, if a subject initially refuses implant, but later decides to receive an implant, a ‘Device Change’ CRF shall be completed (see Section 6.11).

6.9.2 Implant Acceptance

The following information is required to be collected for subjects that receive an ICD/CRT-D implant:

- Date of implant
- System implant information
- Device interrogation

6.9.3 Device programming at implant

Prior to the subject leaving the hospital, verify that the subject is programmed according to Table 8. Some settings are not available in all devices. If a certain parameter is not available to be programmed on a device, it is not a study deviation.

Pre-programmed settings will be provided to sites by Medtronic via USB (Get-Save tool), which facilitates uploading correct programming requirements. The tool does not work in some older device models (e.g., Maximo, Marquis, and earlier Medtronic ICD models); however, the utilization of this tool is strongly recommended when possible. The pre-programmed USB upload does not contain investigational programming or software; the purpose is to increase compliance of study-required programming at implant.

Consistent programming is desirable in order to compare groups during statistical analysis. Programming changes during the study that are required in order to treat a subject's medical condition are permitted. Compliance to the device programming will be verified by Medtronic via device interrogations throughout the study, and a Study Deviation Case Report Form should be reported in instances where the programming requirements are not followed.

Table 8: Programming requirements at implant

Parameter	Required Programming
VFDI	300 ms
VFNID	30/40
VT Enable	ON
VTDI	360 ms
VTNID	24
SVT limit	260 ms
High Rate Timeout	
All Zones	OFF
VF Zone Only	DR/CRT-D: OFF; VR: ON - .75min Timeout
AF/AFI Rejection	ON
Sinus Tach	ON
Wavelet*	ON, 70%
EGM 2	Can-RV Coil or RV Coil - SVC Coil
Wavelet Template	Perform manual template collection at all visits
T wave discrimination	ON
RV Lead Noise	ON+.75min timeout
RV Lead Integrity	ON
Stability	OFF
Onset	OFF
Monitor Zone	ON (Monitor)
VT Monitor Interval	450 ms
VT Monitor NID	32
Confirmation+	ON
VF Therapy #1	ATP During Charging and Max Output Shock
ATP Delivery R-R	240 ms
Therapy Type	Burst
Smart Mode	ON
Chargesaver	ON, Successful ATP:1
VT Rx 1	ATP Burst 8@88% (3 seq)
Monitored EGMs	EGM 1 and EGM 2
EGM 1	Atip-Aring or RV Sense Vector
Pre-Arrhythmia EGM	ON continuous for first 12 months of follow-up

*Wavelet is only available VR devices and Protect/Evera DR/CRT and Viva CRT devices. PR Logic is not available in VR devices.

6.10 Subject Follow-up-up Visits

Subjects should have a scheduled follow-up visit every 6 months post-implant (Arms A, C, and E) or implant refusal (Arms D, and F) until study closure, subject exit or death, with the exception of secondary prevention subjects who do not receive an implant (Group B); these subjects will be exited following implant refusal (Figure 1).

After completion of the Implant/Implant Refusal eCRF, Medtronic will provide the target dates and windows for each visit to the implanting site. Perform scheduled follow-up visits every 6 months according to Table 9. Follow-up visit windows are based on days post-implant. If a subject is seen beyond their 60-month visit, windows will continue on the same pattern with a width of 120 days. Should a subject visit fall outside the pre-specified window, a study deviation must be reported and the original follow-up schedule maintained for subsequent visits.

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

Table 9: Follow-up windows

Study Follow-up Visit	**Window (Calculated days post-implant)**		
	Window Start (days post-implant)	Target (days post-implant)	Window End (days post-implant)
6 month	123	183	243
12 month	305	365	425
18 month	488	548	608
24 month	671	731	791
30 month	853	913	973
36 month	1036	1096	1156
42 month	1218	1278	1338
48 month	1401	1461	1521
54 month	1584	1644	1704
60 month	1766	1826	1886

Complete a Subject Contact CRF for each follow-up visit. If more than one visit (contact) occurs during a window, complete an additional unscheduled Subject Contact visit CRF.

During follow-up visits, information will be collected on the subject's vital status and use of Amiodarone, and subjects with an implanted device will have the device interrogated, either in office or via CareLink. Subjects who have access to CareLink will be asked to transmit data every 3 months when possible, and will not be required to do an in-person visit.

At 6-months post-implant, EQ-5D will be assessed again for all 1.5 subjects, regardless of implant status. Instructions for administering this test over the phone will be provided.

At approximately 22 months past the final enrollment, centers will be notified that study closure is about to occur and that they should attempt to make one final study contact with each subject to maximize overall study follow-up.

6.10.1 Subjects with no device

Subject contact visits are not required to be performed in person (e.g., phone call is acceptable).

At the 12 month and 24 month visits, primary prevention subjects (1.0 or 1.5) who were not implanted with a device will be offered additional ambulatory monitoring

(e.g., Holter). The rationale for this additional test is that NSVT and PVC burden may not show up on every test given their frequency of occurrence and relatively short monitoring time. If NSVT or frequent PVCs are noted at a later ambulatory test, the subject may want to reconsider having an implant. Although this ambulatory monitoring should be offered to subjects, if a subject refuses, a Study Deviation is not required.

If a subject (either after a Holter or for any other reason) does decide to undergo an implant, they will be included in the primary objective analysis beginning from the time of implant (see section 12.2 for details). In these cases, a Device Change eCRF must be completed.

Because these subjects implanted later in the study can be used in the primary analysis, available 1.5 criteria should be collected at the time of implant. If LVEF has been retested since the 1.5 Criteria Assessment or Syncope has been noted, this can be recorded, but no additional tests for these will be offered. These variables will be recorded on the 1.5 Criteria section of the Device Change eCRF.

6.10.2 Subjects with device

Subject contact visits are not required to be performed in person if the device data can be transmitted remotely, for example, through CareLink. The use of CareLink in this study is strongly encouraged. If device data cannot be transmitted remotely, the subject should come into the office for the device interrogation.

Device interrogation (save-to-disk)
For all visits occurring at the study site, an initial full “Interrogate ALL” device interrogation file (.pdd) must be obtained and saved in a digital format (e.g., USB memory stick). It is recommended that data are not cleared during any interrogation or save-to-disk. Retain one copy (USB memory stick) for the subject file and submit the other copy to Medtronic via Clinical Transfer.

Device data will be reviewed in a timely manner by an Episode Review Committee. This committee will consist of independent physicians and potentially Medtronic engineers to evaluate appropriateness of therapy (ICD/CRT-D shock or anti-tachycardia pacing (ATP). Episodes will be reviewed, and therapy appropriateness will be identified based on adjudicated rhythm and the device episode log information. This information will be used for the primary objective analysis.

6.10.3 Device programming

Verify that the device is programmed according to Table 8.

6.10.4 Deviations (all subjects)

A study deviation is defined as an event within a study that did not occur according to the CIP or the Clinical Trial Agreement. Study deviations must be reported to Medtronic according to Section 6.10.4.

6.11 Device Change

A Device Change eCRF will be completed if one of the following occurs:

- Device is explanted, and replaced (e.g., device reaches end of life, device upgrade)
- Device is explanted, and not replaced

- New ICD/CRT-D device implant (i.e., subject initially refuses an implant [baseline], but later decides to have a device implanted)
    - In this case, complete the 1.5 Criteria section of the Device Change eCRF.
- Device is permanently disabled and not replaced.

If a new device is implanted during a device change, a device interrogation should be performed prior to explant (in the instance of a device replacement) and again after new device implant. System information (e.g., device manufacturer) will be collected for the new device. Subject follow-up visit windows will not change following a Device Change, even if the device is explanted and not replaced.

6.12 Study Exit

A Study Exit eCRF is required when living subjects exit the study. Following exit, subjects will continue to receive standard medical care by their treating physician. All data available through the time of the subject's exit will be used for analysis.

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

- Subject does not meet inclusion/exclusion criteria
- Subject is implanted with a non-Medtronic device
- Subject lost to follow-up
- Subject chooses to withdraw
- Investigator deems withdrawal necessary (e.g., medically justified, failure of subject to maintain adequate study compliance)

The following information is required to be collected at study exit:

- Date of exit
- Date of last contact (this will be different from date of exit if the subject is lost to follow-up)
- Reason for exit
- Final device interrogation (interrogate all) (if available)

At the end of the study, subjects will not be required to complete an Exit CRF. Instead, a study contact visit form should be completed when subject is notified of closure.

At exit, it is recommended that pre-arrhythmia EGM is programmed to 'off' to save battery life.

6.12.1 Lost to follow-up

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

6.13 Subject Death

In the event of subject death, a Death eCRF should be completed. An Exit eCRF will not be completed if a Death eCRF is completed. The following information will be required to be collected:

- Date of death
- Primary cause of death, if known
- Description of subject's death, if available
- Death classification, as determined by the Primary Investigator (See Section 9.1.2)
- Final device interrogation (e.g., Save-to-disk), if possible

For ICD/CRT-D systems, the VT and VF detection capabilities should be disabled at death to avoid inadvertent shocks. If any system component is returned to Medtronic, internal return product reporting systems may be used to gather additional information about the returned device/component.

6.14 Medications

Cardiovascular medication categories specific for systolic heart failure will be collected at the baseline visit for characterization of the population, including:

- Anti-arrhythmics
- Anticoagulants
- ACE Inhibitors
- Angiotensin II Receptor Blockers/Inhibitors
- Diuretics
- Vasodilators

It is expected that patients will be on chronic, guideline-directed medical therapy at baseline (e.g., Beta Blockers, ACE inhibitors minimally); this is consistent with both the ACC/AHA/HRS and ESC Guidelines. Following device implant, Amiodarone should be discontinued for subjects taking it prophylactically (e.g., for preventative reasons). Amiodarone use for symptom control is permitted. Subjects will be asked at follow-up visits if they are taking Amiodarone. No other medication changes will be tracked throughout the study.

7 INVESTIGATIONAL DEVICE/SOFTWARE STORAGE, HANDLING AND TRACEABILITY

All products used in this study are market released in the geographies they are used, and therefore will not be tracked in the study. Device and lead information of implanted product will be collected at implant (e.g., model number).

If there are additional local requirements related to implanted information beyond what is collected by Medtronic on the electronic Case Report Form, this is the Investigator's responsibility and should be recorded in the subject's medical records, but will not be collected by Medtronic (e.g., national registration card number, identification code linked to names and contact information, log of all subjects enrolled in the clinical study, lot or batch number).

8 STUDY DEVIATIONS

A study deviation is defined as an event within a study that did not occur according to the Clinical Investigation Plan or the Clinical Trial Agreement. Examples of study deviations include, but are not limited to, the following:

- Subject enrolled during lapse of Ethics Committee approval
- Patient informed consent not obtained prior to participation in the study
- Incorrect version of the PIC provided to the subject
- Visit outside of the protocol defined window
- Visit not completed
- Protocol-required testing or programming not done
- Source data permanently missing
- Unauthorized physician or study personnel performing study procedures

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

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

All study deviations must be reported on the Case Report Form regardless of whether medically justifiable, pre-approved by Medtronic, an inadvertent occurrence, or taken to protect the subject in an emergency. In the occurrence of a corrupted device interrogation file, Medtronic may request a deviation to document that a readable interrogation file is unavailable.

In the event the deviation involves a failure to obtain a subject's consent, or is made to protect the life or physical well-being of a subject in an emergency, the deviation must be reported to the Ethics Committee as well as Medtronic within five (5) working days. Reporting of all other study deviations should comply with Ethics Committee policies and/or local laws and must be reported to Medtronic as soon as possible upon the site becoming aware of the deviation. Reporting of deviations must comply with Ethics Committee policies, local laws, and/or regulatory agency requirements. Refer to Section 16.2 for reporting requirements and timeframes for reporting to Medtronic and/or regulatory bodies.

Medtronic is responsible for analyzing deviations, assessing their significance, and identifying any additional corrective and/or preventive actions (e.g., amend the Clinical Investigation Plan, conduct additional training, or terminate the investigation). Repetitive or serious investigator compliance issues may result in initiation of a corrective action plan with the investigator and site, and in some cases, necessitate suspending

enrollment until the problem is resolved or ultimately terminating the investigator's participation in the study.

9 ADVERSE EVENTS AND DEVICE DEFICIENCIES

The products used in the clinical trial are market approved/released and used within the current indications for use as indicated in the product labeling. The collection of adverse event data is not required to meet the objectives of this clinical trial; it is the responsibility of the Investigator to abide by any adverse event reporting requirements stipulated by the site's Institutional Review Board (IRB) or Medical Ethics Committee (MEC). User (Investigator) reporting of events to regulatory authorities related to market approved/released products may be required. Refer to local regulations for reporting requirements.

Device deficiencies are not required to be collected because it is a post-market study. However, if there should be any alleged device-related death, serious injury, device malfunction, or complaint reported, the event should be reported as described in Section 9.2.

9.1 Subject Death

9.1.1 Death data collection

All subject deaths must be reported by the investigator to Medtronic on a Subject Death form as soon as possible after the investigator first learns of the death.

9.1.2 Death classification and reporting

Sufficient information will be collected by the Investigator in order to properly classify the subject's death, though not all of these data will be collected by the Sponsor. The Investigator shall classify each subject death per the following definitions:

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

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

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

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

Unknown Cardiac Classification: A death in which there is no clinical evidence to support:

- A direct relatedness to the system component or
- A probable cause relatedness to the system component or
- No relatedness to the system component

The Investigator's assessment of primary cause of death and cardiac classification will be used in the study and will not be adjudicated by an Adverse Event Adjudication Committee, as no investigational devices are being used and cause of death is not related to any of the study objectives.

Regulatory reporting of Subject Deaths will be completed according to local regulatory requirements.

9.2 Vigilance Reporting

All devices used in this study are market-released. Therefore, Post Market Surveillance and product complaint reporting is applicable to all market-released devices used in the study, including leads.

The reporting of product complaints is not part of the clinical study. The following reporting requirements are included as reminders. In addition, since non-Medtronic leads are permitted in the study, investigators are responsible for reporting product complaints of non-Medtronic product to the appropriate manufacturer. It is the responsibility of the investigator to abide by the reporting requirements in place for that particular geography. Refer to local regulations for reporting requirements. The reporting process will be outlined in the safety plan.

Product Complaint: Any written, electronic or oral communication that alleges deficiencies related to the identity, quality, durability, reliability, safety, effectiveness or performance of a medical device that has been placed on the market.

It is the responsibility of the investigator to report all product complaint(s) associated with a medical device distributed by Medtronic, regardless whether they are related to intended use, misuse or abuse of the product. Reporting must be done immediately and via the regular channels for market-released products. It is the responsibility of the investigator to abide by the reporting requirements in place for that particular geography.

Medtronic will notify the regulatory authorities (e.g. Competent Authority) according to the applicable local regulations applicable for the following incidents immediately upon learning of them:

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

These device deficiencies are not intended to be collected in the clinical study, as reporting should be done through regular channels for post-market products. However, if Medtronic is informed of any of these items within the study, it will be reported.

10 RISK ANALYSIS

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

All devices used in the Improve SCA study are commercially released and used in accordance with their approved labeling. There are potential risks and side effects associated with a device implant. The risk associated with the study is consistent with market-released ICD/CRT-D systems. There are no experimental procedures involved in this study. As such, a Data Monitoring Committee (DMC) will not be utilized.

10.1 Potential Benefits

Participation in the Improve SCA study may offer no benefit. Subjects enrolled in the study may have additional contact with their physicians or other medical care staff beyond their normal standard of care visits, which may provide benefit from a patient care perspective. The information gained from this study could result in the improved management of primary prevention indicated patients through improved referral linkages, reimbursement coverage updates, and user adoption. Additionally, information collected from this study may assist in the design of new product(s)/therapy(ies), and/or instructions for use.

10.2 Potential Risks

The study programming requires Pre-arrhythmia EGM to be programmed on for at least the first 12 months following implant, which allows the device to store more data. While this is not considered investigational programming, this programming reduces device longevity. The benefit of using this programming is that it is useful in arrhythmia episode adjudication, which is required for the analysis of the primary study objective.

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

11.1 Planned Study Closure

Study Closure is a process initiated by distribution of a study closure letter. Study closure is defined as closure of a clinical study that occurs when requirements have been satisfied per the CIP and/or by a decision by Medtronic or regulatory authority), whichever occurs first. The study closure process is complete upon distribution of the Final Report or after final payments, whichever occurs last. Ongoing Ethics Committee oversight is required until the overall study closure process is complete. Following closure, subjects should be seen by their physicians per their normal standard of care. Refer to Section 6.12 on Page 39 for additional information regarding study exit procedures.

11.2 Early Termination or Suspension

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

11.2.1 Study-wide termination or suspension

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

- Decision by Medtronic or regulatory body (where the study is operating under regulatory body authority)
- Enrollment is slower than anticipated

11.2.2 Investigator/site termination or suspension

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

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

11.3 Procedures for Termination or Suspension

11.3.1 Medtronic-initiated and regulatory authority-initiated

- Medtronic will promptly inform the clinical investigators of the termination or suspension and the reasons and inform the regulatory authority(ies) where required
- In the case of study termination or suspension for reasons other than a temporary Ethics Committee approval lapse, the investigator will promptly inform the Ethics Committee and the institution (where required per regulatory requirements)
- In the case of study termination, the investigator must inform the subjects, or legally-authorized designees or guardians and may inform the personal physician of the subjects to ensure appropriate care and follow-up is provided
- In the case of a study suspension, subject enrollment must stop until the suspension is lifted by Medtronic
- In the case of a study suspension, enrolled subjects should continue to be followed out of consideration of their safety, rights and welfare

11.3.2 Investigator-initiated

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

11.3.3 Ethics committee-initiated

- The investigator will inform Medtronic and provide a detailed written explanation of the termination or suspension within 5 business days
- Subject enrollment must stop until the suspension is lifted
- Subjects already enrolled should continue to be followed in accordance with Ethics Committee policy or its determination that an overriding safety concern or ethical issue is involved
- The investigator will inform his/her institution (where required per local requirements)
- The investigator will promptly inform the subjects, or legally-authorized designees or guardians and/or the personal physician of the subjects, with the rationale for the study termination or suspension
- The investigator will inform local regulatory authority, where required per regulatory requirements

12 STATISTICAL METHODS AND DATA ANALYSIS

12.1 General considerations

Data analysis will be performed by Medtronic statisticians.

The data will not be analyzed until study completion, which will be approximately two years after the final study enrollment.

Where applicable, missing data is addressed within each objective.

Generally, subjects will be included in their baseline groups in analyses. For example, a subject who is in a primary prevention arm will remain in that arm even if he later falls into the secondary prevention group due to a VT/VF episode. The exception will be subjects who get implanted later in the study. These subjects will be included in the primary endpoint in the group to which they belonged (secondary, 1.5, or 1.0) at the time of implant.

There are 6 study cohorts (see Figure 1 on page 11 for more detail):

- Group A: Secondary prevention subjects implanted with an ICD or CRT-D
- Group B: Secondary prevention subjects not implanted with an ICD or CRT-D
- Group C: Primary prevention subjects who meet 1.5 criteria and are implanted with an ICD or CRT-D
- Group D: Primary prevention subjects who meet 1.5 criteria and are not implanted with an ICD or CRT-D
- Group E: Primary prevention subjects who do not meet 1.5 criteria (1.0 subjects) and are implanted with an ICD or CRT-D
- Group F: Primary prevention subjects who do not meet 1.5 criteria (1.0 subjects) and are not implanted with an ICD or CRT-D

The Statistical Analysis Plan (SAP) is a separate document that will include a comprehensive description of the statistical methods to be included in the final study report and main manuscript. Any change to the data analysis methods described in the CIP will require an amendment only if it changes a principal feature of the protocol. Any other change to the data analysis methods described in the protocol, and the justification for making the change, will be described in the clinical study report.

12.2 Primary Objective #1: Appropriate Therapy

Demonstrate that appropriate VT/VF therapy rates (shock and ATP) for subjects meeting 1.5 prevention criteria implanted with a Medtronic device (ICD/CRT-D) are equivalent (within 30%) to rates in subjects meeting secondary prevention criteria.

12.2.1 Hypothesis

The goal of this hypothesis test is to demonstrate that the overall rate of appropriate VT/VF therapy (shock and ATP) over the observed post-implant time in the study is non-inferior in implanted 1.5 prevention patients compared to implanted secondary prevention patients with a non-inferiority margin of 30%.

H_0: Hazard ratio of Implanted 1.5 patients to implanted secondary patients ≤ 0.70
H_A: Hazard ratio of Implanted 1.5 patients to implanted secondary patients > 0.70

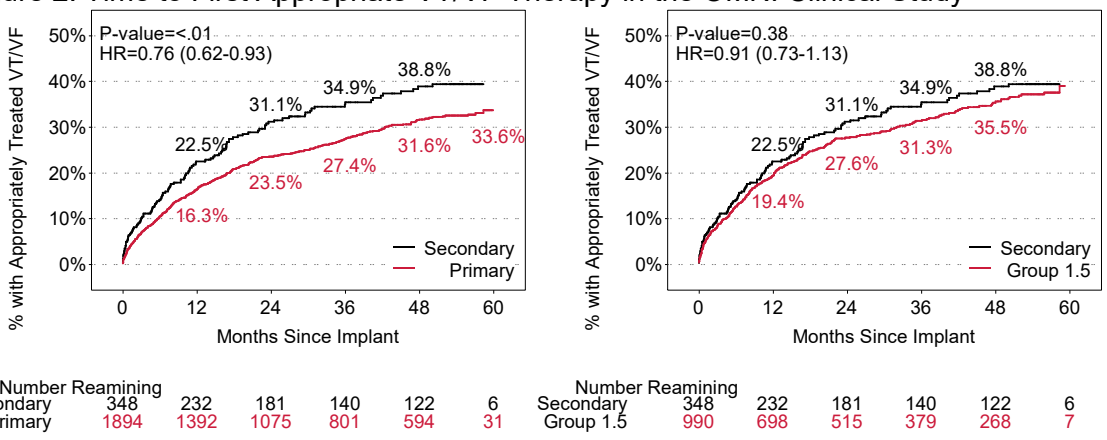
12.2.2 Performance Requirements

The null hypothesis will be rejected if the one-sided 95% lower confidence bound of the hazard ratio of implanted 1.5 subjects to implanted secondary prevention subjects is greater than 0.70.

12.2.3 Rationale for Performance Criteria

Data from the OMNI clinical study was analyzed retrospectively. Figure 2 shows the results, where the hazard ratio between secondary and all primary subjects was 0.76, and the hazard ratio between secondary subjects and the 1.5 subgroup of primary prevention was 0.91. This demonstrates that the 1.5 subgroup may be much more similar to the secondary prevention group than the overall primary prevention group.

Figure 2: Time to First Appropriate VT/VF Therapy in the OMNI Clinical Study



The non-inferiority margin of 30% (corresponding to a hazard ratio of 0.70) was chosen because it is higher than the observed hazard ratio of 1.0 to 1.5 in the OMNI study, which was 0.68. This would demonstrate both that the rate of appropriate VT/VF therapies is similar between 1.5 prevention and secondary prevention patients and that

the 1.5 prevention patients' curve is likely closer to the secondary prevention curve than to the overall primary prevention curve.

In this objective, the direct comparison is only between secondary and 1.5 subjects because it is believed that there will not be enough implanted 1.0 subjects as it is expected that relatively few of these subjects will elect to receive a device.

12.2.4 Analysis Methods

The hypothesis will be tested using a Cox proportional hazards model with survival time and first appropriate VT/VF episode as the dependent variable and group (secondary or 1.5) as the independent variable. A 95% one-sided lower confidence bound for the hazard ratio and a p-value will also be calculated. The data will be presented in a format similar to the right panel of Figure 2.

Adequate power is needed to perform the hypothesis test. Without adequate power, a non-significant test has little meaning. Therefore, the hypothesis test will not be performed and a p-value will not be calculated if there are fewer than 400 subjects in the implanted 1.5 prevention group. In that case, event rates and confidence intervals will be presented.

Time 0 will be the implant date and subjects will be censored on the date of their latest device interrogation. Only spontaneous, appropriately treated VT/VF episodes as adjudicated by the episode review committee will count toward the endpoint.

VT/VF episodes that cannot be adjudicated (due to not saving full episode data or any other reason) will be ignored. Often, these episodes are followed by episodes that can be adjudicated, and since the endpoint is time to first episode, effects on the results from these events will be minimal. In addition, these should be balanced between the comparison groups.

12.2.5 Determination of Patients/Data for Analysis

All 1.5 prevention and secondary prevention subjects with an ICD/CRT-D implant will be included in the primary analysis hypothesis test. This includes subjects implanted with a device after the initial enrollment period. These later implants will be included if they are secondary or 1.5 at the time of implant.

12.2.6 Sample Size

A simulation program was written to determine the sample size for the study. Assumptions are based on the OMNI data and estimates from steering committee physicians:

- 60% of enrollments will be secondary prevention and 40% primary prevention
- 50% of primary subjects will be in the 1.5 group
- 57% of secondary subjects will get an ICD (includes CRT-D)
- 45% of 1.5 subjects will get an ICD
- 22% of 1.0 subjects will get an ICD
- Annual attrition (includes exits and deaths) will be 10%
- The study will end two years after the last enrollment

- 4000 patients will take 2 years to enroll with enrollment beginning slowly, then accelerating to a steady 246 per month.
- Expected rates of appropriately treated VT/VF in secondary subjects follow Figure 2, with a higher rate in the first year (22.5%), then a constant rate (11.1%) thereafter.
- The hazard ratio of 1.5 to secondary is 0.91

Under the above assumptions and using the hypothesis test stated above, 4800 subjects will have 80% power to reject the null hypothesis. With 4800 enrolled patients, it is expected that approximately 1650 secondary prevention subjects will be implanted, 430 1.5 prevention subjects will be implanted, and 200 1.0 subjects will be implanted.

12.2.7 Sample Size Re-estimation

Because most of the assumptions above are based only on investigator opinion, the sample size will be re-estimated during the study using the same simulation methods, but changing the following assumptions using the study data:

- % of enrollments will be secondary prevention
- % of primary patients in the 1.5 group
- % of secondary patients who will get an ICD (includes CRT-D)
- % of 1.5 patients who will get an ICD
- % of 1.0 patients who will get an ICD
- Annual attrition (includes exits and deaths)
- Enrollment rate

With this re-estimation of sample size, the length of follow-up after the last enrollment may be changed as well.

Because no comparisons will be done at the point of re-estimation, alpha is not affected and the final analysis can compare the p-value to a 0.05 alpha level.

The sample size re-estimation will occur at the later of:

- One year after the 400th subject has been enrolled
- The time of the 2000th enrollment.

It is the study sponsor's discretion to increase (to a maximum of 8000 subjects) or decrease the sample size, or decrease or increase the length of follow-up after last enrollment.

If fewer subjects are required, the study sponsor may either lower the sample size, or increase the power of the study (possibly keeping the original sample size). If more subjects are required, the study sponsor may elect to not increase the sample size, but may increase the length of follow-up to ensure adequate power for the study.

Study sites will be notified of any change in sample size and length of follow-up (if applicable) at that time. The investigational plan will not be changed.

12.3 Secondary Objective: Mortality

Compare the mortality rates for patients meeting 1.5 prevention criteria between those implanted with a device (ICD/CRT-D) and those not implanted.

12.3.1 Hypothesis

Although this is an exploratory objective and is not powered, a hypothesis test will be done and compared to an alpha level of 0.05. To preserve overall type I error, this test is only valid if the primary endpoint is statistically significant.

Compare the mortality rates for patients meeting 1.5 prevention criteria between those implanted with a device (ICD/CRT-D) and those not implanted.

H_0: Hazard ratio of non-implanted to implanted 1.5 patients = 1
H_A: Hazard ratio of non-implanted to implanted 1.5 patients ≠ 1

12.3.2 Analysis Methods

This analysis will be a comparison of mortality in 1.5 implanted and non-implanted subjects. Time 0 will be the date of enrollment, and all living subjects will be censored on the last date they were confirmed to be alive.

The analysis, to control for potential imbalance between groups due to not randomizing the subjects to implant or no implant, will include covariates in a Cox proportional hazards model along with implant/no implant as the independent variable. The covariates will include age, sex, country of enrollment, ischemic, LVEF, QRS duration, NYHA, history of syncope, history of NSVT, and history of PVCs. Further baseline covariates or time-dependent covariates may be added in the statistical analysis plan prior to any analysis. ICD/CRT-D will not be a covariate since it will not be known whether non-implanted subjects would have received a CRT-D or not. However, the covariates include all the variables that are commonly used to determine CRT-D use.

12.3.3 Power

This objective is not powered and the likelihood of a statistically significant test is not known. So, it should not be a surprise if the endpoint is not statistically significant.

The following table shows what the power of the endpoint would be under various scenarios if doing a log-rank test. It is not known what effect adding covariates in a Cox proportional hazards model will have on the power.

In a retrospective analysis of SCD-HeFT, 1.5 prevention subjects without an ICD had a 25.7% mortality rate at 3 years compared to 18.5% for 1.5 subjects with an ICD. Under the sample size assumptions, it is expected that approximately 430 1.5 subjects will be implanted and 540 will not.

Table 10: Power for 1.5 Prevention Mortality Endpoint

1.5 implanted sample size	1.5 **not** implanted sample size	Assumed 3-year Mortality				
		26% no ICD 18% ICD	26% no ICD 20% ICD	26% no ICD 22% ICD	22% no ICD 14% ICD	30% no ICD 22% ICD
450	550	88%	63%	32%	93%	82%
350	650	85%	60%	30%	91%	79%
360	440	80%	53%	27%	87%	73%
350	350	74%	48%	24%	83%	67%

12.3.4 Determination of Patients/Data for Analysis

All subjects in the 1.5 prevention cohort at the time of enrollment will be included.

[redacted]

13 DATA AND QUALITY MANAGEMENT

Data will be collected and signed and dated by the principal investigator or his/her authorized designee(s) using an electronic data management system for clinical studies. eCRF data will be stored in a secure, password-protected database which will be backed up nightly. Data will be reviewed using programmed and manual data checks. Data queries will be made available to sites for resolution. Study management reports may be generated to monitor data quality and study progress. At the end of the study, the data will be frozen and will be retained indefinitely by Medtronic.

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

The data reported on the eCRFs shall be derived from source documents and be consistent with these source documents, and any discrepancies shall be explained in writing. In some cases, items on the CRFs may be considered source as long as there is evidence of the visit in the subject's record. Even when the eCRF may be considered as source, an alternate method of source documentation is always strongly encouraged. The eCRF may be considered source for deviations.

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

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

14 WARRANTY/INSURANCE INFORMATION

14.1 Warranty

Warranty information is provided in the product packaging for the commercially released devices and leads; additional copies are available upon request.

14.2 Insurance (Central and Eastern Europe, Middle East and Africa))

Medtronic Bakken Research Center B.V. is a wholly owned subsidiary of Medtronic, Inc., which as the parent company of such entity maintains appropriate clinical study liability insurance coverage as required under applicable laws and regulations and will comply with applicable local law and custom concerning specific insurance coverage. If required, a Clinical Trial insurance statement/certificate will be provided to the Ethics Committee.

14.3 Insurance (India)

India Medtronic Pvt. Ltd is a wholly owned subsidiary of Medtronic, Inc., which as the parent company of such entity maintains appropriate clinical trial liability insurance coverage as required under applicable laws and regulations and will comply with applicable local law and custom concerning specific insurance coverage. If required, a Clinical Trial insurance statement/certificate will be provided to the Ethics Board.

14.4 Insurance (Association of Southeast Asian Nations (ASEAN)

Medtronic International Ltd. is a wholly owned subsidiary of Medtronic, Inc., which as the parent company of such entity maintains appropriate clinical trial liability insurance coverage as required under applicable laws and regulations and will comply with applicable local law and custom concerning specific insurance coverage. If required, a Clinical Trial insurance statement/certificate will be provided to the Ethics Board.

14.5 Insurance (Greater China)

Medtronic (Shanghai) Management Co., Ltd. a wholly owned subsidiary of Medtronic, Inc., which as the parent company of such entity maintains appropriate clinical study liability insurance coverage as required under applicable laws and regulations and will comply with applicable local law and custom concerning specific insurance coverage. As Ethics Committee of local clinical center may have special requirements on the insurance policy or other formal arrangement, it is necessary to provide a Clinical Study insurance statement/certificate to the Ethics Committee for review and obtain favorable opinion.

Medtronic (Taiwan) Ltd. is a wholly owned subsidiary of Medtronic, Inc., which as the parent company of such entity maintains appropriate clinical trial liability insurance coverage as required under applicable laws and regulations and will comply with applicable local law and custom concerning specific insurance coverage. If required, a Clinical Trial insurance statement/certificate will be provided to the Ethics Board.

14.6 Insurance (Korea)

Medtronic Korea Co., Ltd. is a wholly owned subsidiary of Medtronic, Inc., which as the parent company of such entity maintains appropriate clinical trial liability insurance coverage as required under applicable laws and regulations and will comply with applicable local law and custom concerning specific insurance coverage. If required, a Clinical Trial insurance statement/certificate will be provided to the Ethics Board.

14.7 Insurance (Latin America)

Medtronic Logistics LLC is a wholly owned subsidiary of Medtronic USA, Inc., which as the parent company of such entity maintains appropriate clinical trial liability insurance coverage as required under applicable laws and regulations and will comply with applicable local law and custom concerning specific insurance coverage. If required, a Clinical Trial insurance statement/certificate will be provided to the Ethics Committee/Institutional Review Board.

15 MONITORING

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

15.1 Monitoring Visits

Frequency of monitoring visits may be based upon subject enrollment, duration of the study, study compliance, number of deviations, findings from previous monitoring visits and any suspected inconsistency in data that requires investigation. Regulatory documents (e.g., Ethics Committee approval letters, Clinical Trial Agreements) may be reviewed at each study site. Monitoring for the study, including site qualification visits, site initiation visits, interim monitoring visits, and closeout visits, will be done in accordance to the study-specific monitoring plan.

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

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

16 REQUIRED RECORDS AND REPORTS

16.1 Investigator Records

The investigator is responsible for the preparation and retention of the records cited below. All of the below records, with the exception of case history records and case report forms, should be kept in the Investigator Site File (i.e., the study binder provided to the investigator) or Subject Study Binder. CRFs may be maintained and signed electronically within the electronic data capture system during the study.

The following records are subject to inspection and must be retained for a period of two years (or longer as local law or hospital administration requires) after the investigation is terminated.

- All correspondence between the Ethics Committee, Sponsor, monitor, regulatory authority and/or the investigator that pertains to the investigation, including required reports.
- Subject's case history records, including:
    - Signed and dated informed consent form:
        - In China, Central and Eastern Europe, Middle East, Africa, India, Korea, Malaysia, Singapore, Taiwan, signed and dated by subject or legally authorized representative and investigator. If patient unable to read and/or write, supervised oral process with an independent witness who need to be present throughout the process; witness need to sign in addition to subject and investigator.
        - In Latin America: signed and dated by Person conducting consent process and subject, one or two witnesses are required according to specific country law and the study PIC template should be modified accordingly.
    - Medical history
    - Implant and follow-up data (if applicable)
    - Documentation of the dates and rationale for any deviation from the protocol
- Electronically signed and dated CRFs and blank set of CRFs, if required by local law.
- All approved versions of the CIP and PIC
- Signed and dated Clinical Trial Agreement.
- Current (within the last 2 years) CV of Principal Investigator
    - CV must be signed and dated (Central and Eastern Europe, Middle East, Africa, Latin America; best practice in all other geographies)
    - CV of other investigators prior to their activation, and CV of other key members of the investigation site team where required by local law
- Documentation of delegated tasks.

- Ethics Committee approval documentation including written information that the investigator or other study staff, when member of the Ethics Committee, did not participate in the approval process.
    - Approval documentation must include the list of documents approved identified by version and/or date and the Ethics Board composition where required per local law.
- Regulatory authority notification, correspondence and approval, as required per local law.
- Study training records for site staff.
- Insurance certificates, where required per local law (ASEAN, Central and Eastern Europe, Middle East, Africa, India, Greater China, Korea and Latin America).
- Any other records that local regulatory agencies require to be maintained.
- Final Study Report including the statistical analysis.

16.2 Investigator Reports

The investigator is responsible for the preparation (review and signature) and submission to the sponsor of all case report forms, deaths, and any deviations from the clinical investigation plan. If any action is taken by an Ethics Committee with respect to this clinical study, copies of all pertinent documentation must be forwarded to Medtronic in a timely manner. Reports are subject to inspection and to the retention requirements as described above for investigator records.

The investigator shall prepare and submit in a complete, accurate and timely manner the reports listed in this section, as well as any other reports required by local law.

Table 11: Investigator reports applicable for all geographies per Medtronic requirements

Report	Submit to	Description/Constraints
Withdrawal of Ethics Board approval	Sponsor	The investigator must report a withdrawal of approval by the reviewing Ethics Board of the investigator's part of the investigation within 5 working days.
Study Deviations	Sponsor and Ethics Board	Any deviation from the clinical investigational plan shall be recorded together with the explanation of the deviation. Notice of deviations from the CIP to protect the life or physical well-being of a subject in an emergency shall be given as soon as possible, but no later than 5 working days after the emergency occurred. Except in such emergency, prior approval is required for changes in the plan or deviations.
Final Report	Ethics Board and Relevant Authorities	This report must be submitted within 3 months of study completion or termination.
Progress Report	Sponsor and Ethics Board	Provide if required by local law or Ethics Board.

16.3 Sponsor Records

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

- All correspondence which pertains to the investigation
- Signed Clinical Trial Agreements, current (within the last 2 years) CV of Principal Investigator (signed and dated if required) and key members of the investigation site team (as required by local law), and delegated task list
- All signed and dated electronic case report forms submitted by investigator, including eCRF corrections
- Informed consent templates, and other information provided to the subjects and advertisements, including translations
- Copies of all Ethics Committee approval letters and relevant Ethics Committee correspondence and Ethics Committee voting list/roster/letter of assurance
- Names of the institutions (and corresponding investigator) in which the clinical study will be conducted
- Regulatory authorities correspondence, notification or approval as required by national legislation
- Insurance certificates, if applicable (e.g., Central and Eastern Europe, Middle East, Africa, India, Greater China and Korea, Latin America)
- Names/contact addresses of monitors
- Statistical analyses and underlying supporting data
- Final report of the clinical study
- The Clinical Investigation Plan and study related reports, and revisions
- Study training records for site personnel and Medtronic personnel involved in the study
- Any other records that local regulatory agencies require to be maintained.

16.4 Sponsor Reports

Medtronic shall prepare and submit the following complete, accurate, and timely reports listed in the table below. In addition to the reports listed below, Medtronic shall, upon request of reviewing Ethics Committee or regulatory agency, provide accurate, complete and current information about any aspect of the investigation.

Table 12: Sponsor reports for all geographies

Report	Submit to	Description/Constraints
Withdrawal of IRB/MEC approval	Investigators, Head of Institution, Ethics Committee, and relevant authorities	Investigators, Ethics Committees will be notified only if required by local laws or by the Ethics Committee.

Report	Submit to	Description/Constraints
Withdrawal of Competent Authority (CA) approval	Investigators, Head of Institution, Ethics Committee, and regulatory authorities, upon request	Investigators, Ethics Committee will be notified only if required by local laws or by the Ethics Committee.
Progress Reports, if applicable	Ethics Committee and regulatory authorities, upon request	These will be submitted to the Ethics Committee only if required by the Ethics Committee.
Final report	Investigators, Ethics Committee, and Regulatory authorities, upon request	This will be submitted to the Ethics Committee only if required by the Ethics Committee.
Study deviation	Investigators	Site specific study deviations will be submitted to investigators periodically.

Electronic versions of the Medtronic reports will be kept on a password-protected document management system. After closure of the study, all records and reports will be archived indefinitely.

Appendix A: Study Overview

Study Purpose

The purpose of this study is to demonstrate that primary prevention patients with additional risk factors (1.5 prevention criteria) are at a similar risk of life threatening ventricular arrhythmias when compared to secondary prevention patients, and would benefit from an ICD/CRT-D implant.

Study Scope and Design

Medtronic, Inc. is sponsoring the Improve SCA study, a prospective, non-randomized, non-blinded, global, interventional, multi-site post-market study.

The study is expected to be conducted at approximately 100 sites worldwide, and to achieve approximately 2300 implants, the study is expected to enroll approximately 4800 subjects. However, a sample size re-estimation will occur partway through the study, so the actual sample size may be as high as 8000 (see page 52). Based on input from the Improve SCA steering committee, it is estimated that sites will identify an average of 3 subjects per site per month.

Participating geographies are expected to include, but not limited to: Association of Southeast Asian Nations (ASEAN), Central and Eastern Europe (CEE), Greater China (including China and Taiwan), India, Latin America, Middle East and Africa (MEA), and South Korea.

There is no minimum requirement for enrollments per site for this study. To ensure a widespread distribution of data and minimize site bias in study results, the maximum number of subjects enrolled at a single site will be limited to enroll approximately 5% of total study subjects.

Study Objectives

Primary Objective

Demonstrate that appropriate therapy rates for subjects meeting 1.5 prevention criteria implanted with a Medtronic device (ICD/CRT-D) are equivalent (within 30%) to rates in subjects meeting secondary prevention criteria.

Secondary Objective

Compare the mortality rates for patients meeting 1.5 prevention criteria between those implanted with a device (ICD/CRT-D) and those not implanted.

[redacted]

- [redacted].

Subject Selection

Patients of both genders who have a guideline recommendation for a single, dual, or triple chamber defibrillator will be approached regarding enrollment in the study. Subjects receiving a device implant will be required to have a Medtronic device implanted, because data stored in the device will be retrieved and analyzed by Medtronic as part of the study. Subjects currently implanted with an implantable pulse generator (IPG) are eligible for participation in the study, assuming the previous device is explanted at the time of implant.

Inclusion Criteria

- Subject has a Class I indication for implantation of an ICD according to the ACC/AHA/HRS or ESC Guidelines
- Subject (or subject's legally authorized representative) is willing and able to sign and date the Patient Informed Consent Form.

Exclusion Criteria

- Subject is ≤ 18 years of age
- Subject with any exclusion criteria as required by local law (e.g., age, pregnancy, breast feeding)
- Subject is enrolled in a concurrent study that has not been approved for concurrent enrollment by the Medtronic Clinical Trial Leader
- Subject has any contraindication for ICD/CRT-D

Study Procedures

Subjects meeting ACC/AHA/HRS or ESC Class I guidelines for an ICD (or CRT-D) implant are eligible for enrollment and will be considered enrolled upon informed consent completion. At baseline, subjects will be assessed to determine if they fall into the primary prevention, 1.5 prevention, or secondary prevention group. A 1.5 prevention assessment will include an assessment of syncope/pre-syncope, low left ventricular ejection fraction, non-sustained ventricular tachycardia, and frequent premature ventricular contractions. In addition, a quality of life questionnaire (EQ-5E) will be collected at baseline and at the 6 month follow-up visit for 1.5 prevention subjects.

Subjects will not be randomized, but will be asked if they desire an ICD/CRT-D implant. All subjects will be followed every six months until exit or closure, with the exception of secondary prevention subjects who do not receive an implant who will be exited following implant. Device data will be collected via interrogations at all follow-up visits (either via CareLink or in-office visit); information on device changes will be collected if applicable. At the 12 and 24 month visits, primary prevention (1.0 and 1.5 subjects) will be provided with the option of another ambulatory test to reassess the 1.5 criteria.

Study Duration

The study will be closed approximately two years after the final subject enrollment. At approximately 22 months past the final enrollment, centers will be notified that study closure is about to occur and that they should attempt to make one final study contact with each subject to maximize overall study follow-up.

Appendix B: Preliminary Publication Plan

Publications from the Improve SCA Study will be handled according to Cardiac Rhythm Disease Management Standard Operating Procedures and as indicated in the Clinical Trial Agreement.

Publication Committee

The Steering Committee will serve as members of the Publication Committee, in addition to Medtronic representative(s). This committee will manage study publications with the goal of publishing findings from the data. The Publication Committee will develop the final Publication Plan as a separate document.

The Publication Committee's role is to:

1) manage elements addressed in the publication plan as outlined in this appendix,
2) develop the final Publication Plan under separate cover,
3) execute the Publication Plan,
4) oversee the publication of primary, secondary and [redacted] study results,
5) review and prioritize publication proposals,
6) provide input on publication content, and
7) determine authorship.

In addition, the committee will apply and reinforce the authorship guidelines set forth in the Publication Plan. Membership in the Publication Committee does not guarantee authorship. The committee will meet as needed.

Management of Primary, Secondary and [redacted] Publications

The Publication Committee reviews, prioritizes, and manages all publications including primary, secondary and [redacted] publications. Primary and secondary publications are those that address analyses of any or all primary objectives or secondary objectives, respectively, as specified in the Clinical Investigation Plan.

[redacted]

The committee may decide that no publications, including abstracts, will be published prior to the end of the study or with individual site data. Requests for publications on study objectives utilizing subset data (e.g., regional) will be evaluated for scientific validity and the ability of Medtronic to provide resources.

Criteria for Determining Authorship

Publications will adhere to authorship criteria defined by the International Committee of Medical Journal Editors (ICMJE, Uniform requirements for manuscripts submitted to biomedical journals, www.icmje.org). Individual authorship criteria defined by the target journal or conference will be followed when it differs from ICMJE criteria.

Authors, including Medtronic personnel, must at a minimum meet all of the conditions below:

- Substantial contribution to conception and design, or acquisition of data, or analysis and interpretation of data
- Drafting the article or revising it critically for important intellectual content
- Final approval of the version to be published

Decisions regarding authorship and contributor-ship will be made by the committee. The selected authors will be responsible for drafting the publication. All selected authors must fulfill the authorship conditions stated above to be listed as authors, and all contributors who fulfill the conditions must be listed as authors.

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

Transparency

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

- a final report, describing the results of all objectives and analysis, will be distributed to all investigators, Ethics Committees and Competent Authorities of participating countries when required by local law
- registering and posting the study results on ClinicalTrials.gov based on the posting rules stipulated
- submitting for publication the primary study results
- disclosing conflicts of interest (e.g., financial) of the co-authors of publications according to the policies set forth by the corresponding journals and conferences
- making an individual sites study data accessible to the corresponding investigator after the completion of the study, if requested

Appendix C: Data Monitoring Committee (DMC)

A Data Monitoring Committee (DMC) is not needed for this study. This decision was made based on the following criteria:

- there are no interim analysis to test the primary objective,
- all devices used in the Improve SCA study are commercially released and used in accordance with their approved labeling, and,
- there are no experimental procedures involved in this study and therefore Medtronic does not anticipate incremental risks introduced to the subject as a result of participation in this study

Appendix D: Draft Data Collection Elements

Draft Case Report Forms for the Improve SCA study will be provided under separate cover. Final CRFs will be provided to sites via the electronic data management system after the site has fulfilled all requirements for database access.

Appendix E: Patient Informed Consent Templates

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

Appendix F: Participating Investigators and Institutions

At the time of the Improve SCA Clinical Investigation Plan Version 1.0 completion, site confirmation was not finalized. A complete list of participating investigators and institutions where study activities will be conducted will be distributed under a separate cover when available upon request.

Appendix G: Labeling

All components used within the Improve SCA study will be market released. Labeling for all market approved system components can be found with each package insert.

Appendix H: Committees

The Improve SCA Study will have the following committees:

Steering Committee

The steering committee members are appointed by the sponsor to assist in development and execution of this investigation. Nine steering committee members were chosen for this study. Additional members may be added at a later date. A listing of the members is provided in Table 3.

Publication Committee

The Steering Committee will serve as members of the Publication Committee, in addition to Medtronic representative(s). This committee will manage study publications with the goal of publishing findings from the data. The Publication Committee will develop the final Publication Plan as a separate document.

Episode Review Committee

An Episode Review Committee (ERC) will be responsible for evaluating device-treated ventricular episodes according to the ERC Charter. Device-treated ventricular episodes in the device episode log with EGM will be reviewed by the ERC, and adjudicated based on appropriateness of therapy (shocks and ATP) delivered to subjects. Inappropriate therapy will be identified based on adjudication rhythm truth and device episode log information.

This committee will consist of independent physicians and may include Medtronic personnel. At the time of the Improve SCA Clinical Investigation Plan Version 1 completion, committee members had not been identified. The ERC Member list will be under a separate cover when available upon request.

Education Committee

An education committee will be appointed to help with the development of educational and enrollment tools to support referring physicians. Education committee members will consist of approximately five interventional cardiologists or physicians with similar background or experience from various geographies. The educational committee is not finalized at the time of this CIP approval, and a listing of members will be provided when finalized upon request.

Appendix I: Abbreviations and Acronyms

Table 13: List of Abbreviations and Acronyms	
ACC	American College of Cardiology
ACE	Angiotensin-Converting Enzyme
ADE	Adverse Device Effect
AE	Adverse Event
AEAC	Adverse Events Adjudication Committee
AF	Atrial Fibrillation
AHA	American Heart Association
ARB	Angiotensin Receptor Blocker
ASEAN	Association of Southeast Asian Nations
ATP	Anti-tachycardia Pacing
BPM	Beats per Minute
CABG	Coronary Artery Bypass Graft
CAD	Coronary Artery Disease
CD	Compact Disc
CEE	Central and Eastern Europe
CFR	Code of Federal Regulations
CIP	Clinical Investigation Plan
CRF/ e-CRF	Case Report Form / electronic-CRF
CRT	Cardiac Resynchronization Therapy
CRT-D	Cardiac Resynchronization Therapy- Defibrillator
CTA	Clinical Trial Agreement
CV	Curriculum Vitae
DMC	Data Monitoring Committee
ECG	Electrocardiogram
EP	Electrophysiology/ Electrophysiologist
ERC	Episode Review Committee
ESC	European Society of Cardiology
FDA	Food and Drug Administration

HF	Heart Failure
HRS	Heart Rhythm Society
ICD	Implantable Cardioverter Defibrillator
IRB	Investigational Review Board
KG	Kilogram
LBBB	Left Bundle Branch Block
LLT	Lowest Level Term
LV	Left Ventricular
LVEF	Left Ventricular Ejection Fraction
MEA	Middle East and Africa
MEC	Medical Ethics Committee
MedDRA	Medical Dictionary for Regulatory Activities
MRI	Magnetic Resonance Imaging
NNT	Number Needed to Treat
NSVT	Non-sustained Ventricular Tachycardia
NYHA	New York Heart Association
OPC	Objective Performance Criterion
P/A	Posterior/Anterior
PI	Principal Investigator
PIC	Patient Informed Consent
PMA	Pre-Market Approval
POR	Power On Reset
PPR	Product Performance Report
PSA	Pacing System Analyzer
PVC	Premature Ventricular Contraction
QALY	Quality Adjusted Life Years
QoL	Quality of Life
RA	Right Atrium
RV	Right Ventricle
SAE	Serious Adverse Event
SADE	Serious Adverse Device Effect

SCA	Sudden Cardiac Arrest
SCD	Sudden Cardiac Death
SOC	System Organ Class
SOP	Standard Operating Procedure
SVT	Supraventricular Tachycardia
UADE	Unanticipated Adverse Device Effect
US	United States
VT	Ventricular Tachycardia
VF	Ventricular Fibrillation

Appendix J: Clinical Investigation Plan Signature Page (if applicable)

Improve SCA Study

The Improve SCA study is a prospective, non-randomized, non-blinded, global, interventional, multi-site post-market study. The purpose of this study is to demonstrate that primary prevention patients with one or more additional risk factors (1.5 prevention criteria) are at a similar risk of life-threatening ventricular arrhythmias when compared to secondary prevention patients, and would receive similar benefit from an ICD (or CRT-D) implant.

Clinical Investigation Plan Version 1.0 - December 23, 2013

I/we acknowledge that I/we have read, understood and agreed to abide by all conditions, instructions and restrictions contained in the above mentioned Clinical Investigation Plan. I/we agree to carry out all of its items in accordance with applicable regulations and in full compliance with the guidelines.

Hospital		
Title, First and last Name	**Signature**	**Date**