Official Title: Efficacy and Safety of Implantable Cardioverter-Defibrillator (ICD) Implantation in the Elderly (I-70)

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VA Cooperative Studies Program #592

Efficacy and Safety of ICD Implantation in the Elderly

Study Protocol

Version 2.3.2

June 15, 2016

Principal Investigator: **Steven Singh, M.D.**

Biostatisticians: **Michael Wininger, Ph.D.,**

Jane Zhang, Ph.D.

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LETTERS OF SUBMITTAL

Principal Proponent

DEPARTMENT OF VETERANS AFFAIRS
VA Connecticut Healthcare System
950 Campbell Avenue
West Haven, CT 06516

October 15, 2013
Timothy J. O'Leary, MD, PhD
Acting Chief Research and Development Officer
VA Central Office
810 Vermont Avenue, NW
Washington, DC 20420

Dear Dr. O'Leary:

We hereby submit CSP-592 for review by the Cooperative Studies Scientific Evaluation Committee. The study is intended to determine the survival benefit of the internal cardioverter defibrillator (ICD), as compared to the Optimum Standard of Care (OSC) in patients greater than or equal to 70 years old with systolic heart failure and reduced ejection fraction.

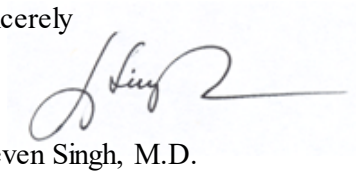
Sudden Cardiac Death (SCD) is a major public health issue affecting over 500,000 Americans each year. While the ICD has been shown to improve survival in patients with heart failure, its use in the 'elderly' has been questioned, since such patients were either excluded from or under-represented in trials. Thus the use of the ICD in this population is being individualized, and therapy is empiric.

We hypothesize that the ICD will reduce all cause mortality compared to Standard of Care. The study will last 5 years with 3 years of intake and a minimum of 2 years of follow-up. Seeking a 25% reduction in the hazard ratio (23.5% relative risk reduction) and a 2-sided alpha of $p<0.05$, a sample of 1,488 patients is needed. We have identified 40 potential sites, and expect to operate with a full complement of 30 sites.

The study is very important not only to our Veterans but to the public as well. The results of this study whether positive or negative will undoubtedly change the practice of medicine. After numerous meetings and lengthy discussions, we believe that our protocol is ready for review.

Thanks for your consideration,

Sincerely



Steven Singh, M.D.
Study Proponent

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Principal Proponent (Revision)

DEPARTMENT OF VETERANS AFFAIRS
VA Connecticut Healthcare System
950 Campbell Avenue
West Haven, CT 06516

February 20, 2015
Timothy J. O'Leary, MD, PhD
Acting Chief Research and Development Officer
VA Central Office
810 Vermont Avenue, NW
Washington, DC 20420

Dear Dr. O'Leary:

We hereby submit this revised protocol for CSP-592 following review by the Central Institutional Review Board (CIRB), and the convening of our Pre-Kick Off meeting; both occurring last month. Following extensive collaboration on the part of the Executive Committee and the staff at the Coordinating Center, we have refined our study and Protocol. The objective of the full study phase is to determine the survival benefit of the internal cardioverter defibrillator (ICD), as an additive therapy on top of Optimal Medical Therapy (OMT) in patients greater than or equal to 70 years old with systolic heart failure and reduced ejection fraction. We hypothesize that the OMT + ICD will reduce all-cause mortality compared to OMT without device. The objective of the Pilot study is to determine the feasibility of recruitment for the full study phase. We summarize the changes in greater detail in an accompanying Impact Statement, and submit to you at this time two copies of this Protocol: 1) a tracked-changes version, and 2) a "clean" copy of the latest version.

The Pilot phase will operate at 6 sites for 1 year; with a target of recruitment of 102 participants. If the study proves feasible during the Pilot, and is approved by CSP to continue, Phase 2 would expand to a five-year study with a full complement of 27 sites, with 3 years of intake and a minimum of 2 years of follow-up. Seeking a 25% reduction in the hazard ratio (23.5% relative risk reduction) and a 2-sided alpha of $p<0.05$, a sample of 1,462 patients is needed.

The study is very important not only to our Veterans but to the public as well. The results of this study whether positive or negative will undoubtedly change the practice of medicine.

Thank you for your support of this study,

Sincerely

Steven Singh, M.D.
Study Proponent

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Director: Cooperative Studies Program Coordinating Center

DEPARTMENT OF VETERANS AFFAIRS
VA Connecticut Healthcare System
950 Campbell Avenue
West Haven, CT 06516
COOPERATIVE STUDIES PROGRAM COORDINATING CENTER

In Reply Refer To: 689/151A

February 20, 2015
Timothy J. O'Leary, MD, PhD
Acting Chief Research and Development Officer
VA Central Office
810 Vermont Avenue, NW
Washington, DC 20420

Dear Dr. O'Leary:

Attached is a revision of CSP #592, "Efficacy and Safety of ICD Implantation in the Elderly" from the Principal Proponent, Steven Singh, MD and the Study Biostatisticians, Michael Wininger, PhD, and Jane Zhang, PhD.

The ICD (implantable cardioverter defibrillator) has a single, but powerful action: prevention of sudden cardiac death by restoring normal rhythm in the event of a life-threatening ventricular tachyarrhythmia. While ICD therapy is proven to be effective at preventing death in younger patients, its impact on all-cause mortality in those with advanced age is unclear.

Study Design
CSP #592 is a multi-center, randomized trial of two treatment strategies for prevention of sudden cardiac death, the second largest cause of death in the United States.

The study will operate in two stages: a Pilot study to determine feasibility of recruitment, and a full-scope study to assess the main study hypotheses. The Pilot study will operate for 1 year at 6 sites. The study in its full-scale implementation will recruit for an additional 3 years at 27 sites, and is designed to answers the question: does an ICD provide a mortality benefit in older heart failure patients? The primary objective is to compare the effect on all-cause mortality of two different treatment strategies: 1) optimal medical therapy including management with appropriate heart failure medications, and education in lifestyle modification and disease management, vs. 2) optimal medical therapy plus implantation of an ICD device. Secondary objectives are to compare the effect of the two treatment strategies on quality of life and whether there is a differential benefit under the conditions of high versus low co-morbid burden.

The target study population is Veterans over the age of 70 years and meeting Central Medicare and Medicaid Services guidelines for primary prevention of sudden cardiac death, including low ejection fraction, and New York Heart Association Class I, II, or III. The eligibility criteria are relatively simple to maximize the study's generalizability and to recruit a broad representative sample of older Veterans with heart failure. Seventy years of age was selected as the minimum age for eligibility for the trial because it is evident from VA databases that utilization of ICD therapy declines rapidly after age 70 and there have been few individuals over the age of 70 years that have been included in previous ICD clinical trials.

Sample Size

The target sample size is 1,462 total participants (731 per treatment group) enrolled from 27 VA medical centers. This sample size will provide 90% power to detect a 25% reduction in the hazard from all-cause mortality, and will provide ample power to identify clinically meaningful differences in treatment effect across co-morbidity levels.

Analytic Plans

The statistical analysis plans are straightforward and appropriate. The primary outcome of all-cause mortality will be analyzed as time to event and tested by the stratified log rank statistic (stratified by site and Charlson score <3 versus ≥ 3) with a type I error of 0.05 (2-sided). Patients who are lost or withdraw prior to an outcome assessment, or who do not experience an event will be right-censored at date of last contact, date withdrawn, or date of study exit. VA Vital Status File will be used to determine the vital status of all study participants who are lost to follow-up at study exit.

Budget

The total estimated study budget is $12.5 million. The budget is based on 3 years of participant intake and minimum follow-up of 2 years, with follow-up completed centrally after completion of post-implantation clinic visit, and accounts for both the Pilot and Full-scope stages of the study.

Peter Guarino, MPH, PhD
Director, WH-CSPCC

Director: Cooperative Studies Program Clinical Research Pharmacy Coordinating Center

DEPARTMENT OF VETERANS AFFAIRS
VA Cooperative Studies Program
Clinical Research Pharmacy Coordinating Center (151-I)
2401 Centre Avenue SE
Albuquerque NM 87106-4180

February 20, 2015

501/151-1
In Reply Refer To: CSP #95/CSP #592
File: STD_DOC

Timothy J. O'Leary, MD, PhD
Acting Chief Research and Development Officer
VA Central Office
810 Vermont Avenue, NW
Washington, DC 20420

Dear Dr. O'Leary:

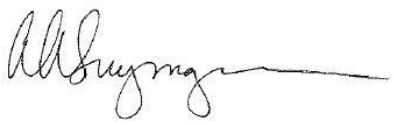
SUBJ: CSPCRPCC Issues Letter for CSP #592 / "Efficacy and Safety of ICD Implantation in the Elderly"

There are no PCC issues related to this study. The PCC will provide safety monitoring and MedDRA coding for the duration of the study. The study does not require either an Investigational New Drug (IND) or Investigational Device Exemption (IDE) application.

A CSP policy decision was made to require (i) Good Clinical Practices (GCP) training for study personnel (nurse coordinators and site investigators) at study initiation meetings, and (ii) in addition to central monitoring, periodic site monitoring/auditing of all CSP studies regardless of whether the study is to be conducted under an IND or IDE. A site initiation visit, annual site monitoring, and closeout visits were used in formulating the outline of the GCP training and monitoring/auditing plan included in the submission. The personnel and travel costs for providing GCP training and for the monitoring/auditing of sites are in the Site Monitoring, Auditing and Resource Team (SMART), portion of the PCC budget.

Should you have any questions or need additional information, contact me at (505) 248-3203.

Sincerely yours,



ALEXANDRA A. SCRYMGEOUR, Pharm. D.
Clinical Research Pharmacist
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EXECUTIVE SUMMARY/ABSTRACT

Background: Sudden cardiac death (SCD) is the second greatest cause of death in the United States, after all cancers combined. The implantable cardioverter defibrillator (ICD) has shown great efficacy in reducing all-cause mortality, and specifically SCD, by continuously monitoring the electrophysiological signatures of the heart, and intervening with a therapeutic shock in case of a detected arrhythmia. However, whereas the landmark clinical trials demonstrating ICD efficacy have included primarily middle-aged patients, there is little known of the impact of the ICD on older patients; clinicians often treat the elderly based on empiric judgments, rather than robust clinical evidence. There is an emergent need to study both efficacy and safety of the ICD in patients with advanced age.

Objectives: The overall aim of CSP #592 is to study the safety and efficacy of ICD implantation as a primary prevention strategy of SCD in patients 70 years and older. In particular, this study is designed to determine the comparative effectiveness of ICD, in addition to optimal medical therapy (OMT), in reducing all-cause mortality, versus OMT alone; OMT includes standard intervention for chronic heart failure patients, i.e. maintenance of proper heart-failure medications, lifestyle modification, disease management, adoption of healthy diet and exercise practices, etcetera. One particularly important secondary objective is to assess treatment efficacy under the conditions of high versus low co-morbidity burden.

Research Plan: This study will be conducted in two stages. The first phase will be a one-year Pilot study with 6 participating sites. If the study proves feasible during the Pilot phase, Phase 2 would expand to a five-year study in its full scope with the number of sites expanded to 27. The objective of the full study phase is to assess the safety and efficacy of implantable cardioverter

defibrillator (ICD) therapy in the elderly; the objective of the Pilot study is to determine feasibility of recruitment for the full study phase. The Pilot and main study are designed to recruit an average of 17 patients per site per year, of both genders and all ethnic/racial and socioeconomic backgrounds. All participants will meet CMS criteria for ICD implantation, and be stable on optimal medical therapy. Otherwise, the inclusion criteria are broad and the exclusion criteria are few; participants with most co-morbid general medical conditions are generally included to provide a broadly representative sample.

Participants will be randomized (1:1 ratio) to ICD + OMT (n=731), or OMT alone (n=731) stratified by participating site and co-morbidity level (Charlson score <3 versus ≥3). The sole acute treatment visit will occur on day of implantation (ICD arm); central follow-up will occur at 1-4 months post-randomization, and at every 6 months thereafter, until study close. Neither the participant nor the treating clinician will be masked to treatment.

We postulate that ICD + OMT will result in a 25% reduction in the hazard for all-cause mortality (42.0% versus 34.1% cumulative mortality after accounting for administrative losses). Using a log-rank test with a 2-sided test of significance, $\alpha = 0.05$, a sample size of 1,462 participants will be required to test the primary hypothesis with 90% power, adjusted for crossovers and losses. The plan study duration is six years in total: 1 year of Pilot phase + 5 years of full-scale phase; participants will be recruited through year 3 of the full-study phase, and followed for up to 5 years.

Public Health Significance: The impact of ICD implantation on the elderly has never before been studied as a primary objective in a clinical trial. This study will therefore have a major

impact on public health, whatever its outcome. There are many competing factors involved with primary prevention of SCD in the elderly via ICD, including 1) the impact on mortality, especially in the context of a declining rate of sudden death with advanced age, and 2) the impact on quality of life. Whereas the ICD implantation is an expensive and invasive procedure, patients and practitioners alike will look to CSP #592 as the first instance of highest-level clinical evidence as to the effect of ICD implantation on older patients.

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I. INTRODUCTION AND BACKGROUND

A. Background on Sudden Cardiac Death (SCD)

1. Overview of SCD

Sudden cardiac death (SCD) describes the unexpected natural death from a cardiac cause within a short window of time after the onset of symptoms, typically within one hour [1,2]. While the pathophysiology of cardiac arrest may be either mechanical or arrhythmic [3], the rapid death of SCD is usually attributed to a cardiac arrhythmia, although accurate classification of cause of death can be confounded since many sudden deaths are un-witnessed [2,4].

Risk factors for SCD include coronary artery disease, cardiomyopathy, cardiac rhythm disturbances including long QT syndrome and other ion channel diseases, hypertensive heart disease, as well as family history of cardiac disease [3,5,6]. Up to 80% of individuals who suffer from SCD have coronary heart disease[2] and anatomic findings at autopsy include acute changes in coronary plaque morphology, e.g., thrombus or plaque disruption, and active coronary lesions. Plaque rupture and apoptosis may participate in the genesis of some cardiac arrhythmias or conduction disturbances responsible for SCD [2,7]. Heart failure is also commonly associated with SCD and afflicts approximately 5 million people in the United States, with over 550,000 new cases diagnosed each year [8].

2. Incidence of SCD in the United States

SCD accounts for 300,000 – 450,000 deaths per year, with estimated incidence rates ranging from 150-250 events per hundred thousand individuals a year in the United States, depending on the definition used 9–12 (Table 1). Since coronary artery disease is a risk factor for SCD, the

incidence of SCD is highest amongst subgroups at risk for coronary artery disease, e.g., men and adults between 45 and 75 years of age 2.

Table 1. Incidence of sudden cardiac death (SCD) in the United States.		
Demographic Group	Incidence (per year)	Study
Men, 35-74 years	191 per 100,000 men	Gillum, 1989 [139]
Women, 35-74 years	57 per 100,000 women	
Adults (undefined)	100-200 per 100,000 adults	Zipes, 1998 [2]

3. SCD Prevention: Primary versus Secondary

The strategies for reducing mortality among patients at high risk for SCD are categorized as primary or secondary. Candidates for primary prevention have not yet had the clinical expression of a potentially fatal arrhythmia, but are identified by pre-existing disease indicating high risk for one [14]. Secondary prevention refers to interventions in patients who have survived a cardiac arrest due to ventricular tachyarrhythmia [14,15]. Thus, the distinction between primary and secondary prevention is whether a potentially fatal arrhythmia has already been experienced. The guidelines and data for primary versus secondary prevention are different.

4. SCD Prevention Options

There is a wide variety of anti-arrhythmic drugs that shape the cardiac action potential by interacting with either the beta-adrenoreceptor ("beta blockers") or a specific type of ion channel. However, except for studies of beta blockers, no placebo-controlled anti-arrhythmic drug trials have reported a benefit in reduction of all-cause mortality [16,17]. Beta blockers are widely accepted

as a highly effective therapy that can significantly reduce morbidity and mortality in patients with heart failure associated with left ventricular systolic dysfunction [18,19].

The mechanism by which beta blockers are thought to decrease the risk of SCD may be related to its elevation of ventricular fibrillation threshold. This effect is in addition to beta blockers' suppression of premature ventricular contractions (PVCs) or ventricular tachycardia (VT) events, which in themselves carry a potential risk. By contrast, the mechanism of the single-lead shock-only implantable cardioverter defibrillator (ICD) is to continually monitor the electrophysiology of the heart for sustained ventricular tachycardia or ventricular fibrillation, delivering an electrical shock if either are detected to reset the pace-making activity of the heart and return it to sinus rhythm. There are several different types of ICDs, produced by a handful of manufacturers. Each ICD is programmable to deliver therapy within a specific range of heart rate, heart rhythm, and ventricular beat morphology. There is now broad clinical evidence of the efficacy of ICDs beyond that of beta blockers in reducing SCD mortality in heart failure patients.

B. ICD as Interventional Therapy

1. Rationale for Use of ICD

There exists broad evidence of ICD efficacy for reducing mortality for adult patients with left ventricular systolic dysfunction, especially those with a history of myocardial infarction [20,21]. Also, because half of all deaths from heart failure are sudden events thought to be attributable primarily to lethal arrhythmias, ICD can be a highly effective treatment strategy in adults with heart failure [22,23]. Furthermore, there are few external impediments to ICD implantation: Central Medicare and Medicaid Services (CMS) expanded its ICD coverage, thus reducing the financial

burden associated with ICD implantation [24]. In addition, both device efficacy (99%) and rate of success of ICD implantation (99%) are excellent [21,25].

2. Early Case Studies

The ICD was first described for its ability to achieve ventricular defibrillation in active conscious dogs [26], and subsequently piloted in a 57-year-old woman, a 16-year-old boy, and a 43-year-old-man, yielding satisfactory discharges in all three cases [27]. However, while the ICD has demonstrated termination of tachy-arrhythmias [28], successful shock therapy does not necessarily translate into improved survival [10]. Primary prevention of sudden cardiac death and reduction of overall mortality in patients with left ventricular dysfunction was subsequently proven via randomized controlled clinical trials [29,30].

3. ICDs in Clinical Trials

Several landmark studies have demonstrated clinical efficacy in reducing all-cause mortality with ICD therapy. The primary findings of a selection of randomized clinical trials (RCTs), of primary- prevention type are shown in Table 2.

Table 2. Efficacy of ICD in reducing all-cause mortality in randomized clinical trials (RCT). †= hazard ratio (95% Confidence Interval); ‡=log-rank of cumulative survival versus anti-arrhythmic medication, placebo, or conventional therapy. CB=Coronary bypass, DC=Dilated cardiomyopathy, MI=Myocardial infarction.

Outcome	Study	Summary (Sample size, median follow-up, patient pool)
0.46 (0.26 – 0.82)†	MADIT-I [31]	N=196, 27 months; NYHA class I-III, with prior MI
1.07 (0.81 – 1.42)†	CABG-Patch [32]	N=1055, 32 months; CB patients <80 years old
10% (*P*=0.554) ‡	CAT [33]	N=104, 22.8 months; idiopathic DC
0.69 (0.51 – 0.93)†	MADIT-II [34]	N=1232, 20 months; NYHA class I-III, with prior MI

1% (*P*=0.800) ‡	AMIOVIRT [35]	N=103, 36 months; non-ischemic DC
0.65 (0.40 – 1.06)†	DEFINITE [30]	N=458, 29 months; non-ischemic DC
0. 77 (0.62 – 0.96)†	SCD-HeFT [29]	N=2521, 45.5 months; NYHA class II or III

From this evidence, the reproducibility of the apparent therapeutic benefit of ICD implantation at 23-35% supports the current guidelines that recommend that physicians should carefully consider the potential benefit of ICD therapy in eligible patients [23].

4. Guidelines and Support for ICD Implantation

On the basis of favorable outcomes reported among ICD recipients in RCTs, the American College of Cardiology and American Heart Association in 1995 established guidelines for heart failure to include ICD therapy for primary prevention of sudden cardiac death in patients with ischemic (class I, evidence A) and non-ischemic (class I, evidence B) heart disease and left ventricular ejection fraction (LVEF) of 30% or less who are receiving long-term optimal medical therapy and have a reasonable expectation of survival with good functional status for greater than 1 year [8]. Later that same year, after SCD-HeFT was published, the Centers for Medicare & Medicaid Services (CMS) approved reimbursement for ICD implantation in patients with ischemic or non-ischemic heart disease, LVEF of 35% or less, and New York Heart Association (NYHA) class II or III heart failure [24]. Subsequently the 2008 American College of Cardiology and American Heart Association guidelines extended the class one indication for ICD implant to the same population with an EF of 35% or less covered by the CMS criteria. ICD therapy is thus generally accepted as a safe and efficacious therapy.

5. Under-Utilization of ICD

Despite widely recognized record of safety and efficacy, ICD therapy is considered to be an under-utilized treatment option. Observational studies that have examined ICD implantation rates among potentially eligible patients with heart failure and low LVEF discharged from hospitals show several trends (Table 3). First, ICD utilization appears to be low in general: typically less than 40% of eligible patients have, or plan to receive, an ICD implant. Second, there are prominent sex and ethnic differences, with higher rates of ICD implantation among men than women, and whites versus blacks. Furthermore, there appears to be an age effect in the use of ICDs [36]. These findings on the under-utilization of ICD persist even after accounting for presence of severe co-morbid conditions that might make an otherwise eligible patient an unsuitable candidate for implantation.

Table 3. Utilization of Implantable Cardioverter Defibrillator (ICD) in the United States.

Demographic Group	Utilization	Source
Eligible patients	36.5 to 56.5%	Ruskin, 2002 [37]
Eligible patients	35.4%	Hernandez, 2007 [23]
Eligible patients	38.4%	Saba, 2009 [38]
Eligible patients	43.3%	Lakshmanadoss, 2011 [39]
Black women	28.2%	Hernandez, 2007 [23]
White women	29.8%	
Black men	33.4%	
White men	43.6%	
Women	35%	Lakshmanadoss, 2011 [39]
Men	48%	

It is noted that these estimates of ICD utilization must be interpreted with some caution as the rate of ICD utilization is difficult to estimate among potentially eligible patients. LVEF measurement is an important quality metric among patients with heart failure because it helps to inform many treatment decisions, including ICD therapy. However, up to 20% of patients with heart failure do not have LVEF recorded in their medical records and non-conformity rates increase substantially when patients with no documentation of LVEF are including. Furthermore, patients with no plans to receive ICD at the time of the survey, but later elect to receive an ICD would inflate estimated non-conformity rates [23]. For these reasons, ICD utilization rates can be difficult to estimate with precision.

6. Reasons for Non-Utilization of ICD

a) Contraindications

There are several specific contraindications to ICD therapy: NYHA class IV heart failure, cardiogenic shock or symptomatic hypotension while in a stable rhythm, coronary artery bypass graft (CABG) or percutaneous transluminal coronary angioplasty (PTCA) in the past 3 months, acute myocardial infarction in the past 30 days, candidacy for coronary revascularization, irreversible brain damage from cardiovascular disease, or disease with life expectancy less than 1 year [8]. While the ICD is a powerful corrector of tachyarrhythmia, not all SCDs are due to ventricular arrhythmia [21]. Concurrent myocardial infarction represents a potentially reversible cause for aborted sudden death, and constitutes a major contra-indication for cardioverter defibrillator implantation [40].

b) Watchful Waiting

Analyses of baseline mortality risk scores amongst participants receiving an ICD have found that individuals with a low risk of death or a high risk of non-sudden death experience minimal benefit from ICD therapy [41–43]. There is modest evidence that the proportion of patients matching the criteria for ICD implantation drops significantly after 6 months on optimal medical treatment, with a low rate of total mortality and especially SCD [44]. This may predispose some clinicians to a more conservative response to patient presentation with candidacy for ICD implantation and instead opt for watchful waiting while continuing optimal medical treatment.

c) Perceived Impact on Life and Lifestyle

An important consideration in the decision-making process prior to ICD election is whether the device will extend life without maintaining or improving Quality of Life (QoL). There is mixed evidence about the QoL following ICD implantation. For instance, anxiety, depression and fear are common psychosocial responses after implantation of an ICD; mood disturbance is especially high at the time of hospitalization for implantation, and recurs after resuscitation [45]. However, single-lead ICD therapy has shown little association with detectable adverse QoL effects in long-term follow-up [46].

The mechanism of action of an ICD is singular and instantaneous, whereas most anti-arrhythmic medications and cardio-therapeutics are ongoing and multifaceted and in addition to their effect on mortality they may also improve symptoms and disability [21]. In contrast, the ICD reduces the probability of SCD, which for some individuals may be a preferred mode of death [21].

d) Cultural Barriers

For reasons not apparently related to clinical need or device effectiveness, significant sex and ethnic differences persist in ICD utilization rates. For example, women are 16-32% less likely to have an ICD than men, and black patients are 5-24% less likely to have an ICD than white patients despite a higher risk for SCD [47] (Table 3). The reason for these disparities cannot be explained by practice guidelines or treatment evidence. The ACC/AHA guidelines recommend equal treatment, regardless of sex, race or ethnicity [8], and no major interaction effects between sex, race or ethnicity and ICD efficacy have emerged from RCTs [23].

Two possible explanations for lower ICD implantation rates in black individuals are: 1) a reduced preference for adoption of a "technological innovation," such as the implantable device; and 2) socio-economic drivers, e.g. reduced access to medical care or receiving treatment at a facility that does not provide quality ICD care [23]. However, these factors were not found to have an impact in several other studies [23,46,48]. While it is possible that demographic factors impact an individual's predilection for compliance with a physician's recommendation, in actuality little is known regarding the characteristics of patients who refuse ICD implantation [49,50].

e) Clinician Bias & Infrastructure

Historically, new technologies, such as the ICD, are expensive and thus their accessibility is limited. The consequent limit on number of procedures that can be performed in a given period results in a rationing behavior among clinicians [21]. In addition to patient preference and supply constraint, it has been suggested that low utilization of ICD among candidate patients could reflect referral bias. There is a direct relation between utilization of services, particularly invasive procedures, and in-hospital availability of specialists [51].

Age bias is a particularly prominent theory in the effort to explain under-utilization of ICD. While age is not an explicit contraindication for implantation, age compounds the clinician's perception of risks associated with ICD implantation [52–54]. There is some evidence that intervention using an ICD is best suited for patients of an intermediate risk category [41], and while age and co-morbidity are strongly associated with immediate risk, clinicians may be reluctant to implant due to a perception of increased risks associated with implantation from these factors [43]. From a published analysis of data obtained from the National Cardiovascular Data Registry, the authors concluded that physicians are conservatively selecting older adults for ICD implantation and deferring referral of older adults with high co-morbid burden [43]. Thus, without strong objective evidence, it appears that age is an important factor whether a patient is referred for ICD implantation or whether or not to implant a device.

7. Erroneous ICD Implantation

In contrast to the putative under-utilization of ICD among qualified patients, is the circumstance of implantation into individuals not meeting the evidence-based criteria of ICD. One recent survey of a registry of 111,707 patients revealed 25,145 (22.5%) receiving non–evidenced-based ICD implants [55]. If implantations are taken into account that are performed as a result of over-diagnosis of conditions for which ICD therapy is warranted, the rate of inappropriate implantation may be even higher [56]. Of note, some implantations found in registries not meeting evidence-based guidelines were not necessarily "inappropriate," since some variables in the registry may not be accurate [57].

C. Study Rationale: ICD Implantation Among the Elderly

1. ICD Prevention of SCD in Aged Patients

One of the interests of the clinical community with regard to ICD implantation is to better understand which patients groups will benefit and which will not [58,59], especially since the benefit of ICD therapy to prevent SCD and reduce overall mortality appears to be different across some patient subgroups [20,29,30,34,60]. For heart failure patients, age is a particularly important consideration, as the proportion of patients dying due to sudden cardiac death decreases steadily with age [61]. It is reasonable to expect that elderly patients with severe left ventricular dysfunction would not gain the same overall survival benefit from prophylactic ICD therapy as would younger patients because the survival benefit of ICD therapy is directly dependent on its effect on SCD –the only preventable outcome with ICDs– and not on overall mortality [62]. On the other hand, there is evidence suggesting that a population with higher baseline all-cause mortality risk does not preclude it from receiving substantial benefit from ICD therapy [53].

2. Age Demographics in Previous ICD Studies

The age ranges of patients receiving ICDs in major clinical trials over the past 15 to 20 years are summarized in Table 4 below. The mean and median age of study populations of these past trials range between 50 and 65 years of age.

Table 4. Statistics on age of patients receiving ICD in previously published clinical trials. *= mean ± std; †= median: range; ‡= median: inter-quartile range.		
Age in Years	Size of ICD Group	Study
62 ± 9*	95	MADIT-I [31]
64 ± 9*	446	CABG-Patch [32]
65 ± 11*	507	AVID [63]
58 ± 11*	99	CASH [64]
63 ± 10*	328	CIDS [65]
52 ± 12*	50	CAT [33]
64 ± 10*	742	MADIT-II [34]
58 ± 11*	51	AMIOVIRT [35]
58.4 : 20.3 – 83.9 †	229	DEFINITE [30]
60.1 : 51.9 – 69.2 ‡	829	SCD-HeFT [29]

Among the studies with a mean and standard deviation listed, the age of the 75th percentile is likely to be at or near 70 years of age. In the SCD-HeFT trial, which is noteworthy for its size (*N*=2,521); 70 years was the approximate threshold for the upper-quartile of participant age range.

3. Age as a Sub-Analysis in Previous Studies

Previous prominent clinical trials have analyzed the efficacy of ICD therapy in older participants via subgroup analysis. Table 5 displays the effect of subgroup analyses across different age groups in three major clinical trials of ICD for primary prevention patients.

Table 5. Sub-group analyses of ICD efficacy vs. anti-arrhythmic drug therapy in reducing all-cause mortality in aged cohorts in previously published clinical trials.		
Sub-Group Age	HR (95% CI)	Study
60 – 69 >70	0.80 (0.45 – 1.28) 0.64 (0.36 – 0.96)	MADIT-II [34]
<65 >65	0.67 (0.27 – 1.37) 0.64 (0.24 – 1.28)	DEFINITE [30]
<65 >65	0.68 (0.50 – 0.93) 0.86 (0.62 – 1.18)	SCD-HeFT [29]

The summarized results in Table 5 show a benefit of ICD in older populations but no consistent trend between age and ICD efficacy in reducing the risk of death from any cause.

4. Correlation of ICD Implantation and Age

In order to better understand the correlation of age and ICD usage, we reviewed the VA patient electronic medical records. Patient records from the National Data Service were assessed for match to systolic heart failure (SHF) and ICD within any of their diagnostic codes. Age of ICD implantation was estimated for those patients with both SHF and ICD codes. For those patients with only SHF codes, their age was noted at the time of their visit; if a given patient was observed on multiple visit occasions, a representative age was selected randomly from among their visit profile. In this way, a "snapshot" is generated of the potentially implant-eligible patient population at a given time, i.e. SHF patients in FY 2009, and a separate snapshot is generated of the age distribution of patients at the time of device receipt. Due to the comparatively low proportion of patients with both SHF and ICD diagnosis codes, age-at-implantation data were aggregated over 5 years (2008-2012), and the histogram data normalized this time period in order to scale it to the single-year snapshot of the SHF data.

A scatter plot is shown representing the ICD implantation rate among potential candidates by age (Figure 1). A constant scatter plot would indicate uniform implantation rate across age; positive or negative slopes indicate increasing or decreasing ratio with age.

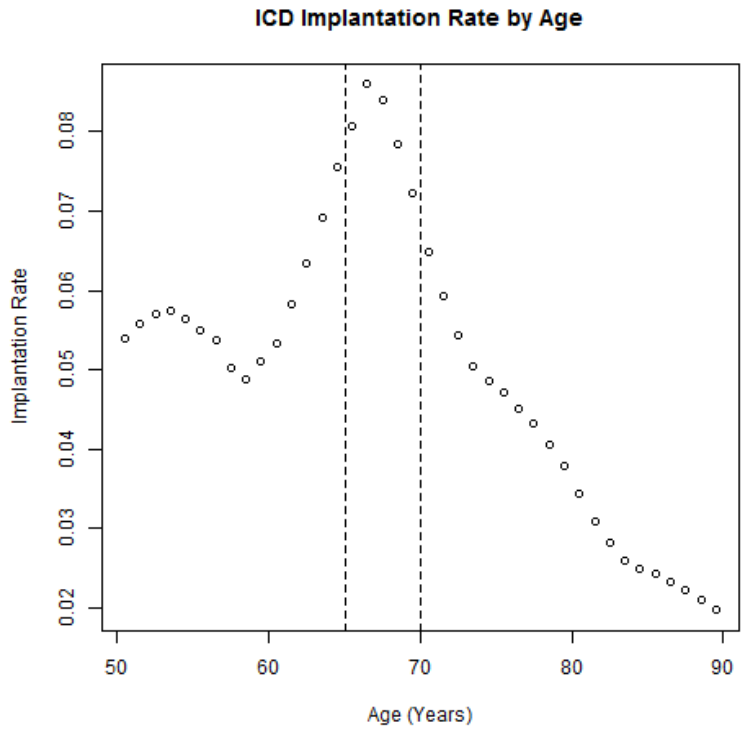


Figure 1: Scatter plot of ICD implantation rate with age.

As can be seen in Figure 1, the proportion of potentially eligible VA patients implanted with an ICD peaks at approximately 67 years of age and declines continuously thereafter. This data-driven assessment of the potentially available patient pool within the VA Healthcare System shows that there is a non-monotonic decrease in ICD implantation starting just before the 70th year.

5. Focused Study of Aged Cohorts

Despite the attention paid to age in subgroup analyses in major clinical trials, no randomized clinical trials have focused solely on an older population. Moreover, in the few recent non-randomized studies that have examined the efficacy of ICD therapy in older patients, the results are inconclusive. In one recent prospective cohort study of 965 patients with ischemic and non-ischemic cardiomyopathies (ejection fraction ≤35%), found that the efficacy of ICD therapy was consistent across age subgroups [53]. The hazard ratio and 95% confidence intervals for the sub-group analysis by age in this study were: <65 years (N=383): 0.74 (0.43, 1.28), 65-74 years (N=313): 0.76 (0.45, 1.29), and ≥75 years (N=269), 0.59 (0.39, 0.90).

In contrast, a meta-analysis of several primary prevention studies (MADIT-II, DINAMIT, DEFINITE, SCD-HeFT and IRIS) concluded that prophylactic ICD therapy may be less beneficial for elderly patients [62], defined as over 60 and over 65 years. However, the study's analytical approach of pooling data from subgroup analyses is susceptible to type I error. In addition, as with any meta-analysis, the results are subject to bias due to the choice of studies that are included and the heterogeneity of methodology used in each study. The authors acknowledged the limitations of their study due to the substantial qualitative heterogeneity among included trials and the fact that four important trials (MADIT-I, CABG-Patch, CAT, and AMIOVIRT) were not included because mortality data by age group were not available, and further concluded that the results of their meta-analysis demonstrated the need for a properly designed randomized trial of prophylactic device therapy in elderly patients [62].

6. Clinicians' Call for Study of ICD in Aged Populations

The community of practitioners has repeatedly called for a study focused on the impact of ICD on all-cause mortality in elderly patients.

Table 6. Appeals for a study of ICD in aged populations

Pull-out quote	Publication
"I would recommend that the Medicare Coverage Advisory Committee … advise CMS to issue a national coverage determination for ICDs only for the populations where evidence is strong that they actually gain desired outcomes, which may mean that only a small part of the Medicare population should be covered now, and certainly does not now include elderly..."	Phurrough, 2003 [66]
"The validity of this observation [that ICDs may be less effective in older patients] requires confirmation in prospective trials with adequate enrollment of patients with a wide range in age including the elderly..."	Krahn, 2004 [61]
"… a randomized controlled trial is the only proper way to address this question [of the effectiveness of ICD among elderly patients]."	Healey, 2007 [67]
"Future studies should help to further define the category of eligible heart failure patients who will derive a significant benefit from ICD therapy."	Hernandez, 2007 [23]
"Although retrospective analyses of the elderly in clinical trials have suggested that ICD and CRT therapy afford benefit, inclusion biases may have been present. Given that more than 40% of ICDs implanted are for primary prevention in patients older than 70 years and that only approximately 1,000 patients in this age range were included in randomized controlled clinical trials with ICDs, clinical trials of device efficacy in the elderly are needed."	Epstein, 2009 [68]
"Is there an age limit beyond which there is a poor value from an ICD? Yes, but we still need additional well-designed study outcome studies… to determine what age this might be and to fill in the many other knowledge gaps not addressed by clinical trials."	Heidenreich, 2009 [69]
"Our findings call for a properly designed randomized trial of prophylactic device therapy in elderly patients….. Because of the overall increase in life expectancy of the population and the fact that elderly patients benefit from medical therapies that were not always used in the older ICD trials, … we suggest that future trials consider enrolling elderly patients…."	Santangeli, 2010 [62]
"Primary prevention may be beneficial in older patients, but our findings need to be validated by future studies."	Kong, 2011 [70]

It is clear that there is an identified need for a study that tests as its primary objective the safety and efficacy of ICD therapy in an aged cohort. To provide the most convincing evidence of whether ICD therapy is effective on top of optimal medical therapy in the elderly, a prospective randomized controlled clinical trial is needed.

D. ICD Efficacy and General Health Status

Despite the guidelines for referral for implantation based on prognosis, age appears to predominate all other factors in referral for ICD [14]. However, decisions regarding ICD therapy should not be based on age alone, but rather should consider key factors that predispose to mortality without defibrillator implantation [71]. Nevertheless, following the completion of the landmark randomized clinical trials of ICD efficacy, it is evident that general health status is not typically measured, and rarely included as a variable of stratification [52,72]. Consequently, the therapeutic effect of ICDs in patients with high co-morbid burden remains an open question (Chan et al. 2009). To provide the most convincing evidence of whether ICD therapy is effective on top of optimal medical therapy in the elderly, a prospective randomized controlled clinical trial is needed.

E. Summary of Study Goals

The implantable cardioverter defibrillator has a single, but powerful action: to prevent sudden cardiac death by restoring normal rhythm in the event of a life-threatening ventricular tachyarrhythmia. While ICD therapy is proven as an effective preventer of SCD in younger patients, its ability to reduce all-cause mortality in those with advanced age is unclear. To answer this important question, we propose here a randomized controlled clinical trial of the safety and efficacy of ICDs in persons age 70 or older. At the same time, we will provide the most

convincing evidence of whether ICD therapy is effective on top of optimal medical therapy in the elderly with high- and low co-morbidity burden.

II. STUDY OBJECTIVES AND HYPOTHESES

A. Primary Objective

The primary objective of CSP #592 is to determine if a primary prevention strategy with ICD implantation in addition to optimal medical therapy (OMT) is effective in reducing all-cause mortality compared to OMT alone in patients ≥70 years of age who are eligible for ICD therapy according to current Centers for Medicare & Medicaid Services (CMS) criteria.

B. Primary Hypothesis

The primary hypothesis of CSP #592 is that implantation of an ICD plus optimal medical therapy will reduce all-cause mortality in patients ≥70 years of age versus OMT alone.

C. Secondary Objectives

1. Co-morbidity Burden

A secondary objective of this study is to ascertain whether age, co-morbidity burden, or age and burden together, are determinants in mortality outcomes in the OMT versus ICD + OMT group.

2. Quality of Life

An additional secondary objective of the study is to determine the effect of ICD implantation plus optimal medical therapy on QoL among elderly patients compared with optimal medical therapy without ICD.

D. Exploratory Analyses

1. Prevention of Sudden Cardiac Death

This study will also ascertain whether –irrespective of the effect of ICD on all-cause mortality– the ICD is effective in its designed mechanism of action, i.e. preventing sudden cardiac death.

2. Reduction in All-Cause Hospitalization

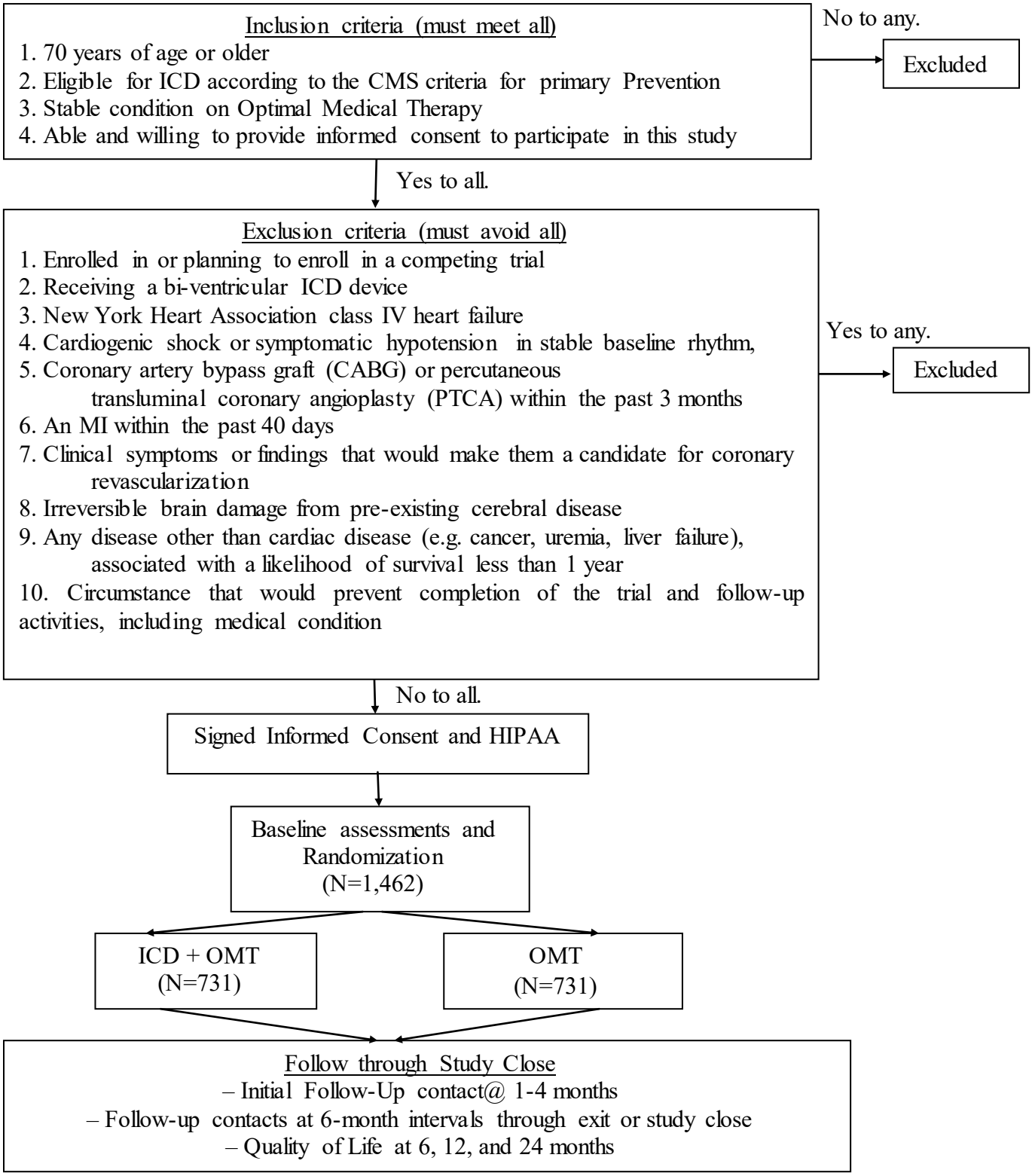
As an additional exploratory analysis, CSP #592 decreases the number of hospitalizations versus those with optimal medical therapy alone.

III. SUMMARY OF STUDY DESIGN

A. Overview

This aim of this study is to test the safety and efficacy of ICD therapy as a strategy for the primary prevention of sudden cardiac death (SCD) in elderly patients meeting the standard ICD implantation criteria. CSP #592 is a two-arm study, with participants randomizing either to 1) ICD therapy plus optimal medical therapy, or 2) optimal medical therapy alone. The primary hypothesis is that ICD therapy + optimal medical therapy reduces all-cause mortality compared to optimal medical therapy alone. The secondary objectives of the study are to examine the influence of co-morbidity burden on the effect of ICD therapy, and to establish the impact of ICD therapy on QoL, sudden cardiac death, and all-cause hospitalization. This study will operate in a two-stage format: a one-year Pilot to assess feasibility of recruitment, followed by a five-year study wherein the main study objectives will be accomplished. The Pilot study will operate at 6 sites; the study in its full scope will operate at 27 sites, pending outcome of the Pilot stage.

Figure 2: CSP #592, multi-site, prospective, randomized clinical trial comparing ICD therapy against optimal medical therapy (OMT).



B. Study Population and Rationale

CSP #592 will enroll 1,462 total participants (an average of approximately 55 participants from each of the 27 participating sites). Patients who meet the standard profile of a candidate for ICD therapy according to current Centers for Medicare & Medicaid Services criteria for primary prevention and are at least 70 years of age will be screened for eligibility. CMS criteria primarily include patients with an established diagnosis of chronic heart failure, a qualifying ejection fraction, and survivability beyond 12 months. The primary exclusion criteria for the study are: 1) contemporaneous participation in an ongoing interventional clinical trial, 2) inability to complete study protocol, or 3) election into receiving a bi-ventricular ICD device. Details of the eligibility criteria are provided in Chapter V. The inclusion criteria were designed to include a broad sample of elderly patients eligible for an ICD with few exclusions, in order to maximize generalizability.

C. Treatments and Rationale

1. Overview

The primary goal of this study is to compare ICD on top of optimal medical therapy against optimal medical therapy alone in reducing overall mortality in the patients with advanced age. For those participants randomized to the ICD group, implantation will occur as soon as possible after enrollment, with a target of 1 week post-randomization. A thorough medical history will be recorded prior to randomization for all participants, and stability on optimal medical stability will be established before participant can be randomized. After randomization, all participants will be returned to clinical care for continuation of their optimal medical therapy, according to local standard care for heart failure patients. Study follow-up phone callswill be scheduled for months

1 to 4, and at 6-month intervals post-randomization (6 months, 12 months, 18 months, etc.), all conducted by the study Central Follow-Up office; maximum follow-up will be 5 years.

2. Prior to Randomization

Recommendations for consideration of ICD therapy, particularly those for primary prevention, apply only to patients who are already receiving optimal medical therapy [68]. To ensure that the participants are truly in need of an ICD, they must be at least 40-days post-MI, and have a NYHA functional Class of II or III, and have recorded a qualifying ejection fraction in the past 6 months while being "clinically stable". Referring clinicians will be advised to treat patients beyond this minimal duration if they feel more time on medical therapy is warranted. They will be encouraged to refer patients to the study once they believe a patient is eligible after consistently receiving optimal medical therapy.

3. ICD Implantation

Patients interested and eligible to receive single- or dual-chamber ICD devices for primary prevention will be screened for study eligibility by the site investigator. Those patients who are eligible and provide written informed consent will be enrolled and randomized. Participants randomized to ICD therapy will be implanted as soon as possible, with a recommendation of less than 1 week following randomization.

4. Optimal Medical Therapy

All participants in CSP #592 will continue to receive optimal medical therapy designed to meet the Guidelines of the American Heart Association for primary prevention of cardiovascular disease and stroke [73]. This includes:

- Monitoring of clinical findings and therapies, both for suitability and compliance, e.g. blood pressure, blood lipids, and the use of medications such as angiotensin converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARB), aldosterone receptor blockers, beta blockers, aspirin, and statins, as specified in standard therapy guidelines and as applicable to the participant;
- Recommendation to engage in regular physical activity, if appropriate;
- Heart healthy diet counseling; and
- Healthy lifestyle management and counseling, including smoking cessation, alcohol consumption limits, weight management, and care of co-morbid conditions.

While these lifestyle modifications cannot be mandated, participant compliance with these conventions will be strongly encouraged. Per clinical trial evidence linking outcome to dose, all participants will be strongly recommended to be on maximum tolerated doses of a beta blocker and an ACE inhibitor or ARB[74] to be eligible for entry into the study. Optimal medical therapy was chosen to explicitly test the efficacy and safety of the ICD on top of guideline-driven medical care.

D. Outcome Measures and Rationale

This study is designed to compare the efficacy and safety of ICD implantation in an aged population in reducing all-cause mortality. The primary outcome is measured by survival time. The study is designed to detect 25% reduction in the hazard of all-cause mortality among participants randomized to ICD with an estimated average follow-up of 3.6 years. Key secondary analyses will be quality of life and the effect of ICD in high- versus low co-morbidity burden. Quality of life (QoL) will be measured by the Minnesota Living with Heart Failure

questionnaire, a cardiac disease-specific QoL instrument. Quality of Life will be measured at baseline, six months, twelve months, and twenty-four months.

E. Sample Size

The target sample size for CSP #592 is 1,462 total participants (731 per treatment group to achieve a total of 565 primary outcome events). This sample size will provide 90% power to detect a 25% reduction in hazard from all-cause mortality between ICD + OMT and OMT alone, and will provide ample power to identify clinically meaningful differences between treatments in longer-term safety and Quality of Life measures, as well as significance in the treatment interaction based on co-morbidity burden.

F. Data Collection and Assessments

Study participants will be assessed at baseline via in-person clinic visit and at month 1 to 4 following randomization and every 6 months thereafter via phone-based centralized follow-up; information related to the device will be collected on the day of implantation. The maximum follow-up is 5 years, the average participant follow-up across all participants (recruited in the pilot and full-scale stages) is 3.6 years. Chapter VIII provides details of the baseline assessments and procedures and Chapter 0 describes details of the follow-up schedule and procedures.

G. Alternate Design Considerations

1. Age Eligibility Criterion

Several different age cut-offs ranging between 65 and 80 years of age were considered for the primary inclusion criterion for this study. The age cutoff of 70 years was selected on the basis that it would yield a population that has not been previously studied well. Importantly, 70 years

is just above the age boundary of the upper quartile of enrollment of many previous clinical trials (See Table 4). Moreover, based on data queries performed within the National Data Service (NDS), and direct communications with investigators from one of these previous trials (SCD-HeFT), a cutoff of 70 years of age is likely to capture the patients for whom the steady decline in utilization of ICD is incipient. An older age cutoff was decided against because it would limit the study's generalizability and could compromise its feasibility due to the increased restriction of the eligible patient pool; whereas, a younger age cutoff, would include many patients where the evidence in support of the efficacy of an ICD is stronger and limit the study's ability to answer the study's primary question, i.e., is ICD implantation safe and effective on top of OMT in reducing mortality in the elderly. We believe that a minimum age of 70 years provides maximum opportunity to extend the extant literature; lowering the minimum enrollment age would dilute the study sample (limiting the study's value in extending the knowledge base), while raising the minimum enrollment age might exclude patients for whom the question of efficacy still appears to exist.

2. Co-morbidities and Functional Status

In addition to age as the primary entry criterion of the study, co-morbidity level and functional status was were considered as an eligibility criterion. It is clear that age is an imperfect predictor of mortality risk: a young person with more co-morbid conditions can have a greater mortality risk than an otherwise healthy aged person. Extensive consideration was given to the possibility of including younger patients with co-morbid conditions, but composing a list of conditions or risk level that was clinically meaningful was considered impractical, particularly because of the need to specify for each condition, or combination of conditions, a severity range that would constitute "moderate" risk. A general health status index, e.g., the Charlson Index, was

determined to be the most practical measure of disease burden as a complement to age. The Charlson score will be calculated upon study entry, and will be used as a stratification criterion, but will not be used explicitly as part of the eligibility criteria: entry to the study is based strictly on candidacy as determined through the CMS guidelines for implantation, which doesn't exclude an exclusion for co-morbidity but does list survivability beyond 1 year as a criterion. In addition, the general function level of participants will be measured at baseline using a six-minute walk test for exploratory analysis but not as an eligibility criterion. Therefore, to maximize the simplicity, generalizability and impact of the study, CSP #592 will select patients based solely on their age, without regard to their functional status per AHA/ACC guidelines [73].

3. Stratification Schema

This study is designed to stratify the randomization on two levels: site, and co-morbidity burden (Charlson score <3 and Charlson score ≥3). An alternative schema was considered that did not include stratification by site, but the variability of geography, demography, and local clinical approaches makes site an important co-variate that should be accounted for in the final analysis. Co-morbidity burden was chosen instead of age, because stratification by co-morbidity will allow for direct testing of the possible treatment interactions by co-morbidity level. A stratification involving all three variables (i.e. site, age, and co-morbidity) was determined to not be feasible given the sample size and number of sites involved in this study.

4. Generator Changes

Consideration was given to including patients 70 years of age or older in need of an ICD generator replacement. The ICD generator requires replacement every 5-7 years depending on use with a relatively less invasive surgical procedure compared to a new ICD implantation. The

decision on whether to include elderly patients due for a generator change involved consideration of several aspects of high relevance to this study including implications of ethics, study design, and the impact of the trial. It was ultimately decided that patients in need of a generator replacement are too dissimilar from patients requiring a new implantation to include both patient groups in the trial. Patients in need of a generator replacement who have experienced shocks vs. those that have not would also introduce increased study population heterogeneity. In addition, the inclusion of 5-year survivors of heart failure with an ICD could skew mortality risk, introduce a survivorship bias, or risk introducing uncontrolled devices, device elements, or implantation variables into CSP #592. Therefore, patients with an ICD due for a generator change will not be eligible for this study.

5. Additional Considerations

Conventional ICDs are implanted under the skin with the generator positioned beneath the collarbone; the defibrillation lead is inserted through the veins that enter the heart, allowing for direct attachment to the inside of the right ventricle. Sub-cutaneous ICD implantation provides patients with the same protection against sudden cardiac death as conventional ICDs, but leaves the heart and vasculature untouched: the lead does not course through the central veins of the chest, and does not attach within the chambers of the heart. This reduces complications associated with transvenous lead removal as might be indicated for lead infections, fractures, or mechanical blockage that prevents effective action of the ICD. Whereas the sub-cutaneous ICD has the same mechanism of action as conventional ICD, and is among the treatment options available in general practice, CSP#592 will allow for use of sub-cutaneous implants.

6. Aggregation to Registry

CSP #592 presents a unique opportunity to collect data during recruitment and enrollment, such that some advancement may be made against the question "Why do some eligible candidates elect into ICD therapy, versus not." This is an interesting question for its relevance both to the low ICD utilization rate (Section I.B.5) as well as the propensity for erroneous implantation (Section I.B.7). We will collect this data and review it both for interim evaluation of study entrance criteria, and for post facto reporting on recruitment statistics. This registry will be used locally to facilitate recruitment at each site, and may contain PHI; the local study team will be the only team members with access to this PHI. A de-identified version of this registry will be uploaded to the Coordinating Center on a regular basis, containing information about all screened patients, stripped of PHI, but retaining variables salient to understanding who is being screened, who becomes randomized, and their pathway to study entry, including: date screened, referral source, gender, age, race, ethnicity, and either date of enrollment or reasons for non-enrollment. These data will be considered a registry, and not a repository: the data will be used only for the purposes of CSP#592, and not for use beyond the completion of the study's aims. We note in particular that one of this study's aims is to assess feasibility of a study like CSP#592, with a 50-50 chance of randomization to OMT versus ICD + OMT; accordingly it is expected that this study will produce manuscripts for publication related to the screening and consent into CSP#592.

IV. IMPORTANCE TO THE VETERANS ADMINISTRATION

The Department of Veterans Affairs has anticipated the need to provide health care for an aging patient population since the return of soldiers following WWII, and along with the need to care for an aging population the VA has recognized the need for the inclusion of elderly participants in clinical trials [75]. CSP #592 is specifically designed to target this population and a condition that has one of the greatest impacts on the elderly. Sudden cardiac death accounts for 300,000 – 450,000 deaths per year, with an incidence rate of approximately 1.5-2.5 events per thousand individuals, depending on the definition used [9–12]. SCD is the second largest cause of death after all cancers combined, and more than twice the rate of the next-most common cause of death, chronic lower respiratory diseases [76]. Ventricular fibrillation, the most common cause of SCD, was once a uniformly fatal condition, but is now highly survivable with proper intervention [77], including a strategy of anti-arrhythmic medication and ICD implantation in patients meeting a small set of objective criteria.

The standard guidelines for ICD implantation, disseminated by the American Heart Association, the American College of Cardiology, and the Heart Rhythm Society, and adopted by the CMS in indicating Medicare coverage, are unambiguous and easily practiced. Despite the clarity of these Guidelines, it is speculated that ICD utilization among those eligible for implantation is less than 30% in some groups [23,37–39]. One major contributing factor to this gross under-utilization of ICD among the elderly is a lack of data related to the safety and efficacy associated with implantation in the elderly, as evidenced by the many appeals for a focused clinical study of implantation outcomes [23,61,62,67,69,70], and a knowledge gap recognized in the ICD implementation Guidelines: "Unfortunately, few clinical trials of device-based therapy have enrolled enough elderly patients … to reliably estimate the benefits of device-based therapy in this group" [68].

Heart failure, the major eligibility criteria for ICD implementation, is the number one reason for hospital admission in the VA [78]: we estimate that there are 13,882 patients over 70 years of age in a single calendar year within 40 potential VAMC study sites who meet the criteria for ICD implantation, of whom at maximum 4,505 (32.5%) have received ICD therapy based on a search of records within the National Data Service (NDS) and the VA Cardiac Device Surveillance Database (See Chapter XVI for details). Furthermore, while the number of elderly patients receiving ICD implants is relatively small (approximately 2,000-2,500 patients per year 2005-2010), the number of VA patients whose dual enrollment in Medicare allows them to receive ICD at a non-VA provider is large (approximately 20,000) [79]. Thus, this study has implications for a large number of Veterans, whether they are receiving treatment at the VA or not. By addressing impact on both mortality and Quality of Life, CSP #592 will have direct and major implications, not only for a rapidly growing segment of the VA patient base, but for the standard of care provided by the VA.

CSP #592 is a prospective randomized controlled clinical trial to compare the effect of ICD implantation plus optimal medical therapy vs. optimal medical therapy alone in the elderly. Whatever the results of this trial, it will have a major impact on clinical practice and will provide definitive evidence to inform ICD implantation guidelines and change clinical practice in the VA and throughout the world.

V. STUDY POPULATION

A. Inclusion Criteria

All patients with documented heart failure will be included if they meet all of the following eligibility criteria [68]:

1) 70 years of age or older
2) Eligible for ICD implementation according to the CMS criteria for primary prevention by one of the following conditions:
    (a) Documented prior MI and a measured LVEF ≤30% (includes NYHA class I, II, or III)
    (b) Coronary artery disease with a documented prior MI, a measured left ventricular ejection fraction ≤35%, and inducible, sustained VT or VF at EP study
    (c) Ischemic dilated cardiomyopathy (IDCM), documented prior MI, NYHA class II and III heart failure, and measured LVEF ≤35%
    (d) Non-ischemic dilated cardiomyopathy (NIDCM) > 3 months, NYHA Class II and III heart failure, and measured LVEF ≤35%
3) Stable condition on Optimal Medical Therapy
4) Able and willing to provide informed consent to participate in this study

As evaluation of above inclusion criteria, the ejection fractions must be measured by angiography, radionuclide scanning, or echocardiography, and MI's must be documented and defined according to the consensus document of the Joint European Society of Cardiology/American College of Cardiology Committee for the Redefinition of Myocardial

Infarction Ejection fraction must be measured within 6 months of consenting to be considered eligible for entry. This study will allow the recruitment of inpatients.

B. Exclusion Criteria

All patients satisfying the inclusion criteria will be excluded for any of the following criteria [68]:

1) Enrolled in or planning to enroll in a conflicting trial
2) Receiving a bi-ventricular ICD device
3) New York Heart Association class IV heart failure
4) Cardiogenic shock or symptomatic hypotension while in stable baseline rhythm,
5) Coronary artery bypass graft (CABG) or percutaneous transluminal coronary angioplasty (PTCA) within the past 3 months
6) An MI within the past 40 days
7) Clinical symptoms or findings that would make them a candidate for coronary revascularization
8) Irreversible brain damage from pre-existing cerebral disease
9) Any disease other than cardiac disease (e.g. cancer, uremia, liver failure), associated with a likelihood of survival less than 1 year
10) Circumstance that would prevent completion of the trial and follow-up activities, including medical condition

Regarding co-enrollment in CSP#592 and another trial: in order both study chairs must concur on the dual-enrollment. Both chairs must agree that the co-enrollment does not adversely effect the rights or well-being of the participant, and by either the sponsor (CSPCO) or by one or more of the studies. It is the responsibility of the Principal Investigator or Local Site Investigator

to determine if it is appropriate for a participant to be in more than one study concurrently. This may require, contacting the Principal Investigator of the other study to determine appropriateness. Where practicable, the LSI is encouraged to discuss with the Study Chair and the Executive Committee.

C. Inclusion of Women and Minorities

Because female Veterans comprise such a small proportion of the VA population, participating VA medical centers will be requested to make a special effort to recruit female veterans. No special recruitment of minorities is planned because they are well-represented among the VA population. Demographics, including race/ethnicity and sex, will be monitored for randomized, as well as excluded patients. All adult patients fulfilling the inclusion and exclusion criteria will considered for enrollment into the study. No patients will be excluded on the basis of gender, race or ethnicity.

D. Justification of Age Cutoff at 70 years

From inspection of the NDS database, it is evident that utilization of ICD therapy begins a steady and unceasing decline between age 65 and 70. Furthermore, there have been few individuals over the age of 70 years that have been included in ICD clinical trials. For these reasons, 70 years of age was selected as the minimum age of eligibility for CSP #592 as it represents both an incremental advance on the age profile of the previously studied population (while also maintaining adequate comparability to the existing literature), and targets with high precision the age at which there appears to be a turning point in the utilization of ICD in prevention of sudden cardiac death in high-risk patients.

E. Projected Health Status of the Study Population

Pursuant towards a full understanding of the potentially available study population, the general health status was assessed from the electronic medical records of systolic heart failure patients utilizing the VA Healthcare System in FY2009. For all patients with SHF codes, a Charlson co-morbidity index score was calculated using an algorithm according to the original Charlson framework [80], but using updated coding paradigms reflecting the Enhanced ICD-9-CM database [81,82].

Patients with SHF codes were categorized as a) having no ICD, or b) having ICD, based on the appearance of ICD-9 device code V45.02 anywhere in their medical record. For those with no record of ICD possession, a 'benchmark' visit date was taken from the FY2009 medical record; if a patient made multiple visits in FY2009, a representative visit was selected at random from all FY2009 visits (see Section I.C.4). For those with ICD, a surrogate "date of implantation" was estimated according to the date at which the device code first appeared in the medical record following at least one visit with SHF code but no device code. Charlson co-morbidity index score was calculated following interrogation of all medical records in the two years preceding the benchmark (SHF) and surrogate implantation (SHF + ICD) dates.

By computing the Charlson score for both SHF patients without ICD as well as ICD-implanted patients, it is possible to both: ascertain the general health status of the potentially eligible patient pool, as well as to make preliminary inferences as to whether there is a systematic difference between those who are eligible to receive versus those who receive ICD, in terms of co-morbidity burden. Summary results are presented in Table 7.

Table 7. General health status of CSP #592 potentially eligible patient population: Co-morbidity burden of SHF patients (*top series*), mirror that of patients already in receipt of ICD (*bottom series*); Source: National Data Service.						
Charlson Score	1	2	3	4	5+	Total
SHF Patients without ICD						
N	316	511	561	616	2,066	4,070
Percentage	7.8%	12.6%	13.8%	15.1%	50.8%	100%
SHF recipients with ICD (on day of ICD receipt)						
N	86	195	264	268	820	1,633
Percentage	5.2%	11.9%	16.2%	16.4%	50.2%	100%

Here, two inferences are made: Firstly, the potentially eligible patient population is, –in general– heavily burdened: All patients have Charlson ≥1; the majority of patients have Charlson ≥5; Charlson scores in this higher range are associated with a greatly elevated mortality risk. Secondly, it is evident that there is high concordance between the Charlson score distribution across SHF patients with- and without ICDs: there does not appear to be a systematic difference in general health status between those who receive and those who do not receive and ICD.

F. Implantation Rates by Disease Category

Following the calculation of aggregate Charlson scores, ICD implantation rate by disease category was assessed. For each of the seventeen disease states comprising the Charlson co-morbidity index, the proportion of SHF patients without ICD was compared against the proportion of SHF patients with ICD

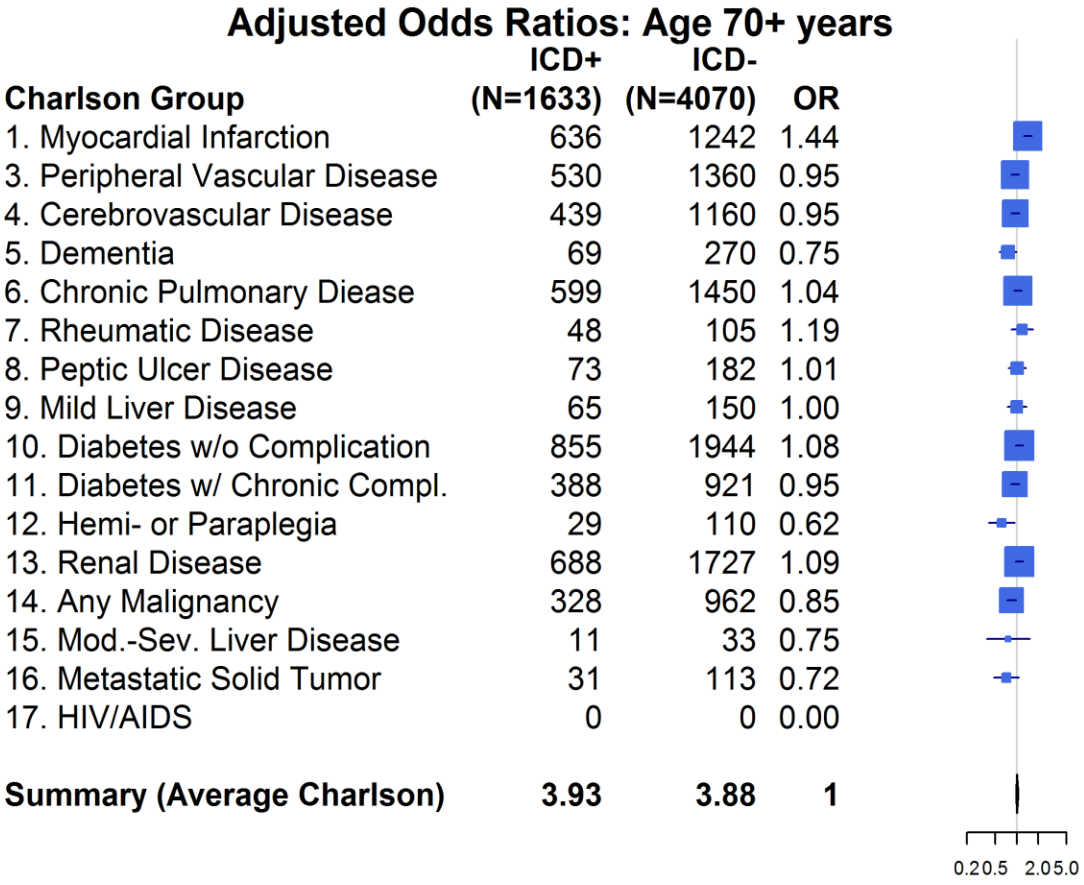


Figure 3: Forest plots of ICD implantation rate (versus non-implantation) for SHF patients in possession of diagnostic codes from among each of the seventeen Charlson co-morbidity index disease categories. (*Not shown: Charlson category 2, i.e. congestive heart failure*).

From Figure 3 it is seen that there is only one condition for which there is a significantly greater likelihood of ICD implantation (history of Myocardial Infarction; Odds Ratio = 1.44, 95% CI = 1.27 – 1.62, $P<0.001$). There are three conditions where the ICD is utilized less: Dementia (OR = 0.75, 95% CI = 0.57 – 0.99, $P=0.045$), Hemi- or Paraplegia (OR = 0.62, 95% CI = 0.41 – 0.94, $P=0.024$), and Malignancies (OR = 0.85, 95% CI = 0.73 – 0.98, $P=0.022$). Otherwise, the proportion of ICD patients with a given condition is similar to the proportion of SHF patients

without ICD; the aggregate Charlson score is similar across the SHF and SHF + ICD groups: 3.93 versus 3.88, OR = 1.01, 95% CI = 0.98 – 1.05 (cf. Figure 3 and Table 7).

G. Age versus Health Status as a Determinant in Implantation

As a final assessment of factors associated with ICD implantation within the potentially eligible patient pool, implantation status was regressed against three factors: age (as a continuous predictor), history of myocardial infarction (per Figure 3) and a modified Charlson score (as a continuous variable excluding MI). Results are shown in Table 8.

Table 8. Logistic regression of ICD implantation against age, general health status without considering history of myocardial infarction (charlsonNonMI, i.e. aggregate Charlson score not accounting for MI), and separate predictor of MI history.

	Estimate	Std. Error	z	Pr(|z|)
Intercept	6.01	1.04	5.78	<0.001
age	–0.09	0.01	–6.75	<0.001
charlsonNonMI	–0.26	0.20	–1.26	0.21
historyMI	3.72	1.78	2.09	0.04
Interactions	No significant interaction terms			

Here it is seen that age and history of MI are significant predictors in receipt of ICD; the modified Charlson score (i.e. Charlson that accounts for all non-MI co-morbidities) does not otherwise predict ICD receipt.

H. Justification of Stratification at Charlson Index 3

Though general health status does not appear to be associated with the rate of ICD implantation, whether there exists an interaction between co-morbid burden and treatment effect remains to be seen. Accordingly, this study will stratify on the basis disease burden, specifically participants will be stratified into "fair" and "poor" health status, on the basis of their Charlson score being lesser versus greater than/equal to 3. This threshold was established following the database review, and in consideration of the general criteria for implantation. Because those patients with the highest co-morbidity score would likely be determined to be ineligible for study (on the basis of 1-year survivability) we estimated the median Charlson score of study-eligible patients would be closer to Charlson score of 3. In this context, a classification of "fair" health status as corresponding to Charlson score of <3 is well-suited in terms of study feasibility, and would commensurate with the existing body of literature to which this study will ultimately be compared. This stratification is in addition to stratification by site.

VI. OUTCOME MEASURES

A. Primary Outcome

The primary outcome measure for this study will be death from any cause analyzed as time to event. The date of randomization will be used as the time origin. VA Vital Status File will be used to determine the vital status of all study participants who are lost to follow-up at study exit. The VA Vital Status File has been shown to be highly accurate compared to the National Death Index (NDI) [83]. As cause of death is not available from the VA Vital Status File, a NDI Plus database search will be performed for all participants who are found to have died through the database search in order to adjudicate the cause of death for secondary outcomes.

B. Secondary Outcomes and Exploratory Analyses

1. Quality of Life

Among the cardiac-specific quality of life (QoL) instruments, the Minnesota Living with Heart Failure questionnaire (MLHF) is considered to be among the best [84]. It has been widely validated [85–87], and it is more sensitive than the generic QoL measures in detecting clinically important changes over time in patients with heart failure [88,89]. The MLHF was also chosen as the QoL measure for this study because it is simple, inexpensive, short, easily understood by ill and elderly individuals, self-administered, and easy to score [90–97].

The MLHF questionnaire is designed to specifically assess the impact of heart failure on QoL. It consists of 21 questions that measure the effect of symptoms specifically related to heart failure and its treatment in adults [98,99]. The response to each question is scored on a 6-point Likert scale

(0-5). There are two subscales to MLHF: physical and emotional. The effect size outcomes of several studies employing QoL are summarized in the following table.

Table 9: Effect sizes reported using Minnesota Living with Heart Failure survey. MLHF on 105-point scale, including their calculated significance. Original references listed.

Effect Size	Interpretation	Source
1	Not significant	Rector, 1992 [97]
1.6	Not significant (P=0.33)	Kasper, 2002 [96]
4	P<0.001	Rector, 1992 [97]
5	Not significant	Owen, 2000 [94]
6.6	P=0.0006	Kasper, 2002 [96]
6.7	Not significant (P=0.41)	Curiati, 2005 [99]
9.6	P=0.01	Kasper, 2002 [96]
11.6	P=0.02	Curiati, 2005 [99]

A disease-specific instrument was chosen in favor of a broader ("generic") QoL assessment for the reason that questionnaires with greater emphasis on ICD-specific and arrhythmia-specific measures may be more sensitive to changes in outcome, and would be more impactful in addressing ICD as a treatment choice for life threatening arrhythmias [100]. The Minnesota Living with Heart Failure is designed to capture both physical and emotional (anxiety or distress) dimensions of patient well-being and is considered an effective and efficient instrument [101]. The MLHF is a proprietary instrument; its use requires procurement of a one-time licensing contract through the University of Minnesota.

2. Co-morbidity Burden

One of the primary reasons for doing a study like CSP #592 is to determine whether there are differential risk-benefit issues in the elderly: in patients with declined health status, the

likelihood of surviving long enough to derive benefit from device implantation is decreased. This study will test whether poor general health status shifts the risk-benefit profile. In this way, the Charlson Co-Morbidity Index is the most practical tool for incorporation into CSP #592, as it is an extensively validated method of measuring the prognostic impact of co-morbid disease [80,102].

3. Sudden Cardiac Death

Sudden cardiac death will include deaths that occur unexpectedly that is not preceded by an acute myocardial infarction. SCD will include the following events [103]:

- Death witnessed and instantaneous without new or worsening symptoms;
- Death witnessed within 60 minutes of the onset of new or worsening cardiac symptoms, unless the symptoms suggest an acute myocardial infarction;
- Death witnessed and attributed to an identified arrhythmia, e.g., captured on an electrocardiographic (ECG) recording, witnessed on a monitor, or unwitnessed but found on implantable cardioverter-defibrillator review;
- Death after unsuccessful resuscitation from cardiac arrest;
- Death after successful resuscitation from cardiac arrest and without identification of a non-cardiac etiology (Post-Cardiac Arrest Syndrome); and
- Unwitnessed death without other cause of death (information regarding the participant's clinical status preceding death should be provided, if available).

General considerations for SCD are that a subject seen alive and clinically stable 12-24 hours prior to being found dead without any evidence or information of a specific cause of death should be classified as SCD. Deaths for which there is no information beyond "Patient found

dead at home" may be classified as "death due to other cardiovascular causes" or "undetermined cause of death" [103]. A strategy for dealing with such deaths will be decided on by the Executive Committee prior to study initiation. Cause of death determination will be National Death Index (National Center for Health Statistics); the NDI *Plus* database has been shown to be highly accurate in resolving cause of death [104]; an Adjudication Committee may be assembled if deemed necessary by the Executive Committee.

4. All-cause Hospitalization

Hospitalization information will be captured by participant self-report and medical record review. Self-report is valid and reliable, especially with inpatient care and recall periods less than one year [105]; however, hospitalization data will also be collected from VA electronic medical records, and –where feasible– from non-VA providers. The study's case report forms will contain detailed information about the index hospitalization and will note re-hospitalizations, rehabilitation unit admissions, and long-term care facility admissions. Specifically, the case report forms will record the total number of days of hospitalization. Hospitalizations of any type will be considered: there is no minimum time-frame for hospitalization and both admissions and observations will be considered as countable. In this study, hospitalizations associated with index implantation, re-implantation, or generator changes will not be considered as countable all-cause hospitalizations.

C. Device Data

ICDs monitor and store data on a wide range of parameters including battery and lead function, patient activity, heart rate, frequency of pacing, and most importantly tachyarrhythmia events. The ICD stores extensive data on all tachycardia events that trigger therapy including beat to

beat intervals that met the programmed criteria for ICD therapy, electrograms from before, during, and after ICD therapy, the types of ICD therapy employed including shocks and anti-tachycardia pacing (ATP), the results of each therapy attempt, and the final results of ICD treatment. This data can be accessed in clinic using a device called a programmer which interrogates the defibrillator and then displays the results and allows the results to be saved as a PDF file. This data can also be retrieved "remotely" in the patient's home using a home monitoring device that is available to all newly implanted ICD patients. These home monitoring systems interrogate the ICD on a programmable schedule and transmit the data to secure servers via either land line or cell phone systems on a routine usually every 3 month basis and when certain programmable criteria for unscheduled transmissions are met. "On demand" transmissions can also be initiated by patients if they feel they are having a problem or are instructed to do so by their provider. The VA National Cardiac Device Surveillance Center manages the data flow from this remote monitoring and posts PDF files of all transmissions on their web site and alerts providers if there are urgent findings on a transmission. Remote monitoring provides significant benefits to the Study Team, as it 1) provides accurate, objective, and timely record of therapeutic events, and 2) provides a platform for assessing protocol adherence with regard to device programming, and 3) reduces loss to follow-up. CSP#592 study participants should be registered for remote follow-up with the VA National Cardiac Device Surveillance Center. Failureto register within 30 days of implantation will be considered a protocol deviation.

Files documenting all in clinic interrogations will be accessed by the Study Team in a separate and independent transaction from that conducted by the care provider as part of routine clinical practice. by investigators who see patients in clinic and by the VA National Cardiac Device

Surveillance Center. These files will be used most importantly as source documentation for exploratory analyses of ICD therapy events including the frequency of ICD therapy, the appropriateness of ICD therapy, the rhythms that trigger ICD therapy and the overall number of shocks experience by participants with ICDs. These files could also be used for other exploratory analyses focusing on other aspects of ICD function. The data contained within these files may be the result of direct interrogation of the device, or a filtered dataset exported from a larger database used in order to increase the efficiency of data analysis.

Lastly, every effort will be made to interrogate the device upon death. This is standard clinical practice and is often impactful in facilitating determination of the cause of death.

VII. HUMAN RIGHTS ISSUES AND INFORMED CONSENT PROCEDURES

A. Risks and Benefits

The ICD delivers electric shocks when necessary and stops most arrhythmias with weak electrical stimulation that cannot be felt. In the delivery of a strong shock, it is possible to feel a short pain, much like a punch to the chest. Known risks of ICD and implantation include

- swelling and/or bruising;
- bleeding (particularly around the heart, which can be life-threatening);
- cardiac perforation with and without pericardial tamponade, requiring pericardiocentesis or other surgical intervention;
- pneumothorax or hemothorax, requiring prolong hospitalization or chest tube placement;
- infection at the site of the implant, requiring intravenous antibiotics or system removal;
- damage to the vein where the ICD leads are placed;
- generator or lead malfunction requiring reoperation;
- pocket hematoma requiring evacuation, drainage, blood transfusion, hospitalization or extension of hospitalization;
- deep vein thrombosis;
- arterial embolus;
- drug reaction or hemodynamic instability resulting in abortion of the implant procedure;
- ICD shock or cardiac arrest within 24 hours of the procedure; and

- Other medical complications requiring a prolonged hospital stay (e.g. respiratory arrest, drug reaction, or re-hospitalization that is attributable to the implant procedure).

Further risks include those associated with diagnostic x-rays, sedation, and other complications during the implantation procedure. Participants may also receive inappropriate or unnecessary shocks. These shocks can be treated by changing the ICD settings, or by adding an anti-arrhythmic medication. However, because of complications and discomfort that may arise due to implantation and shocks, there is a risk of psychological distress for participants who receive an ICD.

Risks of Optimal Medical Therapy may arise due to changes in diet, exercise, and medication. During a blood draw or placement of intravenous fluid delivery, it is possible to experience some momentary discomfort, bruising, bleeding or pain at the site of needle entry into the vein. There is a very small risk of fainting. There is also a very small risk that infection could occur at the place where the needle goes into the arm.

Those participants receiving an ICD and/or OMT may potentially receive life-saving therapy that would prevent sudden cardiac death. Also close monitoring will occur throughout your participation in the study. Additionally, information we get from this study might help us treat patients in the future

B. Informed Consent Process

When patient eligibility has been confirmed, the study coordinator or site investigator will determine if the patient is willing and able to provide informed consent. The site investigator or designee will review and discuss the study with the potential study participant and answer any

questions that he/she might have. The general purpose of the study, along with detailed information about comparisons between therapy arms, the randomization process, the study timeline, including what is expected of the participant, and the rights of study participants will be clearly described. The risks associated with study therapy and procedures will also be addressed. The importance of patient confidentiality will be stressed, and the process for maintaining confidentiality will be described. Informed consent will be documented in this trial by the use of a standard consent form approved by the Institutional Review Board(s) of record. The consent form will be read verbatim to potential participants who are unable to read the document due to literacy or vision issues.

It must be ensured that the patient understands every aspect of the trial, including its risks and benefits, prior to signing the informed consent. Informed consent requires that the patient understand the details of the study and agrees, without coercion, to participation in the study. Merely obtaining a signature on a consent document does not constitute informed consent.

C. Capacity to Consent

To help ensure that potential study participants understand the study's purpose, procedures, risks, and benefits and his/her rights as a research participant, a standardized set of questions will be developed to assess a patient's actual and perceived understanding of the information presented, i.e. i.e. Informed Consent Questionnaire). The primary purpose of the Informed Consent Questionnaire is to help ensure that participants receive and understand the critical aspects of the study and their rights as a research study participant.

The Informed Consent Questionnaire will be presented to the potential participant after completion of the informed consent discussion. Incorrect answers will be discussed with the patient and the site investigator or coordinator and will emphasize the areas of the consent document where the correct information is stated and will further clarify the information to be certain the participant understands. The results from the informed consent quiz will be recorded on the data form and submitted to WH-CSPCC. Documentation (e.g., a progress note) of the consent process, the administration of the questionnaire, the questionnaire review and the determination of adequate understanding will be retained in the participant's study files. If it is determined that the patient is not able to adequately understand the study or their rights, the patient will be excluded from participating in the trial.

While there is no consensus on how to reliably assess autonomy or decision-making capacity, the use of a standardized questions and information aids can assure that participants receive adequate and consistent information about the trial. While the Informed Consent Questionnaire can assist the investigator in the determination of a patient's decision-making capacity, the final determination is the responsibility of the site investigator and must be carried out in compliance with all applicable local laws and regulations.

D. Surrogate Consent

No surrogate/proxy consent will be allowed to enroll into CSP #592. For patients who are competent to give informed consent and judged not able to carefully read the consent form because of either literacy issues or impaired vision, the informed consent will be read to the patient and his/her written consent will be obtained if he/she is willing to participate. Surrogate consent will be permitted for re-consent or for Release of Information (Form 3).

E. Withdrawal

Participants may withdraw at any time during the study. A withdrawal form (see Appendix E) will be provided to participants who wish to withdrawal. On the withdrawal form, participants will be asked whether they wish to:

- Revoke permission for the study to collect clinical data through VA medical records; or
- Revoke permission for the study coordinator or local site investigator to contact the participant.

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VIII. BASELINE ASSESSMENTS AND PROCEDURES

A. Recruitment and Screening

1. Recruitment Strategies

Several approaches will be used to identify potential participants. Veterans will be recruited for the study directly from each VA heart failure clinic participating in the study as well as cardiology and primary care clinics. Additional recruitment methods will include direct mailings, VA heart attack survivor support groups presentations, and advertisements and in the VA Community newsletter.

The study will also seek a waiver from the IRB for identifying potentially eligible participants through local database searches. In this case, the site investigators will work with primary care physicians and cardiology doctors in order to send letters to potential participants, inviting them to be screened to assess eligibility for the study. To facilitate study recruitment, CSP#592 will employ a Screening Tracker Log to capture patient-level data that will carry relevant information regarding age and source of referral for potentially eligible participants, as well as reasons for non-entry into this study, if applicable. A de-identified version of this Tracker will be passed to the Coordinating Center on a regular basis.

2. Remote VAMCs

Due to the limited number of electrophysiologists within the VA, it is common practice to refer patients to an implanting center from a distant facility; patients referred into CSP592 in this way shall be allowed to enter into the recruitment and collection of baseline data by either by remote methods or by study team member visit to the remote facility. All study-related activities will be

performed by Study Team members. Patients whose primary care is delivered at a VAMC that does not provide implantation may also be recruited for study as is done in standard clinical practice for ICD implementation. Face-to-face consent may be transacted either centrally, e.g. if the patient travels to the implanting center, or locally, e.g. if a qualified Study Team member travels to the local clinic. Remote consent can also be accomplished either through fax or through postal delivery, following delivery by a qualified team member via telephone or video teleconference. Consenting patients who cannot or prefer not to travel to their implanting VA may elect to be randomized during a teleconference where feasible, and will be informed of the outcome of their randomization. Distant participants being randomized to ICD therapy will be prepared to travel to the implanting Center under standard compensation arrangements per local site convention, and will not be specially compensated for this expense. In concurrence with common practice in VA facilities (VAMCs, CBOCs, etcetera) without staff electrophysiologists, recruitment at affiliated facilities will be facilitated by encouraging referrals for ICD consult at the study site.

Engagement of patients at remote VA facilities is meant to ensure broad recruitment into CSP#592 that is representative of the diverse patient pool normally serviced by the implanters within the VA system. Whereas ICD implantation is practiced by a small number of specialists, the implantation procedure is only performed at select VAMCs. Patients from more distant locales routinely consult with the electrophysiology staff at a regional VAMC via telemedicine from a remote VA facility; if implantation is decided, the patient will travel to the implanting center for the procedure. This “remote ICD consult” occurs across the VA, and may occur for any patients for whom ICD implantation may be clinically indicated, regardless of their apparent eligibility for CSP-592.

In many cases, e.g. distant CBOCs, these patients will already be in the implanting center's CPRS; for patients not already in the implanting center's CPRS (e.g. smaller referring hospital), however, once a consult referral is requested of the clinicians at the implanting site, the patient will appear in the local CPRS, and can be contacted in the same way as any patient in the local VAMC system. All recruiting and study activities, possibly including the first research contact, will be performed remotely by a Study Team member via Telemedicine. Essential baseline data in this study can be collected from the medical record, so there is no reason for clinicians at the remote site to be involved in study interventions or study data collection; remote clinicians will, of course, still be responsible for performing standard exams typical of any implantation candidate, but these will occur based purely on clinical indication and without regard to whether the patient has entered into CSP592.

Without this approach, the Study's recruitment will be compromised and may be biased by including only those patients receiving care from major VAMCs; the feasibility and generalizability of this study warrants recruitment at remote VA facilities.

3. Screening

All referred patients who have a diagnosis of heart failure, with low LVEF verified by echocardiogram, multi-gated acquisition scan or cardiac catheterization will be further screened for eligibility. If a patient is determined to be ineligible during the initial screening process, a screening instrument, which will include no patient identifying information, will be completed and submitted to the Coordinating Center. If the patient appears to be eligible based on an initial screening, the patient will be approached for participation in the trial. If the patient is willing to participate, an informed consent document and HIPAA authorization must be signed before

enrollment. For those patients who enroll, complete screening procedures and baseline assessments will be completed including a clinical history, a physical exam and assessment of cardiovascular health. After completion of the screening visit, the site will submit all screening forms and the signed informed consent documents to the WH-CSPCC. Source documentation for the inclusion and exclusion criteria will remain at the site.

B. Baseline Data Collection

When feasible, screening, consenting, baseline data collection and randomization will be completed on the same day. However, in order to provide potential participants time to consider enrollment, minimize participant burden and fatigue, and to provide time to complete all screening and baseline assessments, enrollment activities can be completed after screening and consent and divided into 2 or more sessions if needed. However, all baseline assessments must be completed within one month prior to randomization. If not, then the baseline assessments will be re-assessed or repeated. The results of the baseline assessments will also alert the Study Investigator to any pre-existing problems or medical conditions that might preclude randomization. Only patients meeting the inclusion and exclusion criteria (See Chapter V) after the completion of all baseline assessments will be randomized; patients not meeting these criteria will be excluded and will continue to receive care from by their regular VA physicians.

Listed below are all required baseline assessments. The data forms are provided in Appendix E. Baseline assessments cannot be administered without written informed consent and must be completed prior to randomization.

- Demographics and Military History
- Clinical History
- Laboratory Measurements

- EKG
- Physical Examination
- Six-minute walk test
- Medication Use
- Minnesota Living with Heart Failure Questionnaire

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IX. STRATIFICATION AND RANDOMIZATION

A. Randomization Procedure

Veterans who satisfy all of the study eligibility criteria, provide written informed consent and complete the necessary baseline assessments will be randomized to one of two treatment strategies: ICD therapy + optimal medical therapy, or optimal medical therapy alone. The treatment assignment will be provided through a web-based randomization platform or over the telephone to the site investigator or coordinator. The treatment allocation ratio for the two treatment regimens will be 1:1 within each stratum; participants will be stratified both by medical center and by Charlson score (Charlson <3, and Charlson ≥3), using a random permuted block scheme with randomly varying block size. Charlson score will be calculated using the method described in Section V. E. The random treatment scheme will be generated by the West Haven CSP Coordinating Center (WH-CSPCC). When a subject is to be randomized, the Study Coordinator or Local Site Investigator will complete the eligibility and baseline forms. If all eligibility criteria are satisfied and informed consent has been obtained, a new randomization will be assigned. This procedure will be tested and validated before enrollment begins.

The WH-CSPCC will review the overall and by-site randomization at least weekly during the enrollment phase of the study, and will be monitoring the randomization transactions with equal or greater frequency. The participant's unique study ID number will be linked in the randomization file to the treatment assignment for each individual. The randomization file data will remain separate from the rest of the study data on the central database.

Randomization will occur in most cases on the same day the patient has completed the necessary portions of the Screening and Baseline assessments and is judged eligible for randomization.

Delay in randomization due to participant or medical circumstances are permitted up to a maximum of 30 days past baseline data collection. When a new participant has been enrolled, his/her electronic medical record will be updated indicating participation in the study. Source documentation for eligibility criteria and randomization will be kept at the site with the participant's study folder.

B. Blinding

Neither the participant nor the study personnel at the site will be blinded to the treatment assignment. The variable block sizes included in the randomization scheme will be designed to help conceal the next treatment assignment for each site to reduce the chance of selection bias. The Study Biostatistician and the Data Monitoring Committee will operate with a blinded treatment coding (Treatment A versus Treatment B) for the analysis and review of the data, until such time that the DMC requests removal of the blind. As far as is feasible, decision-making within the study will be performed without removing this treatment code.

X. TREATMENT REGIMENS

A. Overview

Eligible patients who consent for the study will be randomized to ICD implant plus optimal medical therapy vs. optimal medical therapy alone. Standards for optimal medical therapy in the study will be defined by current practice guidelines, but will generally comprise medical therapies and lifestyle modifications. Optimal medical therapy will be closely monitored prior to enrollment, in order to be certain Veterans are receiving the best evidence-based care possible. In addition to optimal medical therapy, participants randomized to the ICD arm will have regular consultation with their Device Technician per standard clinical practice.

B. ICD

1. Overview

Participants randomized to the ICD group will be implanted as soon as possible, with a target window of one week or less between randomization and implantation; this time frame is sought in order to minimize the opportunity for SAEs to accrue before study treatment can be delivered, and to create maximum compatibility between the AE collection window on OMT arm (first 30 days post-randomization) and the OMT + ICD arm (30 days post-implantation). ICD therapy will be standardized with respect to rate cut off zone for defibrillation and anti-tachycardic pacing.

2. Device Specifications

This study will enroll patients eligible for standard single- and dual-chamber ICD devices. A dual-chamber device includes a pacing lead in the right atrium, plus a defibrillator lead in the

right ventricle. The atrial lead provides theoretical advantages to the pacing modality and diagnostics, particularly in the elderly [106], who are at higher risk for both sinus and AV nodal dysfunction. However, the clinical superiority of dual-chamber devices has not yet been shown conclusively and recent guidelines do not specifically address single- versus dual-chamber device selection. Dual-chamber devices may also carry a higher risk of adverse events [68,106,107]. While the prevalence of dual-chamber devices is low or non-existent in the studies that are comparable to CSP #592, i.e. AVID, MADIT and SCD-HeFT [29,34,63], it has been reported that the number of dual-chamber devices in clinical practice are somewhat higher than those studied in clinical trials [108].

CSP #592 will specifically exclude patients who meet the criteria of ICD implantation as secondary prevention, require a generator change on an existing ICD device, or who receive a bi-ventricular ICD device. A bi-ventricular cardioverter-defibrillator (BiV ICD) provides cardiac resynchronization therapy for patients with congestive heart failure and left bundle branch block on EKG. BiV ICD devices require left ventricular epicardial lead placement through the coronary sinus that may extend and complicate the implantation procedure. Cardiac resynchronization therapy is a distinct and dissimilar therapy from that delivered by the ICD, and the patients qualifying for BiV ICD implantation depart from those targeted for enrollment in CSP #592 and historically important clinical trials.

Inclusion of patients due for generator change involves consideration of several aspects of high relevance to this study including implications on ethical treatment and study design. For instance, whether the patient has experienced shocks or not could make stratification intractably complex (or, if pooled with *de novo* implantations: make the patient pool untenably

heterogeneous), and inclusion of 5-year survivors of heart failure could skew mortality risk, introduce a survivorship bias, or risk introducing uncontrolled devices, device elements, or implantation variables into CSP #592.

In summary, participants requiring single- and dual-chamber devices are eligible to enroll in CSP #592; any participants who are due for an ICD generator change, or are receiving a BiV ICD device will not be eligible for this study.

3. Testing

Defibrillation-threshold testing (DFT) involves inducing ventricular fibrillation to ensure reliable sensing, detection, and defibrillation from a recently-implanted device. DFT was considered prudent practice when failure of defibrillation was common, recipients had a high risk of ventricular tachycardia or ventricular fibrillation, and the only therapy for rapid VT or VF was shock [109]. DFT incurs a small, but non-negligible risk of mortality (0.016%) and stroke (0.026%) [110], but may be ineffective in extending one- or five-year mortality [111]. There are currently no guidelines for when DFT should be implemented, and the benefits are thought to outweigh the risks in only a small number of patients [112,113]. Therefore, the decision to carry out DFT will be left to the discretion of Study Investigator, with any such testing being noted in the study data base for possible adjustment in the statistical analyses. The Investigators of CSP #592 will be offered the following guidance: the decision of whether and how to conduct DFT is left to the discretion of the Study Investigator, with the expectation that the frequency of device testing commensurate with the usual practice of the Local Site Investigator.

4. Programming

One potentially deleterious outcome that this study shall seek to avoid is that of inappropriate shocks. Strategically chosen device programming parameters have been shown in a clinical trial setting to significantly reduce the rate of morbidity index events in primary prevention patients when compared with the rate of events for patients in the historical physician-tailored control cohort [114–116]. Specifically, programming strategies that prolong detection duration, increase the heart rate threshold of tachycardia detection, use supraventricular detection discrimination algorithms and ATP, and encourage first shock termination of tachyarrhythmias can safely and substantially reduce the number of tachyarrhythmias subjected to shock therapy [117].

Moreover, it is recommended that single-chamber devices be programmed to back up VVI pacing [29]. The parameters specified below have been shown to provide significant benefit over "discretionary programming" at the time of implant. In particular, brady pacing parameters and tachycardia detection and treatment parameters will be programmed to minimize ventricular pacing and minimize inappropriate therapy. Brady pacing will be set to VVI 40 BPM and tachycardia detection and therapy will be programmed based on parameters shown in randomized controlled trials to reduce the risk of inappropriate ICD therapy, as described in the following tables:

Table 10: Tachycardia Detection					
Make	***detection Rate/cycle length***	***detection Delay or NID***	***Monitor Rate/cycle length***	***Monitor duration/NID***	***Discriminators***
Medtronic	VF: 188 BPM /320 ms	30/40 intervals	171 BPM 350 ms	32 intervals	Stability 50, Wavelet On, SVT limit 300 ms
Boston Scientific	VF: 200 BPM/300 ms	2.5 seconds	170 BPM 350 ms	2.5 seconds	Onset On, stability On
St. Jude	VF: 250 BPM/240 ms VT-2: 214 BPM/280 ms VT-1: 181 BPM/330 ms	VF: 12 intervals VT2: 18 intervals VT-1: 25 intervals	171 BPM 350 ms	20 intervals	Onset On Stability ON Morphology ON "if all" in VT-1 zone only
Biotronik	200 BPM/300 ms	18 out of 24	171 BPM 350 ms	26 intervals	Stability with SMART 12%

and

Table 11: Tachycardia Therapy		
Make	***ATP***	***shocks***
Medtronic	ATP during charging 1 Burst, 88%, 8 pulses	Maximum
Boston Scientific	Quick Convert ATP ON	Maximum
St. Jude	VF: none VT-2: 1 Burst, 85%, 8 stimuli VT-1: 2 Burst, 85%, 8 stimuli	Maximum
Biotronik	ATP One Shot ON 1 Burst, 85%, S1 number 8	Maximum

If during follow-up a clinical situation arises such that a modification of this programming is in the best interest of the patient programming changes are allowed and will not be a protocol violation. However, while the implanting clinician is very strongly advised to adhere to these programming parameters, it is possible that clinician judgment may call for change to some of these parameters. Deviation from this programming at the time of

implantation is allowed, but is considered a Protocol Deviation; in this case, Form 23 should be submitted to notify the study that a change in programming has been made.

Thus, CSP#592 will expect all devices to be so programmed at time of implant. Programming changes that depart from these parameters at time of implant (whether intentionally or unintentionally) will be considered protocol deviation. After day of implantation, programming changes will be allowed based on clinical indications, such as development of heart block, development of slow VT, and syncope with VT/VF. Ultimately, the programming parameters will be left to the discretion of the investigator.

5. Re-implantation

Patients who have previously had an ICD or pacemaker explanted will not be eligible for entry into this study. For patients receiving an ICD as part of CSP592, and then being explanted and re-implanted, e.g. if the study implantation becomes infected and the device is removed and then re-implanted, then no new ICD Implantation Case Report Form (Form 12) is to be completed; the second implantation procedure is to be documented via a Process Note and Site Data Edit Form (Form 22) when the device or procedure information needs to be updated (as well as SAE and Hospitalization Forms, as appropriate). Adverse Events will be collected after any implant procedure; AEs will be assessed in two different analyses: 1) 'index AEs', occurring in the 30 days following the first implantation procedure, and 2) 'all AEs', occurring in the 30 days after any implantation procedure.

C. Optimal Medical Therapy

1. Overview

Optimal Medical Therapy must be established prior to entry into the study, and will be documented at the time of Randomization. Notwithstanding this condition for entry, Study team members will be available to provide guidance on where to learn more about lifestyle modification, exercise training, and disease management as needed, so that every participant will be exposed to the basic skills required to sustain improved health and well-being. Participants will also be encouraged to discuss lifestyle modifications with their regular treating clinician; however, the instructions and –as applicable– educational materials provided by the Study Team will be the same as those that would be provided by the clinical care team outside of the study; there will be no study-wide materials provided. These activities comprise the field guidelines for primary prevention of cardiovascular disease and stroke. Details on these lifestyle principles follow.

2. Physical Activity

AHA Guidelines for Primary Prevention of Cardiovascular Disease and Stroke, suggest moderate-intensity physical activity for 4-7 days of the week, at 40-60% maximum capacity, equivalent to a brisk walk (15-20 min per mile), at a duration greater than 30 minutes. Flexibility and resistance training are also recommended, with additional benefits gained from vigorous-intensity activity (>60% maximum capacity) at a reduced frequency [73]. Where it is anticipated that rigorous physical activity may not be appropriate for every participant in CSP#592, clinician discretion will be urged here.

3. Diet

Participants will be encouraged to adopt a diet that includes a variety of fruits, vegetables, grains, low-fat or non-fat dairy products, fish, legumes, poultry, and lean meats. Energy intake should commensurate with energy needs, and changes should be made to achieve weight loss when indicated. Food choices should reflect a reduction in saturated fats (<10% of calories), cholesterol (<300 mg/day), and trans-fatty acids by substituting grains and unsaturated fatty acids from fish, vegetables, legumes, and nuts. Salt intake should be minimized, and alcohol should be limited: ≤2 drinks per day in men and ≤1 drink per day in women [73].

4. Lifestyle Management

Where appropriate, a management of concomitant risk factors and co-morbidities should be undertaken, in order to mitigate risk of cardiovascular events. Smoking cessation, weight management, and diabetes management are considered essential to a complete risk intervention in cardiovascular disease. Compliance with medications that regulate blood pressure, blood lipids, and normal sinus rhythm should be maintained [73]. All patients will receive guidance on stress management techniques and –as appropriate– technical explanations about their device, as is recommended for best practices in patient education [100,118]; this guidance will come from their regular treating clinicians de rigueur, but will made available upon request by the local Study Team, using whatever educational materials (pamphlets, etcetera) may be available locally..

5. Therapy Delivery

All study participants will engage in an information session with the Local Site Investigator or Study Coordinator prior to randomization. During this session, participants will be advised of the AHA Guidelines for Primary Prevention of Cardiovascular Disease and Stroke, and provided

recommendations on how to implement the Guidelines. Participants will be invited to ask questions to their satisfaction, and a Study Team member will provide clinical referrals and/or provide printed materials as needed.

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XI. FOLLOW-UP

A. Time Table

All randomized participants will be followed at 1 to 4 months post-randomization, and at 6-month intervals starting from their randomization date, through study closeout (maximum follow-up 5 years). Most measurements will be collected at every 6-month visit. The schedule of baseline and follow-up assessments is given in Table 12 below. The estimated time to complete the follow-up is 15-30 minutes. All follow-ups will be performed by Central Follow-Up staff or the Chair's Office. Every effort must be made to ensure equal study follow-up for both study arms. For this reason, participants randomized to OMT will also receive the 1-4 month follow-up. This is an important and purposeful facet of the study design.

Table 12: Schedule of Baseline and Follow-up Assessments								
Evaluation/Form	**Approx. Time to Complete:**	**Screening[1]**	**Baseline[1]**	**Day of Implantation[1]**	**Initial Follow-up[2]**	**Every 6 Months[2]**	**End of Study[2]**	**As Needed[1,2]**
Informed Consent Form	120 min	X						
ICF Questionnaire	5 min	X						
HIPAA Authorization Form	5 min	X						
Form 01: Screening	10 min	X						
Form 02: Participant Contact Information	5 min	X						
Form 03: Release of Information	10 min	X						
Form 04: Baseline Demographics and Military History	10 min		X					
Form 05: Baseline Clinical History	20 min		X					
Form 06: Baseline EKG	30 min		X					
Form 07: Baseline Laboratory Measurements	15 min		X					
Form 08: Physical Examination	30 min		X					
Form 09: Baseline 6-Minute Walking Test	20 min		X					
Form 10: Medication Use	15 min		X		X	X		
Form 11: Quality of Life	10 min		X			X[a]		
Form 12: ICD Implantation	20 min			X				
Form 13: Follow-Up	5 min				X	X		
Form 14: ICD Follow-Up	10 min				X	X		X
Form 15: Therapy Event Report	10 min							X
Form 16: Therapy Event Adjudication Form	20 min							X[3]
Form 17: Adverse Event	30 min							X
Form 18: Serious Adverse Event	15 min							X
Form 19: Hospitalization	20 min							X
Form 20: Adjudication (Death Review)	30 min							X[3]
Form 21: Note-to-File	5 min							X
Form 22: Site Data Edit	5 min							X
Form 23: Protocol Deviation	20 min							X
Form 24: Withdrawal Form	5 min	X						X
Form 25: Exit Form	10 min						X	

[a] Form 11: Quality of Life is only collected at months 6 and 12 and 24 of follow-up., [2]Completed by Central Follow-Up Personnel or Chair's Office, [3]Completed by a designated adjudication committee

B. Follow-up Procedures

1. Measurement of Outcome Variables

Quality of Life will be measured in-person during baseline observation, and over the phone at months 6, 12 and 24.

Additionally, ICD interrogation records will be reviewed for device-related complications, such as lead failure; the device itself will be interrogated to confirm proper functioning, and to determine if any episodes of ICD therapy have occurred. The results of ICD interrogation will be saved in .PDF format, and transmitted to the study center.

2. Remote Monitoring

In addition to regularly scheduled follow-up, participants randomized to the ICD implantation arm will be monitored where possible using standard device interrogation performed either in association with their follow-up phone calls, or whenever device reports are generated, usually following therapy delivery. All therapeutic activities will be recorded via the device's remote monitoring capabilities, which capture salient physiological data prior to a device-delivered therapy, as well as information about the intervention itself and information about device programming changes. As part of routine clinical practice, these data are transmitted from the device to the manufacturer, placed in a VA-sponsored database accessible to the central follow-up office , and communicated to the treating clinician. The CSP#592 Study Team will access this record in parallel, obtaining either from the device manufacturer or the National Registry; the Study Team's access of the record will not interfere with the treating clinician's ability to receive and act on this information. Data are taken from the device in a completely non-invasive way,

i.e. the participant is uninvolved and unaware of the transmission: no participant contact or interaction is necessary for data exchange.

In addition to device interrogation during clinic visits participants in the ICD arm will also be followed via remote monitoring where possible, which is now part of the standard of care for ICD patients in the VA system. Participants may be provided with a home monitoring device that can communicate wirelessly with their ICD and will download and transmit a complete interrogation of the ICD on a regular schedule (usually every 6 months). In addition, unscheduled transmissions can be initiated by the ICD if preprogrammed criteria such as lead or battery failure are met. Finally, the participants can initiate a manual transmission if they are instructed to do so by a member of the Study Team, or if they feel like they may be having an issue with their ICD. PDF files documenting all remote transmissions will be forwarded to the national study center and the site investigators by a VA-sponsored device database .

Data obtained from these transmissions will contain PHI including name and SSN. These reports will be protected in the same way as all other case report forms: their access will be granted to Study Team members on a need-to-know basis, and will be stored behind the VA firewall. Besides the Study Team (Chair's Office, Central Follow-Up Office, and WH-CSPCC), a given report will only be viewable by select members of the Events Adjudication Committee (see Section XII. B.). Permission for the Study Team to access this record is granted by the patient in their consent into the study and through registration for the National Database; there is no need for a separate Data Use Agreement with an external agency or manufacturer.

C. Study Withdrawal and Crossover

A participant may choose to withdraw from the study at any time. If a participant withdraws or is permanently lost to follow-up, a Study Exit Form will be completed. The study will employ an intention-to-treat analysis, i.e. participants will be analyzed as randomized whether or not they receive their protocol-assigned treatment. Patients who wish to withdraw from treatment, e.g., decide against the ICD implant after randomization, request that ICD implant be explanted or disabled, or for those enrolled to the OMT who receive an ICD implant in the follow-up period, will be asked to still complete all follow-up contacts. If a participant withdraws consent to be followed, the person will be withdrawn from further study except for the collection of publicly available data, e.g. survival data. When participants consent to enroll they will be informed that the collection of survival data from public record sources will continue even if they withdraw from follow-up. All other data collected up to the point of withdrawal will be used in the analyses; study follows an "intention-to-treat" design: in the case of 'cross-over,' any patient will be included in the group to which they were assigned.

D. Study Termination and Closeout

The VA Cooperative Studies Program, as the sponsor of the trial, may stop the study at any time based on funding issues or internal or external evidence that the study is no longer feasible or ethical to continue. The Data Monitoring Committee will be the only group that can review unblinded outcome data and can at any time recommend to the sponsor that the trial be terminated because of efficacy, safety, or futility. The DMC will also make a recommendation to Central Office whether to expand the study from Pilot stage to its planned Full-Scope. The Executive Committee, in consultation with the Data Monitoring Committee and the CSP

Director, can also terminate individual sites from participation in the trial. If a site or the entire trial is terminated, participating sites will be notified and given a closeout plan and a schedule at that time.

At the final study follow-up contact, participants will be withdrawn from the trial. Participant exit will be scheduled over the final 3 months of the trial. In most cases, site personnel will be funded for 30 days following the termination of the study or site to clean and store data. After publication of the primary study results, site investigators, if requested, will inform participants of the study's results. The Executive Committee will also consider providing each site investigator with a lay summary of the trial that can be used to be mailed to all participants.

XII. STUDY MONITORING AND QUALITY CONTROL PROCEDURES

A. Overview

The VA Cooperative Studies Program establishes overall policies and procedures that are applied to all VA cooperative studies through the Principal Proponent's office, and the West Haven Cooperative Studies Coordinating Center (WH-CSPCC). The Cooperative Studies Scientific Evaluation Committee (CSSEC) reviews the scientific merit of all new cooperative study proposals. The CSSEC is composed of both VA and non-VA clinical research scientists and biostatisticians. The organizational and administrative structure of this cooperative study is similar to others in the Cooperative Studies Program and includes the components described below.

B. Monitoring Bodies and CSP Monitoring

The Executive Committee is chaired by the Principal Investigator and consists of the study Biostatisticians, study Research Pharmacist, selected participating investigators, and expert consultants. The Executive Committee is concerned with overall study management and is the decision-making body for the operational aspects of the study. The Executive Committee monitors the performance of participating medical centers and quality of data collected, plans the publications, and oversees the publication and presentation of all data from the study. The Executive Committee must grant permission before any study data may be used for presentation or publication. This committee meets by conference call typically on a monthly basis to review the study progress and meets every 12 months to review blinded study data, decide upon changes in the study, determine the fate of sites whose performance is substandard, initiate any sub-protocols, and discuss publication of the study results.

The West Haven Cooperative Studies Program Coordinating Center (CSPCC) and the Principal Investigator administer the trial, oversee its organization, and perform the day-to-day scientific and administrative coordination of the study. These duties include developing the study protocol, operations manual, and case report forms; ensuring the appropriate support for the participating centers; scheduling meetings and conference calls; responding to site queries about the protocol; conducting site visits; publishing newsletters; preparing interim and final progress reports; and archiving study data. Participant accrual and data quality are monitored closely to ensure that the study is progressing satisfactorily.

Local IRBs or the VA Central IRB (CIRB) serves as the oversight body for the protection of human subjects. The study is reviewed and approved by the IRB of record at the initiation and continuing review. If the IRB of record is the VA CIRB, each site's local R&D must also review and approve the local site's involvement in the study.

The CSP Clinical Research Pharmacy Coordinating Center (CSPCRPCC) is responsible for monitoring and reporting the safety of trial participants through the review, assessment, and communication of adverse events and serious adverse events reported by study personnel. The CSPCRPCC's responsibilities occur through ongoing communication with the Study Chair, Executive Committee, West Haven CSPCC, and CSP Central Office. The reporting activities include the filing of regulatory documents involving adverse events to meet applicable federal regulations and CSP policies. In conjunction with the West Haven CSPCC, the CSPCRPCC prepares reports safety data for various committees including the Data Monitoring Committee, the IRB, Executive Committee, and the study group.

The Data Monitoring Committee (DMC) provides interim, independent, and unbiased reviews of the study's ongoing progress. The DMC is composed of clinical and statistical members who have expertise in clinical trials and/or the subject area(s) of the study. These experts are not participants in the trial and have not participated in the planning of the protocol. The Principal Proponent, study Biostatisticians, Clinical Research Pharmacist, and the Director of the CSPCC are *ex officio* (liaison, non-voting) members of the DMC. The DMC meets at least annually to review the progress of the study and monitor participant intake, outcomes, adverse events, serious adverse events, and other issues related to participant safety. At its meetings, the DMC reviews the randomization rates and assess the difference between the actual and the projected rates, as well as the impact of these assessments on overall trial size. If the study enrollment is inadequate, impediments to enrollment will be discussed and the reasons for patient exclusion may be scrutinized and actions may be suggested. The DMC's primary responsibilities are to review safety and the progress of the study and to decide whether or not the study should continue. To help the Committee make its assessment, the Principal Proponent and Study Biostatisticians will provide the DMC with appropriate monitoring data before each meeting. The DMC makes recommendations to the Director, VA CSR&D about whether the study should continue or be stopped.

A member of the Human Rights Committee (HRC) at the Coordinating Center conducts a site visit to at least one participating center during the course of the study to determine if participants' rights and safety are being properly protected. The HRC member may interview study participants during the site visit.

The Adjudication Committee will consist of 3 to 5 members nominated by the Executive Committee and chosen for their clinical and technical expertise. Committee members will establish a standard adjudication procedure. The Committee will periodically review endpoint reports and relevant clinical information and vote as to whether or not reported endpoints satisfy the protocol-defined criteria for cardiovascular or sudden cardiac death.

The ICD Events Committee will comprise qualified members of the Study Team, including Local Site Investigators and Executive Committee members, as well as staff in the Central Follow-Up office; the Committee Chair will be a member of the Executive Committee. Device interrogation reports will be circulated to Committee members who will review and categorize each report. Each report will be read by two Committee members; if the reviewers agree, the classification will be noted, if there is disagreement, the report will be reviewed either by a third Committee member, or the Committee Chair; once the third vote is cast, the classification will be determined by the majority vote. Reviews will be performed *ad hoc*, but the Committee will assure "clearance" of reviews every 6 months in the main study, to ensure timely review and to prevent data backlog.

The Local Site Investigator (LSI) at each participating VA medical center is responsible administratively and scientifically for the conduct of the study at the center. The LSI is expected to attend all annual Study Group meetings, as well as to hire and supervise local study personnel. By agreeing to participate in the study, the VAMC delegates responsibility for global monitoring of the ongoing study to the DMC, the CSPCC Human Rights Committee, the IRB of record, and CSSEC. However, the Research and Development Committee (R&D) of the medical center may require the participating investigator to submit annual reports concerning the status of the study

at the medical center for local monitoring purposes. The LSI will be assisted by the Study Coordinator; it is recommended that the Study Coordinator having a background in nursing, however this is not a strict requirement: hiring of non-nurse Coordinators is allowed.

The Study Group consists of the Principal Proponent, the CSP staff (Biostatisticians, Project Manager, Clinical Research Pharmacist, and others), all participating local site investigators, and research coordinators. The Principal Proponent leads the Study Group, which typically meets monthly by teleconference and once per year in face-to-face meeting to discuss the progress of the study, any problems that the investigators have encountered, and any suggestions for improving the study. No endpoint data are presented to this group while the study is ongoing.

The Site Monitoring, Auditing and Review Team (SMART), located at the CSP Clinical Research Pharmacy Coordinating Center (CSPCRPCC) in Albuquerque, will provide Good Clinical Practices (GCP) training at the kick-off meeting and will conduct monitoring visits at all sites. A SMART member visits participating sites shortly after enrollment is initiated and annually thereafter to monitor investigator regulatory compliance, protocol adherence, and overall research practices. In addition to the regularly scheduled GCP review visits, an independent comprehensive GCP site audit may be conducted at any time at the request of CSP study management.

C. GCP Monitoring Visits

A member of the Site Monitoring and Review Team conducts at least one site visit to each site during the enrollment period for monitoring GCP and study protocol adherence (see Section XIV). The purpose of these visits is to encourage and assess compliance with GCP

requirements. Additional monitoring visits may be conducted as deemed necessary by study leadership or SMART. The investigator is contacted prior to the visit to arrange a mutually agreeable time for the visit. The SMART reviewer is on site for approximately two days to review study records and discuss the conduct of the trial. The SMART reviewer examines participant study files, including source documents held electronically, in clinic files and participants' official medical records and reviews regulatory and essential documents, such as IRB correspondence. Areas of particular concern are informed consent issues, protocol adherence, safety monitoring, IRB reviews and approvals, regulatory documents, participant records, site operations, and investigator involvement. The local site is required to document protocol breaches and any medical center with repeated protocol violations is reported to the Executive Committee and the Director, VA CSR&D. If a participating site investigator feels that adherence to the protocol will be detrimental to a particular participant's health or well-being, the interest of the participant must take precedence. Monitoring may include but is not limited to the informed consent process, data validation, source verification, and safety reporting. The Executive Committee will consider recommending additional SMART site visits for any participating centers with repeated protocol violations to evaluate a sites' need for additional training to remedy compliance concerns. Additional site-specific monitoring may be conducted if triggered by study performance metrics. For-cause audits may be conducted at any time if requested by the study leadership or CSP Central Office. For-cause audits can be announced or unannounced. In addition to SMART visits, WH-CSPCC, the Executive Committee, and DMC will monitor protocol adherence centrally through periodic reports, data queries and coordinator/PI conference calls.

D. Monitoring Participant Intake and Probation or Termination of Participating Sites

The Study's Executive Committee, Principal Proponent and the Study Biostatisticians will monitor the intake rate and operational aspects of the study. The Executive Committee may take action leading to the discontinuation of enrollment at a center with the concurrence of the Director, VA CSR&D. Participating medical centers may continue in the study only if adequate participant intake is maintained.

The target enrollment for the study is 1,462 Veterans. If recruitment is not proceeding at an appropriate rate, the Principal Investigator and the Study Biostatisticians will scrutinize the reasons for participant exclusions and other barriers to recruitment. Based on this information, the Executive Committee may choose, with the approval the Director, VA CSR&D, to drop centers or add additional centers, or with the concurrence of the DMC, and the Director CSR&D make modifications to the inclusion/exclusion criteria, or extend the recruitment period in some or all centers and/or to extend the total length of the study.

Medical centers will only be allowed to continue in the study if adequate participant intake is maintained. The target recruitment for each VA site is 17 participants per year (approximately 1 every 3 weeks). Because there is usually a ramp-up in recruitment early on, during the main study phase, sites that do not enroll at least four participants during their first six months, or twelve participants within the first year, will be considered for probation or reduction in funding. Since the Pilot study will be operating at six sites selected on the basis of projected high recruitment, all sites within the Pilot study must meet at least 90% of the target enrollment of 17 patients within the first year; satisfaction of this recruitment criteria by these "vanguard" sites

will provide evidence of study feasibility in full-scale operation over a wider range of sites. If a medical center is placed on probation, the Principal Investigator and Study Biostatistician confer with the site personnel and, if necessary, visit the site to help improve the rate of recruitment. If there is no improvement in accrual after the probation period, the site may be subject to reduced funding or possible termination as a study site. The Executive Committee only takes actions leading to discontinuation of a center with the concurrence of the Director, VA CSR&D. If a center is terminated from the trial, resources are reallocated to other centers or used to start up a backup site.

E. Monitoring Medical Center Performance

Strict adherence to the protocol is expected of every participating center and monitored by the DMC, the Executive Committee and the Study Group. Data quality and the completeness of data retrieval, including the Screening Tracker, are closely monitored on an ongoing basis by the WH-CSPCC. The Study Biostatistician presents interim monitoring reports, overall and by site, to the Executive Committee and DMC that include the following types of information: recruitment of participants, characteristics of the population, completeness of data retrieval, and data quality. If a site is identified as an outlier in terms of data quality, a site conference call or site visit is initiated to assess the reasons that problems are occurring and how they can be corrected. If the problems continue, the site may be placed on probation or terminated from the study if the problems cannot be corrected.

F. Monitoring Participant Safety

The local site investigator is responsible for following adverse event reporting requirements as outlined below in the Protocol. These responsibilities include: 1) reviewing the accuracy and

completeness of all adverse events reported, 2) compliance with IRB policies for reporting adverse events and/or serious adverse events, and 3) closely monitoring research participants at for Adverse Events (AEs) or Serious Adverse Events (SAEs). All AEs and SAEs are recorded on the appropriate event form(s). Active monitoring of SAEs begin as soon as the study participant provides consent and continue until the participant completes follow-up. In this study, we will only monitor AEs for 30 days post-randomization (OMT arm) or 30 days post-implantation (OMT + ICD arm). We identify several SAEs that will not require immediate reporting to CIRB, in order to enable detection of clinically meaningful safety information. These SAEs include

- Bleeding/Hematoma
- Incisional pain
- Infection: ICD pocket or lead; requiring antibiotic treatment or explant
- Infection: Other, requiring antibiotic treatment
- Lead dislodgement
- Lead fracture
- Pacing parameters require lead replacement or revision
- Pneumothorax
- Myocardial infarction (MI)
- Stroke
- Tachyarrhythmia/atrial fibrillation

Unexpected SAEs will follow regulations for timely reporting to CIRB: All Serious Unanticipated Problems involving risks to subjects or others and all Serious

Unanticipated SAEs as defined by VHA Handbook 1058.01 will be reported to the CIRB within 5 business days of becoming aware of the problem or event.

Sites will be responsible for safety surveillance in order to capture serious adverse events in a timely manner, e.g. through alerts in the local medical record or periodic searches of the medical record for hospitalizations. Whomever encounters news of an event must report that event via the proper reporting pathways (SAE case report form, and when appropriate for unexpected and related problems: Form 119 to Central IRB). The sites and Central Follow-Up office are asked to notify each other of event discovery for maximum efficiency. Once the initial event report has been processed, its 30-day follow-up will be the responsibility of the Central Follow-Up Office.

G. Adverse Event Definition and Monitoring

While an AE does not necessarily have to have a causal relationship with the research, in CSP #592 only non-serious AEs will be collected, related to the treatment of heart failure. Adverse Events will be collected for 30 days after implantation (OMT + ICD arm) or 30 days post-randomization (OMT arm). Relatedness involves an assessment of the degree of causality (attributability) between the study intervention and the event. Site investigators are asked to provide an assessment of relatedness. All AEs with a reasonable causal relationship to the investigative treatment should be considered "related" and will be collected. A definite relationship does not need to be established. AEs are defined in Section XIV.

H. Serious Adverse Event Definition and Reporting

Serious Adverse Events (SAEs) are defined in Section XIV. All SAEs whether or not they are considered related will be collected in CSP #592. Site investigators will still be asked to provide an assessment of relatedness as the assessment provided by the site investigator is part of the information used by the sponsor to determine if the SAE presents a participant safety concern. Any SAE that originally started as a non-serious AE that was not reported at the time of the event because it was considered unrelated will be reported within 72 hours of becoming an SAE as defined above regardless of relatedness.

I. Minimizing Attrition

As a primary way to minimize drop-out from the study, the investigators provide thorough pre-enrollment education for all prospective participants about the study objectives and procedures in order to assess and confirm the participants' commitment to and feasibility for long-term follow-up. The investigators also provide ongoing education during the study to reinforce the participants' commitment to long-term follow-up. As an alternative to telemedicine, members of the Study Team will be allowed to travel to a location in the community in order to make more convenient contact with the participants for assessments.

To contend with the challenge of getting participants to participate in baseline data collection, attendance at these visits will result in patient compensation; all subsequent follow-ups will be conducted centrally, via telephone, minimizing participant burden, and will therefore not generate participant compensation. All participants would be compensated for each completed in-person visit regardless of whether they continued in the study or exited the study at the completion of the visit. To minimize the risk of financial coercion, the payment will be

relatively modest. In addition, there are minimal risks involved in these assessments (i.e. no invasive procedures, physical demands, or medications interventions are required in order to receive payment). Distant participants will receive this same reimbursement for all compensable study visits; travel to-and-from the implanting Center will not be compensated by the study. These travel costs will be managed per regular VA clinical reimbursement regulations.

J. Remote Monitoring

ICDs are capable of delivering information related to a wide range of parameters including activity level, heart rate variability and battery and lead status. In general clinical practice, the remote monitoring feature may increase quality of care by providing a platform for information-driven decision making and timely event reporting, and may reduce anxiety of a device implantation if the device functionality can be ascertained by trained clinicians or technicians. Remote ICD monitoring reduces emergency department/urgent in-office visits, and in general, total healthcare utilization in patients with ICDs, and in the clinical trial setting, has shown the capacity to increase efficiency for healthcare providers, and improve the quality of care for patients [119]. Remote monitoring also provides benefits to the Study Team, as it 1) provides accurate, objective, and timely record of events, 2) provides a platform for assessing protocol adherence with regard to device programming, and 3) reduce losses to follow-up.

The analysis of remotely acquired data will be limited in scope to Routine assessment of ICD therapy events, and Device interrogation upon death (where feasible).

XIII. QUALITY CONTROL AND DATA MANAGEMENT PROCEDURES

A. Data Collection Methods

1. Data Capture

The data for CSP #592 will be managed by the WH-CSPCC using a web-based data capture system and/or paper / fax based optical character recognition software system. The Cooperative Studies Program may implement a new web-based data capture system prior to the launch of CSP #592 in its full scope. The system will meet or exceed all VA data security requirements and will be fully described in the study's Operations Manual. The system will allow approved site investigators and personnel to enter study participant data directly into web-based forms and thus track and manage their patients, complete randomization, record data in electronic case report forms (CRFs), receive data clarifications, and correct participant data online. Data collected on source documents at the site (paper and/or electronic medical records) will be entered in the data capture system and be submitted to a central study database. Paper versions of the CRFs will be supplied to the sites for recording of source clinical data if needed. This data capture system may be tested for viability during the Pilot phase of CSP#592.

If an electronic data capture system cannot be validated or made accessible by study initiation, the backup data collection system for the study will be a paper based system. If paper forms are used, they will be submitted via tracked overnight mail or fax to the WH-CSPCC fax server (see Section XVIII.A.2.). The PDF forms will be accessed and completed on-line or by copies provided to the sites on their local PC. These forms will be easy to navigate and have data edit checks (e.g. min/max ranges, allowable values, must-enter fields) programmed into the forms

and will be reviewed regularly so that data errors will be reduced and corrections can be made as data are collected. All study data will be transferred into SAS datasets for reporting and analysis.

Updates to the electronic forms and database can be generated during the study without affecting collected data. Study reports will be generated from exported data in order to track the study progress and to monitor adverse events, particularly Serious Adverse Events. Study reports will be circulated to appropriate personnel including the Study Chairman, the Site Investigators, CSP program sites, the Executive Committee, and the Data Monitoring Committee.

2. Paper CRF and Source Document Tools

Although a web-based data capture system is expected to be used to collect study data for the study central database in the study's full-scale implementation, paper data collection tools will still be needed at the sites. Any information that is not recorded in the study participant's VA electronic medical record will need to be recorded on a source document tool or paper study CRF. Paper CRF will be required for two reasons: 1) Collection of participant self-reported responses to study questionnaires, and 2) as a backup in the event that the data collection system is not accessible due to system/network failure or downtime. The paper CRF will be readable by optical character recognition software (e.g. Teleform ® Elite v. 10.0 or higher, by Cardiff, Inc.). Electronic scanner-readable e-PDF versions of the data collection forms will be sent to the sites. The e-PDF versions may be completed on a personal computer at the study site. If a form is completed on a personal computer or terminal, a completed copy of the form must be printed. The printed copy will be faxed to the WH-CSPCC fax data server or mailed via tracked overnight mail to the WH-CSPCC. The printed copy kept at the site will be filed in the participant study folder. Once the forms are received at WH-CSPCC, they will be processed

through the Teleform form reader and verifier software where a research assistant at the WH-CSPCC will review the forms for consistency and completeness. CRFs processed by the Teleform Verifier will be exported to an image file folder, and the extracted data items will be exported to a comma-delimited file in a data capture folder, both on a secure WH-CSPCC file server. In case of persistent fax transmission problems, sites may be asked to post e-versions of the CRFs to their secure study-site sub-page on the CSP592 SharePoint site. All changes or corrections to data entered on paper CRF forms will be dated and initialed by site personnel on the original CRF and the associated data edit sheet if applicable.

B. Data Quality Control

After the study is approved, the Case Report Forms (CRFs) will be field-tested using the data capture or paper-based system. Communication between WH-CSPCC, CSPCRPCC, the Study Sites and the central database will be tested.

On a weekly basis, or more frequently, programmers at WH-CSPCC will transfer the cumulative data in the central database to SAS datasets on the CSPCC UNIX server. SAS programs will be run to generate reports that summarize the accumulated study data and data exceptions (e.g., missing forms or data, any out of range values). These notices may request completion, correction, or verification of specific data items. A computerized record will be kept of the number and types of errors to ensure a high level of data integrity. Interim progress reports of cumulative errors and overall data quality will be sent to the investigators, the Executive Committee, and the DMC. Unresolved data queries will be included in the datasets that will be used in interim reports. However, every effort will be made to resolve all outstanding Data Correction Forms (DCFs) prior to a DMC report.

Data files on the central study database containing the accumulated participant information will be examined for completeness and consistency at regular intervals. Tested and validated computer programs will check newly entered forms for missing or out-of-range values. Computer-generated notices will be mailed to the participating investigators requesting completion for forms and follow-up on DCFs for correction or verification of specific data items. A computerized record of the types of errors will be kept in order to ensure a high level of data integrity.

At periodic intervals, a cumulative record of errors and data quality progress reports will be sent to investigators and the Study Chairman. Data edits and removal of duplicate records will be applied to the data files on a regular basis, and cleaned (final) files through the time of the most recent running of data edits will be created. These final files will be used to run monitoring reports on a regular basis. The progress of data collection will be monitored with computerized data form inventory programs that will produce a profile of all forms expected and received for each study participant. Missing-forms reports will be generated and sent to the sites periodically during the enrollment phase of the study.

Data quality will be monitored on an ongoing basis by the WH-CSPCC. The Study Biostatistician will present interim monitoring reports to the Executive Committee at least monthly and to the DMC at least annually. Interim reports will include recruitment of participants, characteristics of the population, completeness of data retrieval, and data quality. Prototype tables are given in Appendix D and serve as an example of the statistical reports that will be generated for study monitoring by the Executive Committee and the DMC.

C. Electronic Study File

CSP has established a Clinical Trials Management System (CTMS). This system is hosted on a server at a secure VA regional data facility and is based in a MS SharePoint platform. An MS SharePoint site or similar CTMS will be used for maintaining an electronic version of the Central Study File for this study. Participating medical centers will be able to access current and past versions of the Study Protocol, Operations Manual, Operations Memoranda and other work instructions, CRFs, and other study-related documentation, as well as meeting announcements, conference call notices, and study newsletters using the CTMS.

D. Quality Control of the Process

The Study Chairman and the WH-CSPCC will prepare an Operations Manual that will be provided to the local site investigators as a guide to the operation and management of the study as well as a technical reference manual. A training session will be held at the study kick-off meeting(s) for all study personnel in order to: (1) assure uniformity in participant management and data collection procedures, and (2) train the personnel in study procedures and criteria.

Study procedures will be reinforced by the use of regular conference calls, particularly in the first few months of the study and by the periodic distribution of a study newsletter. All study personnel will attend group meetings during the enrollment period when study procedures again will be discussed in detail. The Study Chairman's Office and the WH-CSPCC study personnel will be available to clarify study procedures by telephone, fax and e-mail.

If the Executive Committee determines that a procedure must be changed, the participating sites will be informed by conference call and/or newsletter, and an updated section of the Operations

Manual pertinent to the changed procedure will be provided to all sites. The trial will be conducted in compliance with Good Clinical Practices (see Section XVII).

E. Data Security

CSP has a commitment to maintaining data security and patient privacy. Standard practices and policies as part of the responsible conduct of clinical research studies are implemented and reviewed periodically. CSP Center Directors are responsible for ensuring that all CSP Data Security Policies are enforced within their Centers. All study data collected will be handled, maintained and stored according to CSP standard practices and policies. This includes but is not limited to the following:

- Protected Health Information (PHI) as defined by HIPAA will not be used for any purpose that is not related to the activities of this study.
- Records are identified only by a participant identification number.
    - Patient identification numbers are not derived from or related to information about an individual.
    - All electronic PHI are stored on secure servers and may not be moved to a PC or other external device.
    - Paper CRFs, if any, are stored in locked file cabinets and rooms.
- When necessary, PHI (exclusive of HCPHI) may be transported between secure servers. PHI must be encrypted and password protected while being transferred using a FIPS 140-2 certified program. Any removable storage device used to transfer PHI (e.g., hard-copy printouts, data tapes, encrypted CDs, encrypted USB drives, etc.) should either be destroyed after transfer is complete or given to the Data Security Administrator to be

secured in a secure, fireproof safe. A trackable mail system must be used for the physical data transfers.

- Data from studies are utilized at CSPCC and are not removed from the Center.
- No PHI may be sent via MS Outlook or Exchange unless the message is secured utilizing encryption and VA-authorized security protocol.
- Documents sent for medical evaluation purposes (e.g., endpoint adjudication) are sent via trackable express mail. Personal information is redacted by the VAMC or CSPCC if not determined to be necessary for completing the evaluation.
- Only VA-owned equipment or equipment configured to VA security standards is permitted to directly connect to the CSP networks in accordance with VA Directive 6504. Non-VA sites will submit data through a secure Demilitarized Zone (DMZ).
- Training, reminders, and signed data security statements are used to ensure CSP personnel understand VA policies.
- Sharing of CSP study data outside of CSP requires the approval of the Director, CSR&D, and data use agreements. In addition, sharing of data outside of the VA requires local ISO, PO, and ACOS-R approvals.

Any data capture system used for data collection in this study will be fully compliant with US Federal regulations regarding electronic web-based data capture systems established by the FDA under 21 CFR 11. Data entered directly into the central database provides the official clinical record for data collection. Source documentation is handled in the same manner as a paper based system. All paper-based records will be kept under lock and key.

The electronic data capture system will utilize state-of-the-art technologies that meet or exceed the current VA standards for transport in order to protect the data during transmission. In brief, electronic systems will employ secure socket layer technology and FIPS 140-2 compliant encryption algorithms to ensure that data is not vulnerable during transport. Hard copy data will be sent via a traceable mail system (i.e., UPS), via a courier, or via secure fax.

Access to the study data will be afforded the same level of security as all forms of VA protected and/or highly sensitive information. Access is heavily restricted to individuals with CSP approval to access the data. Individuals must be properly credentialed research staff and must be compliant with VA security trainings (i.e., Research Data Security, HIPAA and VA Privacy Training, Cyber-Security, and Good Clinical Practices). In addition, research data will be stored on VA secure servers with restricted permissions for copying and exporting data. Only properly approved Coordinating Center personnel will have the ability to copy and export data. These individuals have received training on the local SOPs governing their permissions and will not access or export data without written approval from the Coordinating Center Director. Furthermore, the permissions of the electronic systems are structured such that individual sites can only see the data for their study participants, and they cannot see or access the data for another clinical site or for another participant.

Backup copies of the database will be transferred to the WH-CSPCC behind the VA firewall on a frequent basis depending on the study need. These backup copies will be transferred and stored across secure connections according to VA regulations and WH-CSPCC operating procedures. Periodic off-site back-ups will be made as part of a comprehensive disaster recovery plan.

F. Data Management and Access Plan (DMAP)

Upon final analyses of the stated objectives in this proposal, the study plans to submit results for publication in scientific peer-reviewed journals and provide summary results on clinicaltrials.gov. After acceptance of the primary and other stated analyses by a journal, CSP will make these publication(s) available via the National Library of Medicine's PubMed Central within a year of the date of publication.

Digital data underlying primary scientific publications from this study will be held as part of a data sharing resource maintained by the Cooperative Studies Program (CSP). Study data held for this purpose may include data, data content, format, and organization. The data may contain but are not limited to individually identifiable information, other protected health information, and study codes. The data may be available to the public and other VA and non-VA researchers under certain conditions and consistent with the informed consent and CSP policy which prioritize protecting subjects' privacy and confidentiality ot the fullest extent possible. A detailed plan for data sharing will be developed in accordance with current technology, infrastructure, best practices, and policies and procedures in place at the time of oversight committee reviews (e.g. Privacy Board, IRB, Information Security and IT standards). The plan will include how data will be discovered, retrieved, and analyzed, managed and will note the materials that are available in machine readable formats. This plan may be revised to ensure consistency with VA, including CSP, policies and standards for overall management and sharing.

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XIV. ADVERSE EVENT ASSESSMENT AND REPORTING

A. Role of the Local Site Investigator in Event Monitoring

The Local Site Investigator is responsible for the following adverse medical event reporting requirements:

- Reviewing the accuracy and completeness of all adverse events reported
- Complying with study policies as well as IRB policies for reporting adverse events, serious adverse events, and unanticipated adverse device effects
- Report to CSP all SAEs within 72 hours of becoming aware of the event
- Reporting to the IRB safety issues reported to the site by the Sponsor
- Closely monitoring research subjects for any new AEs, UADEs, and SAEs
- Maintaining clinic lists to facilitate near-real time event discovery
- Provide updates to Central Follow-Up Office upon event discovery and upon their request during event follow-up

B. Definitions

1. Adverse Event (AE)

An Adverse Event (AE) is defined as "any untoward physical or psychological occurrence in a human subject participating in research." An AE can be any unfavorable and unintended event, including an abnormal laboratory finding, symptom, or disease associated with the research or the use of a medical investigational test article. While an AE does not necessarily have to have a

causal relationship with the research [120], in CSP #592 AEs will be collected, and only for 30 days after implantation (within the ICD + OMT arm), or 30 days after randomization (OMT arm). We will also collect AEs for 30 days after any re-implantation procedure. For the purposes of this study, we are primarily interested in the following AEs:

- Discomfort at the implant site
- Cosmetic issues (e.g. scars, etc.)
- Psychological issues (e.g. apprehension of an activation, etc.)
- Technical issues related to the device (e.g. actions that may require re-implantation or a generator change)
- Delay angioedema with cough
- Rise in creatinine
- Fatigue
- Slow heart rate

Other adverse events –including those that may not necessarily have to have a causal relationship with this treatment– may also be collected.

2. Unanticipated (or Unexpected) Adverse Event (UAE)

An Unanticipated (or Unexpected) Adverse Event (UAE) is an AE that is new or greater than previously known, in terms of nature, severity, or frequency of occurrence, as documented in the protocol or other materials approved by IRB. Such materials may include, but are not limited to: the informed consent form, clinical investigator's brochure, and product labeling [120].

3. Unanticipated Adverse Device Effect (UADE)

An Unanticipated Adverse Device Effect (UADE) means any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem or death was not previously identified in nature, severity, or degree of incidence in the investigational plan or application, or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects [121].

All AEs and UADEs with a reasonable causal relationship to the investigative treatment should be considered at least "possibly related." A definite relationship does not need to be established.

4. Serious Adverse Event (SAE)

An adverse event is considered a Serious Adverse Events (SAE) if, in the view of either the investigator or Sponsor, it results in any of the following outcomes:

- Death
- A life-threatening adverse event
- Inpatient hospitalization or prolongation of existing hospitalization
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- A congenital anomaly/birth defect
- Any other condition that, based upon medical judgment, may jeopardize the subject and require medical or surgical treatment to prevent one of the above outcomes.

In particular, this study will not consider any of the following as either an SAE or a hospitalization: index implantation of an ICD device, re-implantation of an ICD after explantation, or generator change.

All serious adverse events are collected, including those related and not related to the study intervention. All serious adverse events with a reasonable causal relationship to the investigative treatment should be considered "related". All SAEs will be promptly reported by submission of the event into the CSP #592data capture system within 72 hours of the site investigator being made aware of the event. Email notification of the submission will immediately be relayed by the CSP #592 data capture system to the Study Biostatistician, Clinical Research Pharmacist, and Study Chair. The CSPCRPCC will be responsible for evaluating all serious adverse events for participant safety concerns. Serious adverse events (as defined by CRF 312.32) that are **unanticipated and related to the investigational treatment** are expeditiously reported to the CSPCRPCC Director, CSPCC, CIRB, DMC, and all regulatory agencies.

The Clinical Research Pharmacist and Study Biostatistician generate tabulations of adverse events and present a summary of all AEs and SAEs to the DMC on a schedule set by the DMC. The DMC also determines when they should be unblinded to treatment assignment in reviewing adverse event data. The Study Biostatisticians provides the appropriate data to the DMC at specified intervals for this purpose. Serious adverse events are reported on a regular basis to the DMC for their review. Unanticipated serious adverse events are reported to the DMC as soon as they become known based upon the consensus of the Principal Proponent, the Study Biostatisticians, the Director of the West Haven CSPCC, and the Study Pharmacist.

C. AE/UADE and SAE Monitoring and Reporting

AEs, UADEs and SAEs will be monitored at the study sites throughout the period of the study, beginning as soon the research subject signs the Informed Consent and continuing through end-of-study for each participant. Reportable AEs will be collected and recorded on the appropriate case report form; though we note that while AEs will be continually monitored for closure, new AEs will only be collected for the relevant 30-day window. All UADE and SAEs, including both those related to the study intervention and those not related to the study intervention will be collected and recorded on the appropriate case report form; new UADEs and SAEs will be collected throughout the study. For the purpose of safety monitoring, the study intervention is defined as "ICD implantation" or "Optimal Medical Therapy".

All UADEs/SAEs require expedited reporting. An SAE case report form will be completed and submitted via the data capture system within 72 -hours of the Site Investigator initially becoming aware of the event. The Study Pharmacist at CSPCPRCC will be responsible for evaluating all SAEs/UADEs for participant safety concerns in a timely manner.

UADEs/SAEs that suggest evidence of a causal relationship between one of the study interventions and the adverse medical event and is unexpected will be reviewed by the Study Leadership Team (i.e., Study Chairperson, Study Biostatistician, Study Project Manager, and the Study Pharmacist) prior to notifying VA Central Office.

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XV. BIOSTATISTICAL CONSIDERATIONS

A. Sample Size

The primary outcome of CSP #592 is all-cause mortality analyzed as time to event. The sample size required for this outcome was calculated using the log-rank test to compare survival, where the null hypothesis is that the average risk of death between the two treatment arms are equal [122]. The primary hypothesis is that the ICD arm will have a 25% reduction in the hazard ratio (HR=0.75) (23.5% relative risk reduction in the annual mortality rate). The sample size calculation assumes a 15% annual mortality rate in the control arm. The cumulative event rate by the end of the 5-year trial (3.6 years average follow-up[1]), taking into account administrative censoring, loss, drop-in, and drop-out, is projected to be 42.0% in the control arm versus 34.1% in the ICD arm. The following sections describe the rationale behind these assumptions and the details of the sample size calculations.

1. Hypothesized Event Rates and Treatment Effect Size

Table 13 presents annual mortality rates from the control arms of prior interventional studies of ICD-based therapy.

[1] Five years follow-up for Pilot Study participants (N=102), plus 3.5 years average follow-up for participants in Stage II (N=1360): (6×102 + 3.5×1360) ÷ (102+1360) = 3.60 average years of follow-up.

Table13. Annual mortality rates from control arm in studies of ICD usage in primary prevention.		
Study	ICD Age Subgroup	Annual Mortality Rate
Heidenreich 2009 [69]	Age 71-80	22%
	Age >80	25%
Chan 2009 [53]	Age ≥75	15%
Goldenberg 2008 [41]	>70 years	27%
Groeneveld 2008 [123]	Age > 66	23%

Based on these results, this study's sample size calculation uses an annual event rate of 15% for the control arm. Given that the participant population enrolled in CSP #592 will be very similar to those in the studies shown in Table 13, a 15% annual event rate for the control group can be considered a conservative assumption. This translates into a 42.0% cumulative mortality rate after 3.6 years average follow-up, taking into account administrative censoring, drop-in, and drop-out.

Expected effect size for the sample size calculation was selected based on review of prior studies shown in Table 14.

Table14. Hazard Ratios in Comparable Patient Populations (ICD vs. Conventional Therapy).		
Study	Comparison	Hazard Ratio (95% CI)
Moss 2002 [34]	All patients	0.69 (0.51 – 0.93)
	>70 years	0.66 (0.48 – 0.98)
Kadish 2004 [30]	All patients	0.66 (0.40 – 1.08)
	NYHA Class II	1.02 (0.51 – 2.09)
	NYHA Class III	0.37 (0.15 – 0.90)
Bardy 2005 [29]	All patients	0.77 (0.62 – 0.96)
	Ischemic Chronic Heart Failure	0.79 (0.60 – 1.04)
	Non-Ischemic Chronic Heart Failure	0.73 (0.50 – 1.07)
	NYHA Class II	0.54 (0.40 – 0.74)
	NYHA Class III	1.16 (0.84 – 1.61)
Chan 2009 [53]	>75 years	0.59 (0.39 – 0.90)
Santangeli 2010 [62]	>60-65 years (meta-analysis)	0.75 (0.61 – 0.91)
Kong 2011 [70]	>75 years (meta-analysis)	0.73 (0.51 – 0.97)

The hazard ratio for effect of ICD therapy on all-cause mortality varies widely, primarily because of the differences in the populations analyzed in the various clinical trials. For this reason, it is a challenge to identify specific clinical trials on which to base our effect size assumption. However, two meta-analyses have been published that assess the impact of ICD on the elderly. In the assessment of the MADIT-II, DEFINITE, DINAMIT, SCD-HeFT and IRIS studies, a Hazard Ratio of 0.75 (95% CI 0.61 to 0.91) was found [62]; and in a separate analysis of MADIT-I, MUSTT, MADIT-II, DEFINITE, and SCD-HeFT, a Hazard Ratio of 0.73 (95% CI

0.51 to 0.97) was found [70]. These Hazard Ratios are similar, and based on a sufficiently broad literature basis that they are the best point estimates of expectation for CSP #592. This study will adopt the more conservative of the two estimates, i.e. Hazard Ratio of 0.75.

2. Projected Sample Size

The following assumptions were used for the sample size calculation:

- Two-sided Type I error of 0.05
- Pilot stage with uniform recruitment over 1 year, with uniform follow-up of 5 years for all participants; 17 participants per site at 5 sites, i.e. 102 × 5 = 510 patient follow-up years
- Full-scale stage with uniform recruitment over 3 years (minimum follow-up = 2 years, maximum follow-up = 5 years, median follow-up = 3.5 years)
- Annual event rate of 15% in the control arm
- Hazard ratio of 0.75 (relative risk reduction =23.5%)
- Allocation ratio of 1:1 for the treatment groups
- Annual drop in rate of 2.5% from the control group to the ICD group
- Drop-out rate of 1% from the ICD group to the control group in year 1 only.
- Annual loss-to-follow-up of 1%

Table15. Total Sample Size Under Different Control Rate and Effect Size Assumptions.			
Annual Event Rate in the Control Arm	Hazard Ratio		
	0.70	0.75	0.80
12%	1,177	1,771	2,881
15%	971	1,462	2,384
18%	834	1,258	2,057

Because the VA Vital Status File will be searched for all deaths, loss-to-follow-up for the primary endpoint is considered to be very negligible and was therefore not accounted for in the sample size calculation. Based on a 15% annual event rate in the control arm and a hazard ratio of 0.75, and the other assumptions listed above, a sample size of 1,462 (565 total primary outcome events) will be needed in order to achieve 90% power with a 2-sided Type I error rate of 0.05.

Using the target sample size of 1,462, the following scenarios were considered as sensitivity analyses:

- If the recruitment rate is less than anticipated, the study will still maintain 80% power to detect a hazard ratio of 0.75 with 1,084 participants (422 events).
- If the control group annual event rate was 3% lower than anticipated (i.e. 12% annual mortality rate) the study would still maintain 81.0% power to detect a hazard ratio of 0.75.
- If the effect size is smaller than hypothesized, the study would still maintain 80% power to detect a hazard ratio of 0.78.

3. Power for Secondary Analyses

The secondary objectives for this trial are to test the treatment interactions by co-morbidity level, and to test the change from baseline in the Minnesota Living with Heart Failure score. Neither secondary analysis will require adjustment for type I error, i.e. no "multiple testing" corrections: adjustments for multiple comparisons are required in confirmatory whenever results from multiple tests have to be combined in one final conclusion and decision; in studies with a single primary endpoint, all other endpoints are considered subsidiary and their results can only have an exploratory rather than a confirmatory interpretation – multiplicity corrections are not required [124]. A sample size of 1,462 participants will yield the following power for secondary endpoints:

- Assuming equal enrollment across high- and low-burden groups, this study will reach statistical significance for an increased in therapeutic effect by 50% in the low-burden group (Charlson <3) and decrease in efficacy of 50% in the high-burden group (Charlson ≥3).Assuming a pooled standard deviation of 5 for change from baseline in Minnesota Living with heart failure score, the study will have 80% power to detect a 0.73 difference between groups in mean change from baseline at 12 months.

B. Interim Monitoring and Analysis

Interim monitoring will be performed by the WH-CSPCC and focuses on recruitment (overall and by site), baseline comparability of treatment groups, protocol adherence, completeness of data, accrual of primary endpoint events (i.e., information accrual), safety, and treatment efficacy. Recruitment and completeness of data will also be monitored for purposes of daily trial operations and quality assurance. The WH-CSPCC monitoring provides the basis for reporting to

the Data Monitoring Committee (DMC). A prototype set of tables and figures for presentation to the DMC is given in the Appendix D.

1. Monitoring Recruitment

The WH-CSPCC will monitor all steps in the recruitment process to assure early recognition of inadequate performance and to identify reasons for inadequate performance at each recruitment site and for the trial overall. To assist in this process, the WH-CSPCC will produce weekly data monitoring reports. These reports will include number of screening forms completed, reasons for non-matriculation into study, number of informed consent documents signed, and number of randomizations overall and by medical center. The same reports will be made available to the DMC at each of its meetings. The data gives the DMC a regular opportunity to compare the trial assumptions with the observed data to make early judgments about the merits of continuing the study.

2. Monitoring Protocol Adherence

Protocol adherence will be monitored to assure early identification of poor performance at individual sites and in the trial overall. Periodic reports will be provided to the Executive Committee and to the DMC at each of its meetings. Specific parameters to be monitored include:

- Randomization of ineligible participants
- Treatment allocation errors
- Failure to complete required follow-up assessments on time
- Timely registration with the National Registry
- Loss and withdrawal rates

• Treatment adherence

3. Monitoring Efficacy and Futility

Two interim analyses of the treatment effect on the primary endpoint of all-cause mortality will be performed when approximately half and three quarters of the events are accumulated (~280 and 420, estimated at approximately 3 and 4 years). However, the DMC will have discretion to request additional or different timing of interim analyses. A Haybittle-Peto type stopping boundary ($p<0.001$) will be used for monitoring the study for early efficacy [125].

A futility analysis for the primary endpoint is also planned at the time of the interim analysis. If the analysis shows that the primary endpoint crosses the internal boundary for futility, it would indicate that the observed effect size is much smaller than anticipated and that the trial has very low conditional power to detect the estimated treatment effect for the primary outcome. The proposed stopping boundary for futility is a hazard ratio of between 1.02 and 0.98 (approximate p-value of 0.80).

In addition to these futility analyses, the observed primary outcome event rate and rate of information accrual (number of events) is monitored from the initiation of the trial and compared with the expected rates. Based on these rates, an estimated time for study completion (i.e. time to reach 565 events) and the estimated number of events that will be reached by the scheduled end of the trial will be presented to the DMC. When considering the futility analyses and rate of information accrual, the DMC may also consider other internal or external evidence of futility (i.e., secondary outcomes) and has the option of recommending early termination of the trial for futility, or continuing with a possible adjustment to sample size.

4. Sample Size Re-estimation

CSP #592 is designed as an event driven trial. Therefore, the sample size assumptions regarding the control group event rate and the crossover rate will be re-evaluated at between 6 and 12 months after initiation of the Pilot study, and again approximately six months prior to the end of Full study recruitment to determine whether the estimated sample size and projected follow-up time are sufficient to achieve the target number of events. This will be done blinded to the treatment effect. If necessary, the sample size will be re-estimated based on the accumulated data but under the original hypothesized treatment effect to preserve the Type I error. This information will be presented to the DMC who will make a recommendation to the CSP on whether the sample size for the trial and/or the length of follow-up should be increased to achieve the study objectives. Efficacy and futility analyses, as described above will not be performed until the sample size re-estimation has been completed.

5. Interim Safety Monitoring

Trial safety will be monitored by CSPCC and the CSPCRPCC, and the Study Chair's Office throughout the study. Safety reports will be submitted to the DMC approximately every 6 months after enrollment begins, or more frequently, if requested by the DMC. For reports to the DMC closed session, serious adverse events will be summarized by treatment groups, and relatedness to the assigned interventions.

The proportion of participants experiencing an SAE in each treatment group will be calculated. If the DMC finds the proportion of SAE unacceptably higher in one treatment group compared to another, the DMC may consider recommending that the trial be stopped or that the protocol be modified.

C. Final Statistical Analysis of the Data

All primary analyses will be according to the principle of intent-to-treat; i.e., subjects will be analyzed according to their original treatment assignment regardless of adherence to protocol.

1. Baseline Comparability

Because of the size of this study, we expect that the randomization process will produce reasonably comparable groups of participants. However, the adequacy of the randomization will be assessed by comparing the distribution of baseline demographics, medical history, and clinical characteristics among the treatment groups. Comparability for continuous variables will be examined graphically and by summary statistics (means, medians, quartiles, etc.). Categorical variables will be examined by calculating frequency distributions. Adjustment for significant treatment imbalances in baseline covariates will not be done in the primary analysis because this approach can be biased [126,127]. Instead, sensitivity analyses examining the treatment effect will be conducted using a model adjusted for a predefined set of important clinical covariates known to moderate or mitigate outcomes. They will include age at randomization, number of previous myocardial infarctions (MI), and baseline left ventricular ejection fraction.

2. Analysis of the Primary Outcome

The analysis of the primary outcome, all-cause mortality, will be analyzed as time to event and tested by the stratified log rank statistic (stratified on site and Charlson score <3 versus ≥ 3), with a type I error of 0.05 (2-sided). Cumulative survival rates will be calculated using the method of Kaplan-Meier. The treatment effect will be estimated from a stratified Cox proportional hazards model and summarized as a hazard ratio (ICD versus optimal medical therapy) with a 95% confidence interval. The assumption of proportionality will be tested by treatment by time

interaction term prior to fitting the model. The start time for all time-to-event analyses will be defined as the date of randomization and participants who do not experience an event will be right-censored at the date of last contact, date withdrawn, or date of study exit. VA Vital Status File will be used to determine the vital status of all study participants who are lost to follow-up at study exit.

3. Secondary Analyses

The overall type I error for the secondary outcomes will be of 0.05 (2-sided) without adjustment for multiple comparisons.

a) Treatment Interactions by Co-Morbidity

The primary analysis of the treatment interaction with co-morbidity will take the form of a time to event, and will be analyzed using the same methodology described for the primary outcome at a 0.05 2-sided significance level. A test of treatment interaction by Charlson score <3 versus ≥ 3 (alternative subgroups will also be explored) and by Charlson score as a continuous measure. In addition, a forest plot and treatment interaction will be examined for each type of comorbidity.

b) Quality of Life

The primary analysis of QoL will be a comparison between treatment groups of the change in the Minnesota Living with Heart Failure questionnaire scores at 12 months post-randomization relative to baseline using a two-sample t-test if the data appear sufficiently normal and a non-parametric method if the normality assumption looks like it does not hold.

4. Exploratory Analyses

a) Quality of Life

Early effects (QoL at 6 months), late effects (QoL at 24 months), and longitudinal effects (effect over 24 months) for the Minnesota Living with Heart Failure QoL data will also be assessed by a longitudinal repeated measures mixed effects analysis. All mixed models will be adjusted for the baseline Minnesota Living with Heart Failure score, and for the randomization design (site and co-morbidity burden). Site will be included in the model as a random effect and general health status (Charlson <3 versus ≥3) as a fixed effect. The outcome variable in the model will be the change in the Minnesota Living with Heart Failure Quality of Life Score at each follow-up contact relative to baseline. Model building methods will be used to first determine the best mean structure of the outcome (e.g., time as linear or categorical) and then to determine the best fitting and most parsimonious covariance structure for the data.

b) All-cause Hospitalization

Total hospitalizations, total number of days of hospitalization, and the proportion of participants who require at least one hospitalization during the follow-up period will be compared between treatment groups at a 0.05 significance level. No adjustment will be made for multiple testing for tertiary outcomes because they are considered exploratory in nature. The total hospitalizations and total days of hospitalization will be analyzed using generalized Poisson or negative binomial regression models. Proportion of participants requiring at least one hospitalization will be analyzed using a chi-square test statistic.

c) Sudden Cardiac Death

Time to event for sudden cardiac death will be analyzed using the same methodology described for the primary outcome at a 0.05 2-sided significance level. VA Vital Status File will be used to determine the vital status of all study participants who are lost to follow-up at study exit. VA Vital Status File search plus a NDI Plus database search for all participants who are found to have died through the VA database search in order to adjudicate the cause of death.

5. Analysis of Safety Data

The total number of SAE will be summarized by treatment. The proportion of participants experiencing an SAE will be calculated for each treatment group. A chi-square test for the difference in the proportion of SAEs will be used to compare treatment groups over all at the 0.05 level, and with subgroupings of SAEs and non-serious AEs at the 0.01 significance level. Treatment comparisons will be made for the number of participants experiencing SAE, the number of treatment-related SAE, and for the number of non-serious adverse events.

6. Exploratory Analyses

Additionally, data from the Informed Consent Questionnaire will be used for exploratory analysis of the association between perceived and actual participant understanding of the study.

ICDs are capable of delivering information related to a wide range of parameters including activity level, heart rate variability and battery and lead status. Descriptive analysis will be used to summarize the ICD device data. The analysis will be limited in scope to three activities:

- Routine assessment of device activations to assess shock events;
- Device interrogation upon death; and

- Analysis of device data at follow-up appointments as is done in standard clinical practice.

These activities contribute substantially to optimal medical therapy.

7. Consenting Rates

Whereas there are no known published data on the willingness of elderly patients to consent into a study of this nature, it is incumbent on CSP#592 to measure and report the rates of consent among patients deemed so eligible. Data collected from patients found eligible for entry into the study will be analyzed for rate of consenting into the study, as well as rationale for non-matriculation. This activity contributes substantially to the knowledge base for the design of future clinical trials both in the study of the elderly, and in device-based trials.

XVI. FEASIBILITY

A. Estimating the Patient Population

1. ICD Candidacy among VA Patients

a) Candidacy Criteria

The American College of Cardiology and American Heart Association have established guidelines for device based therapy to include a class I indication of ICD therapy for primary prevention of sudden cardiac death in patients with New York Heart Association class II or III symptoms, ischemic and non-ischemic heart disease and left ventricular ejection fraction (LVEF) of 30% or less, who are receiving long-term optimal medical therapy and have a reasonable expectation of survival with good functional status for greater that 1 year [8]. While it is difficult to determine "long-term optimal medical therapy" and "expectation of survival" from the electronic patient records database, it is possible to identify heart failure patients who may qualify for ICD implantation.

b) Estimating Candidacy from the Patient Records Database

Based on the stated criteria for implantation of an ICD, the primary diagnosis by which study-eligible patients can be identified is that of Systolic Heart Failure (SHF). Additionally, a large segment of patients with a Congestive Heart Failure (CHF) diagnosis may also be eligible, however due to the inconsistencies in diagnostic and coding practices within heart failure patients [128,129], it may be difficult to estimate the exact proportion of CHF patients who meet the implantation criteria. Several surveys report the proportion of CHF patients with low ejection fraction (LVEF $\leq$ 30%) at 22-47% of the CHF population (Table 16).

Table 16. Proportion of non-systolic heart failure patients with suppressed ejection fraction.		
Ejection Fraction	Proportion of CHF patients	Source
≤ 30%	47%	Hallstrom, 1995 [130]
< 30%	30%	Nieminen, 2006 [131]
< 30%	29%	Tavazzi, 2006 [132]
< 30%	22%	Cohen-Solal, 2000 [133]

For the purposes of estimating the volume of potential candidates for this study, we shall adopt the assumption of eligibility for 100% of SHF patients and 30% of all CHF patients (a conservative estimate based on Table 16).

An attempt was made to corroborate these statistics against the VA medical record. Select members of the CSP #592 Planning Committee were asked to provide estimates of the proportion of CHF patients with true candidacy for ICD; this search was to include inspection of the clinic record of ejection fraction estimation, restriction to patients ≥70 years of age, without clearly disqualifying conditions (including contraindication of 1-year survivability). The minimum projected estimates of ICD-eligible patients was 26%; therefore we concluded that an estimate of 30% of CHF patients as candidates for ICD implantation was implantation was conservative. We note that these estimates do not account for the proportion of candidate patients already in receipt of ICD, which varies substantially by VAMC (see Table 18).

c) Patient Eligibility Analysis via National Data Service

An assessment of study participant availability was performed by searching within the National SSN Security Database (NSSD) for unique patients with diagnostic codes of the International

Statistical Classification of Diseases and Related Health Problems, Ninth Revision (ICD-9), associated with congestive heart failure or systolic heart failure and also for possession of a defibrillator device (Table 17).

Table17. Heart Failure Patients Across 40 Select VAMCs (Patients ≥70 years).

Congestive Heart Failure	Systolic Heart Failure
402.01, 402.11, 402.91, 404.01, 404.03, 404.11, 404.13, 404.91, 404.93 428.0, 428.1, 428.40, 428.41, 428.42, 428.43 428.9	428.20, 428.21, 428.22, 428.23
	Implantable Cardioverter Defibrillator
	V45.02

Search criteria involved:

- Six separate databases
    a. Inpatient Encounters (DSN = MDPPRD.MDP.SAS.IE09)
    b. Outpatient Events (DSN = MDPPRD.MDP.SAS.SE09)
    c. Inpatient Acute Care (DSN = MDPPRD.MDP.SAS.PM09)
    d. Inpatient Extended Care (DSN = MDPPRD.MDP.SAS.XM09)
    e. Inpatient Observation Care (DSN = MDPPRD.MDP.SAS.PMO09)
    f. Non-VA Care (DSN = MDPPRD.MDP.SAS.NM09)
- Fiscal Year 2009
- Unique patients (as opposed to assessment of visits)

Furthermore, this search was refined to consider only the 40 sites known to perform ICD implantation, i.e. only those sites that might be eligible for involvement in CSP #592. The total patient pool estimation is given in Table 18:

Table 18. Heart Failure Patients Within Select VAMCs, FY2009 (Patients ≥70 years).

	VAMC	CHF+ ICD–	CHF+ ICD+	SHF+ ICD–	SHF+ ICD+
1.	Albuquerque	431	27	14	1
2.	Ann Arbor	469	29	12	1
3.	Bay Pines	977	77	22	4
4.	Birmingham	523	32	11	1
5.	Buffalo	1499	95	55	7
6.	Cincinnati	388	31	26	1
7.	Cleveland	1015	88	18	2
8.	Columbia	625	45	21	4
9.	Dallas	1127	150	32	3
10.	Atlanta	700	69	17	4
11.	Durham	415	45	13	0
12.	Gainesville	1081	91	31	5
13.	Hines	577	68	3	1
14.	Houston	760	88	6	3
15.	Indianapolis	524	44	15	2
16.	Kansas City	1626	99	39	6
17.	Little Rock	612	73	5	2
18.	Lexington	454	39	3	1
19.	Louisville	424	56	13	3
20.	Milwaukee	589	35	21	0
21.	Minneapolis	850	72	54	10
22.	Nashville	739	87	34	8
23.	New York	424	66	29	10

24.	Oklahoma	673	67	1	0
25.	Omaha	1308	111	11	1
26.	Palo Alto	536	39	21	1
27.	Philadelphia	675	46	14	3
28.	Pittsburgh	577	68	12	3
29.	Portland	735	42	61	6
30.	Richmond	395	47	35	3
31.	St. Louis	1411	78	26	4
32.	Salt Lake City	660	32	18	3
33.	San Diego	529	50	4	3
34.	San Francisco	335	20	8	1
35.	Tampa	652	71	57	12
36.	Tucson	518	28	24	3
37.	Washington, DC.	292	15	2	0
38.	West Los Angeles	628	33	15	1
39.	West Palm Beach	609	59	3	2
40.	West Roxbury	594	40	22	4
	Total (Top-20)	18,353	1,514	537	84
	Total (Top-27)	22,364	1,873	623	102
	Total (Top-30)	23,929	1,977	673	104
	Total (Top-40)	27,956	2,352	828	125
FY2009 data summary: 44,713 records across 130 sites. Top sites selected by # CHF+ ICD–.					

Thus, assuming that among congestive heart failure patients, 30% qualify by sufficiently low ejection fraction, then there are over 6,000 heart failure patients meeting the minimum criteria for ICD eligibility in the 30 largest candidate sites (as given by the number of CHF patients without ICD), without accounting for adequate medical therapy and survivability. This is likely a moderate underestimate of the total number of available patients, as this number reflects patient visits in FY2009, i.e. there may be many eligible patients who did not appear in the patient registry in FY2009

d) Not-previously-seen Patients

It is likely that eligible patients will continually present to the study centers over the three years of enrollment. We estimate the number of newly presenting patients at the 27 enrolling sites throughout the enrollment period. Table 19 displays the number of unique patients in FY2009 with SHF (top row) and CHF (but not SHF, bottom row), as found in FY 2009 (left column), followed by patients not seen at all in before FY2010 (next column).

Table 19. Newly presenting patients in 2008-2010. Recruitment pools summed over years.

DX Code	2008	2009	2010	3 years
CHF+, ICD–	123,580	57,872	48,379	229,831
CHF+, ICD– (× 30%)	37,074	17,362	14,514	68,950
SHF+, ICD–	2,125	1,657	1,941	5,723
Subtotal (i.e. Across VA)	39,199	19,019	16,455	74,673
Subtotal (30% adj. top-27)	19,600	9,510	8.228	37.337

Top-N adjustments: Proportion of Across-VA patient pool within the top-N sites (ref. previous table): Top-27: 22,364 ÷ 44,713=50.0%.

Using these data we estimate that there will be approximately 37,000 unique Veterans eligible for the trial at the 27 participating sites. This was estimated based on a 3-year running total of 5,723 patients with documented systolic heart failure without an ICD (SHF+, ICD–) and a total population of chronic heart failure patients without ICD (and not double-counting those with SHF) of 229,831, of which there are an estimated 30% (=68,950) truly eligible for this study, we project a patient pool of 74,673 patients across all VAMCs. We estimate that a study comprising 27 of the top-implanting sites would avail this study to approximately 50% of the VA heart failure population (37,337).

e) Summary

The available pool of patients ≥ 70 years was estimated by two independent methods: 1) pulling of patient records from the National Data Service for all in- and outpatient visits made in 2010, identifying patients with heart failure + ICD, and 2) extraction of the total number of ICD procedures performed in the VA from the Cardiac Surveillance Database. From these data sources, we estimate there to be nearly 37,000 patients available for study across 27 sites in a 3-year recruitment period. The average number of heart failure patients being seen at each of the 27 selected participating sites is estimated to be more than 440 Veterans per year. Whereas we target a sample size of N=1,462, this equates to an enrollment rate of approximately 3.7% of the potentially eligible patient pool.

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XVII. GOOD CLINICAL PRACTICES

A. Role of Good Clinical Practices

This trial is conducted in compliance with the Good Clinical Practice (GCP) regulations. All investigators and clinical research coordinators are properly trained in Good Clinical Practices and the Protection of Human Subjects in Research. The Site Monitoring, Auditing and Review Team (SMART) is responsible for assessing and promoting compliance with Good Clinical Practices at participating sites throughout the trial. This training is conducted at study start-up by the CSP SMART team. During the start-up phase, SMART develops study specific GCP guidance and tools for the sites, and provides training in the use of these materials and in the principles of GCP both at the study organizational meeting and during subsequent site visits. Monitoring of sites participating in the trial is executed according to the VA Cooperative Studies Program Guidelines.

B. Summary of Monitoring and Auditing Plans

- Monitoring Visits
  - Initiation visits at each site soon after study start-up.
  - Additional monitoring visits may be conducted as deemed necessary by study leadership or SMART.
- Audits
  - Routine audits – independent site visits to one or more sites during the Pilot, and each year during the first three years of the full-scale trial (site selection as determined by SMART).

- For-Cause audits – an independent audit of any participating site as requested by study leadership or CSP Central Office. For-cause audits may be announced or unannounced.

XVIII. PUBLICATIONS

A. Publication Policy

According to the policy of the Cooperative Studies Program, outcome data will not be revealed to the Study Chair or participating site investigators until data collection is completed and the study database is locked. This policy safeguards against possible biases affecting the data collection.

All presentations and publications from this study will follow CSP policy as stated in the CSP Guidelines. The presentation or publication of any or all data collected by site investigators on participants of CSP #592 is under the direct control of the Executive Committee. No individual site investigator has the right to perform analyses, make interpretations, make public presentations, or seek publication of any or all of the data without the approval of the Executive Committee. This is true whether the publication or presentation is concerned with the results of the principal undertaking or is associated with the study in some other way.

The Executive Committee has the authority to establish one or more publication committees (usually comprised of subgroups of site investigators and some members of the Executive Committee) for the purpose of producing manuscripts for presentation and publication. A presentation or publication, formulated by the Executive Committee or its authorized representatives, should be circulated to all members of the Executive Committee for review, comments, and suggestions prior to submission of the manuscript to the presenting or publishing body.

All publications must give proper recognition to the Department of Veterans Affairs Cooperative Studies Program and should list or reference all principal and site investigators in the study. Any manuscript, abstract, or letter to the editor submitted for publication or presentation must be sent

to the CSP Director for approval prior to submission for publication. Primary manuscripts will also be presented to the members of the study's DMC for information purposes.

B. Planned Publications

An intended plan of the main publications is given below:

Table 20. Intended study publication plan	
Manuscript	Projected time of submission
Study design and baseline patient characteristics	6 months after enrollment is completed
Primary efficacy analysis	6-12 months after end of study
Secondary and exploratory outcomes, including safety outcomes	12-18 months after end of study
Effect of atrial fibrillation on the elderly –with or without ICD –with respect to shocks, survival, QoL, etc.	12-18 months after end of study
Density of ICD shocks and hospital admissions for HF, or deterioration of LV function (if follow-up echo data is available)	12-18 months after end of study
Comparison of survival curve: OMT versus ICD without shocks versus ICD with shocks	12-18 months after end of study
Pacing in ICD (33% versus 66% versus 100%) relating to HF or death	12-18 months after end of study
Analysis of race and survival across secondary end-points	12-18 months after end of study
Analysis of beta blocker and survival	12-18 months after end of study
Analysis of enrollment and participation	12-24 months after end of study

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Official Title: Efficacy and Safety of Implantable Cardioverter-Defibrillator (ICD) Implantation in the Elderly (I-70)

ClinicalTrials.gov Identifier: NCT02121158

Document Type: Informed Consent Form

Document Date: 6/17/2016

Participant Name: _____ Date: _____

Title of Study: VA Cooperative Studies Program #592: Efficacy and Safety of Implantable Cardioverter Defibrillator (ICD) Implantation in the Elderly

Local Site Investigator: _____ VA Facility: _____

Principal Investigator for Multisite Study: Steven Singh, MD

You are being invited to take part in a research study that is being funded by the Department of Veterans Affairs. Before you decide to take part, it is important for you to know why the research is being done and what it will involve. This includes any potential risks to you, as well as any potential benefits you might receive.

Read the information below closely, and discuss it with family and friends if you wish. Ask one of the study staff if there is anything that is not clear or if you would like more details. Take your time to decide. If you do decide to take part, your signature on this consent form will show that you received all of the information below, and that you were able to discuss any questions and concerns you had with a member of the study team.

BACKGROUND AND PURPOSE

Patients with heart failure are more likely to die from electrical problems of the heart, like arrhythmia, than those without heart failure. An arrhythmia is an abnormal heart beat that could potentially cause death. These can be prevented with medications, but can also be treated with the use of an ICD. Certain medications and a device, the implantable cardioverter defibrillator (ICD), all approved by the Food and Drug Administration (FDA), have been shown to extend the lives of patients younger than 70 years old with heart failure. Most patients with heart failure will not have a sudden death episode and will eventually die from a progressive weakening of the heart. In clinical studies on younger patients with heart failure, the ICD has proven to be more effective than medication in extending life. However, in older patients, the cause of death is more commonly of a non-cardiac reason. The ability of an ICD in extending life in patients with advanced age has never before been studied directly; we hope to answer this question in this study.

An ICD is an implantable heart device about the size of a pocket watch. It is implanted under the skin typically just below the collarbone on the left or right side of the chest. Wires are attached and then inserted into the heart through a vein. Nothing can be seen from the outside except a lump under the skin. The ICD continuously monitors the heart rhythm. If a dangerous arrhythmia (irregularity of heart beats) is detected, an electrical shock is sent to correct it.

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While the ICD is approved for implantation in adults with heart failure, regardless of age, older patients tend to receive ICD therapy much less frequently than younger patients. The ICD is not an experimental device: this study will test the ICD in an application and a patient population that has already received FDA-approval, and complies with national guidelines for ICD implantation.

On the other hand, it has been shown that all patients with the same type of heart condition you have who receive certain medications, adopt a healthy lifestyle with diet and exercise, and have close follow-up with their health care providers have a lower risk of sudden cardiac death. This is called optimal medical therapy (or OMT). It has been shown that when an ICD is also used with OMT, there is an added benefit of reducing the risk of sudden cardiac death even further in those under the age of 70 years. This benefit from the ICD is also possible those 70 years and older however research is needed to make sure this is true.

Both OMT alone and OMT with the ICD are considered standard of care clinically. Because of the uncertainty of the benefit with ICD in those 70 years and older and the known possible risks (as described later in this consent), the decision is usually made between the doctor and patient as to whether to have the ICD placed in addition to OMT. By participating in this research study, you and your doctor will not be making this decision. Instead, you will be randomly assigned to either continue with OMT alone or to receive an ICD while continuing with OMT. To participate in this study, you should be willing to receive either OMT alone or OMT plus the ICD added.

With this study we hope to learn whether using an ICD together with OMT is more effective than using optimal medical therapy alone in improving survival in older adults with heart failure.

This research is sponsored by VA Cooperative Studies Program, a branch of VA Office of Research & Development which conducts large multiple site clinical trials.

This phase of the research study will include approximately 100 Veterans at 6 different VA Medical Centers. Approximately 17 Veterans will participate at each VA Medical Center. There is the possibility this study will grow to include a total of approximately 1,462 Veterans at about 27 VA Medical Centers. If so, approximately 68 Veterans will participate from each VA Medical Center. This potential increase in enrollment will not affect your participation in any way.

You are invited to participate in this research because you are at least 70 years old, have heart failure, and may be eligible to receive an ICD. You must be willing to potentially receive an ICD if you wish to take part in this study.

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Participant Name: _____ Date: _____

Title of Study: VA Cooperative Studies Program #592: Efficacy and Safety of Implantable Cardioverter Defibrillator (ICD) Implantation in the Elderly

Local Site Investigator: _____ VA Facility: _____

Principal Investigator for Multisite Study: Steven Singh, MD

DURATION OF THE RESEARCH

This research study is expected to take approximately 6 years. If you continue with this study until its conclusion, your participation will last up to 5 years.

STUDY PROCEDURES

If you decide to take part in this study and sign this informed consent form, this is what will happen:

During your Baseline Research Visit, a member of the research study team will review your medical record and ask you questions about your medical history, current state of health, and which medications you are taking. You may have an electrocardiogram (also known as an EKG), blood drawn for laboratory analysis, and/or a routine physical exam. We will administer a questionnaire (the Minnesota Living with Heart Failure Questionnaire) to understand how your life is affected by your health status. If you would rather not answer certain questions, you may skip them. We will also ask you to perform a 6 minute walk test. We will monitor you closely as we see how far you can walk during this time frame. We estimate this visit to take approximately 4 hours or less.

When it is determined you are eligible for this study you will be randomized either to the group receiving an ICD, or to the group not receiving an ICD. You may be randomized during this visit or a later date. Randomization means that you will be assigned to one group or the other by chance, as in the flip of a coin. You will have an equal chance (50/50) of being assigned to either group. Neither you nor the research study staff will be able to choose which group you will be assigned. Following randomization, your clinical care team (i.e. your primary care physician, cardiologist, and other clinical providers) will determine how often and what type of visits you need for your clinical care. These clinical appointments are not part of the research study.

All participants will receive Optimal Medical Therapy: All participants entering into this study will be receiving optimal medical therapy (OMT). All participants will continue to receive OMT throughout the study, regardless of their randomization. OMT will be provided by their regular clinicians. OMT includes education on healthy lifestyle maintenance, changes in diet and exercise, keeping follow-up appointments, and monitoring compliance with medications. It is important that you take medications as prescribed. While we outline the risks and benefits of OMT here, you are strongly encouraged to discuss them with your regular health care provider.

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The clinician providing your follow-up care may or may not be a member of the research study team. If the study team, in consultation with your doctor, cannot establish that you are fully stable on OMT, we will delay your entry into the study until it can be determined that OMT has been reached, and that you are ready to be entered into the study. In this case, your regular treating clinician will work with you to reach Optimal Medical Therapy. You may be reconsidered for entry into the study at any time.

If You Are Randomized to receive an ICD:

You may have already received, or you will receive, education about this device, how it works, potential risks of the procedure, pre-procedure preparation, post-procedure care, and restrictions you will need to follow after receiving an ICD. You will be asked to sign a clinical consent for implantation of the ICD which will explain the procedure and associated risks. The following information gives you an overview of the ICD procedure that will be covered in more detail by your doctor who will do the procedure. However, you are also encouraged to ask questions and discuss anything you do not understand with the study team or your doctor.

Day of the Procedure:

If necessary, upper chest hair (if applicable) may be shaved or clipped. Based on your medical condition and history, you may need to have other specific preparations done. An intravenous (IV) line will be started in your hand or arm prior to the procedure for injection of medication and to give you fluids.

During the Procedure:

The procedure usually takes up to one or two hours, but may take longer. You will lie on your back on a procedure table. A local anesthetic will be injected into the skin at the insertion site. Once this anesthetic has taken effect, the doctor will make a small incision (cut).

A small plastic tube containing wires will be inserted into a blood vessel usually under the collarbone and advanced into the heart. It will be very important for you to remain still during the procedure.

There may be one or two wires inserted, depending on the type of device your doctor has chosen for your condition. Once the wire(s) is inside the heart, it may be tested to verify proper location and that it works. Fluoroscopy (a special type of x-ray that will be displayed on a TV monitor) may be used to help your doctor guide the wire to the right location. The ICD will then be slipped into a pocket under the skin.

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Generally, the ICD will be placed on the non-dominant side. (If you are right-handed, the device will be placed in your upper left chest. If you are left-handed, the device will be placed in your upper right chest).

The skin incision will be closed with stitches, adhesive strips, or special glue. A bandage will cover the incision.

After the Procedure:
After the procedure, you will be taken to the recovery room or to your hospital room. Your blood pressure, breathing, and alertness will be checked often. You will be placed on a heart monitor (like a continuous EKG). The ICD insertion site may be sore or painful. You will be given pain medication if needed. Prior to discharge, you will have a chest x-ray. The ICD will also be tested. If there are any medical problems or concerns following the procedure, you may need to remain in the hospital for more than one night.

You will not be able to drive until your doctor gives you approval. You will also be given instructions about your medications and wound care. You will be instructed about what to do if your ICD discharges a shock.

You will be given written instructions on what to watch for, what to report to your doctor, and precautions to take to ensure your safety. You may be asked to keep a diary in order to record any shocks you receive or symptoms you may experience.

You will receive an ICD patient card upon leaving the hospital. It contains information about your ICD. You should carry this card with you at all times. It is important to share this information with any medical staff prior to having any medical treatment anywhere, including dental procedures.

Remote Monitoring:
In addition to monitoring your heart for dangerous heart beats, the ICD records important information about the device itself, such as battery status, wire information, and programming of the device. This data will be monitored by your regular treating doctor, as part of routine care of patients with an ICD. This may provide a benefit to you by regular monitoring of the activity of your heart and the ICD. The collection of this information is called “remote monitoring” or “home monitoring”. As part of this study, if you are randomized to receive an ICD, you will be enrolled

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in the Remote Monitoring program within 30 days of receiving your ICD. You will be given instructions on how to participate in this program and set up your equipment.

You will be given a small "base unit" that will allow for your ICD to be monitored. Either a land line telephone or being within range of a cell phone tower is needed for remote monitoring. If you don't have either a land line or live close to a cell phone tower, your ICD monitoring will be done during a clinic visit.

Information collected from remote monitoring is part of routine clinical care for patients with ICDs. As part of this study, data collected from the remote monitoring seen by your doctor will also be seen by the research study team. Any information collected by the research study team will be stored in a protected study database.

If at any time, you or your doctor would like to have the device turned off, this option is available to you.

Research Study Follow-Up for All Participants:
The first research study related follow-up visit will occur one to four months after you are randomized. We will review your medications and ask if you have had any hospitalizations, ER visits, or other medical events. If you received an ICD, we will collect ICD information from your clinical records.

Research study follow-ups will occur i) at 1-4 months after randomization, and ii) every six months after randomization; all follow-ups will occur by phone. During the phone calls, we will ask you the same questions about how your life is affected by your health status (Minnesota Quality of Life Questionnaire). We will review your medications and ask if you have had any hospitalizations, ER visits, or other medical events. We estimate these follow-up phone calls will last less than 30 minutes. These "centralized follow-up visits" will be performed for all study participants by the same staff persons from Central Follow-Up staff or the Chair's Office.

As part of optimal medical therapy, you may have additional clinical appointments which are not described in this consent. These appointments are not part of the research study.

Participant Responsibilities:

- Follow the plan of care you and your doctor agree on

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- Keep your study appointments
- Complete your questionnaires as requested
- Ask questions as you think of them
- Tell the study team if you change your mind about staying in the study.

While participating in this study, please do not take part in any other research study without discussing it with this study team. This is for your protection and the integrity of this study.

Members of the Human Rights Committee (HRC) at the VA Cooperative Studies Program Coordinating Center conduct site visits and interviews during the course of the study to determine if participants' rights and safety are being properly protected. An HRC member, or a member of the research study team, may contact you to set up an interview.

POSSIBLE RISKS OR DISCOMFORTS

Optimal Medical Therapy

Risks of optimal medical therapy may arise due to changes in diet, exercise, and medication. These are not risks of the research. Your clinical care team will discuss risks as they relate to you.

6 Minute Walk Test

There are a few risks with this test. You will decide how fast you walk depending on your ability and how you are feeling. Changes in breathing, blood pressure, and/or heart rate may occur. You may sweat, fall, have chest pain, and/or develop leg cramps. You can ask to stop this test at any time.

Blood Draw and IV Placement

During a blood draw or placement of an IV, you may experience some discomfort, bruising, and/or bleeding at the site where the needle goes into the arm as you might during any blood draw or IV procedure. There is also a very small risk that infection could occur or that you may faint.

Psychological Risk

There is a risk of psychological distress from answering the Minnesota Living with Heart Failure Questionnaire throughout the study as some questions may make you sad or upset. You are free to skip any questions you choose not to answer.

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ICD

The ICD delivers electric shocks when necessary and stops most arrhythmias with a weak shock that cannot be felt. If you ever experience a strong shock, you will feel a short pain, much like a hard blow to the chest.

Any procedure has possible risks and discomforts. The ICD procedures in this study may cause all, some or none of the risks or side effects listed below. Known risks of ICD implantation include but are not limited to:

- Swelling, bruising, and/or discomfort at the incision site
- Bleeding (particularly around the heart, which can be life-threatening) or pocket hematoma (blood collection around the ICD) requiring drainage, blood transfusion, hospitalization, and/or extension of hospitalization
- Cardiac perforation possibly requiring additional surgical intervention
- Pneumothorax (lung collapse) or hemothorax (collection of blood in the space between the lung and chest wall) requiring prolonged hospitalization and/or chest tube placement
- Infection at the site of the implant, requiring intravenous antibiotics, debridement (removal of damaged tissue), and/or removal of the ICD
- Damage to the vein where the ICD wires are placed
- ICD or wire malfunction requiring additional surgical procedures
- Blood clots in arteries and/or veins
- Drug reaction or other serious complication during the procedure resulting in inability to implant the ICD
- ICD shock or cardiac arrest within 24 hours of the procedure

- Other serious medical complications related to the implant procedure requiring a prolonged hospital stay such as sepsis (bacteria in the bloodstream), pulmonary edema (buildup of fluid in the lungs), myocardial infarction (heart attack), cardiogenic shock (heart cannot pump enough blood to meet the body's needs), and electrical storm (sustained irregular heart beats resulting in multiple shocks in a 24 hr. period).
- Further risks include those associated with diagnostic x-rays, sedation, and other complications during the procedure
- Unnecessary shocks which can be treated by changing the ICD settings or adding medication

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- Psychological distress from complications and/or discomfort which may arise due to ICD implantation and possible shocks.

Rare, unknown, or unforeseeable (unexpected) risks also may occur. We summarize some of the most well-known risks of ICD implantation in the following table:

Complication	Percentage of patients experiencing	Complication	Percentage of patients experiencing
MAJOR COMPLICATIONS			
Lead replacement	2.7	Pulmonary edema	0.6
Lead repositioning	2.0	Myocardial perforation	0.4
Infection requiring debridement	1.0	Pneumothorax/hemothorax	0.4
Electrical Storm	0.9	Post-implant myocardial infarction	0.2
Lead dislodgement with re-positioning	0.8	Sepsis	0.2
Lead extraction	0.7	Cardiogenic shock	0.2
MINOR COMPLICATIONS			
Incisional infection	1.1	Lead dislodgement not repositioned	0.8
Pocket hematoma	1.0	Subclavian vein thrombosis	0.2
List of known risk frequencies for major and minor complications in new ICD implantation.			

POTENTIAL BENEFITS

We cannot promise that you will get any benefits from taking part in this research study. However, all participants receiving an ICD and/or optimal medical therapy potentially receive life-saving therapy that could prevent sudden cardiac death. Additionally, information we get from this study might help us treat patients in the future.

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LSI Verification Date: N/A

Participant Name: _____ Date: _____

Title of Study: VA Cooperative Studies Program #592: Efficacy and Safety of Implantable Cardioverter Defibrillator (ICD) Implantation in the Elderly

Local Site Investigator: _____ VA Facility: _____

Principal Investigator for Multisite Study: Steven Singh, MD

ALTERNATIVES TO PARTICIPATING IN THIS RESEARCH

You may choose not to participate in this study. If this is your choice, you may receive an ICD or OMT alone outside of the study. You may discuss this and other possible options with your clinical providers.

CONFIDENTIALITY

Taking part in this study will involve collecting private information about you, including health information, name, address, telephone number, and social security number. We will ask you to provide us the name of one or more persons we can contact in case we are not able to contact you for follow-up visits. All data collected as part of this research study will be protected in the following ways:

All research data will be stored on password protected computers or in locked file cabinets. Only approved research staff will have access to this data. Information about you will be combined with information from other people taking part in the study. We will write about the combined data we have gathered. Any talks or papers about this study will not identify you.

We will not share your records or identify you unless we have to by law. There are times when we might have to show your records to other people. For example, someone from the Office of Human Research Protections, the Government Accountability Office, the FDA, the Office of the Inspector General, the VA Office of Research Oversight, the VA Central IRB, our local Research and Development Committee, and other study monitors may look at or copy portions of records that identify you.

If you are a VA patient, you already have a VA medical record. We will put information about your participation in this study into your medical record. This electronic record will be kept in accordance with the VA Records Control schedule and is accessed only by authorized users within the VA Healthcare System. All authorized users in the VA Health Administration can have access to your medical record.

A description of this clinical trial will be available on http://www.ClinicalTrials.gov as required by U.S. Law. This website will not include information that can identify you. At most, the website will include a summary of the results. You can search this website at any time.

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Your SSN will only be used for three purposes: 1) for safety monitoring and auditing purposes, 2) to assess your survival, and 3) to process your payment for participating study visits.

The West Haven VA Cooperative Studies Program Coordinating Center will be the statistical and data coordinating center for this study. The Albuquerque VA Cooperative Studies Program Research Pharmacy Coordinating Center (PCC) will be the central study pharmacy center and safety monitor during the study. The Cooperative Studies Program Site Monitoring, Auditing and Resource Team (SMART) will access your VA medical record using your social security number (SSN) to monitor your participation and safety during the study.

The data that we gather as part of this study will be analyzed and published, as is typical in studies like ours. We may in the future contribute data from this study to a central database where similar studies will also contribute data. While there is currently no database like this, it is possible that one would be created in compliance with national mandates for Federal agencies to share data from sponsored researches. If so, we will comply with any Federal requirements in supplying de-identified data from this study.

COSTS TO PARTICIPANTS AND PAYMENT

You will not be charged co-pays for the implantation procedure (as applicable) and the first research study follow-up visit. If you usually pay co-payments for VA care, you will continue to pay them for all clinical care visits and medications, which may include any future procedures related to your implanted device. There may also be costs associated with transportation to your healthcare facility or time away from work that will not be covered by participation in this study.

Payment Offered for Participation:

For your time, you will be paid $25 for the baseline visit. Payment will be in the form of a debit card or by electronic transfer of funds, or according to local medical center procedures. An Internal Revenue Service (IRS) Form 1099, which documents that you received income, will be generated using your Social Security Number. Because participant compensation for involvement in this study is disbursed through the Bureau of the Fiscal Service, it is possible that your compensation may be reduced (an “offset”), via the Treasury Offset Program (TOP), if the Bureau’s Debt Management Services identifies outstanding debt owed to a Federal agency.

MEDICAL TREATMENT AND COMPENSATION FOR INJURY

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Every reasonable safety measure will be used to protect your well-being. If you are injured as a result of taking part in this study, the VA will provide necessary medical treatment at no cost to you unless the injury was due to your not following the study procedures.

If you should have a medical concern or get hurt or sick as a result of taking part in this study, call:

DURING THE DAY:

Dr./Mr./Ms. _____ at _____ and

AFTER HOURS:

Dr. /Mr./Ms._____ at _____.

Emergency and ongoing medical treatment will be provided as needed.

You do not give up any of your legal rights and you do not release the VA from any liability by signing this form.

PARTICIPATION IS VOLUNTARY

It is up to you to decide whether or not to take part in this study. You are giving us permission to use your personal health information until the goals of this study are met. If you decide to take part, you may still withdraw at any time. You must withdraw in writing in order to withdraw your permission for us to continue to collect and use further information (except from public records, such as survival data). However, the information we already collected before your withdrawal will be used by investigators to complete the study and to record any information that is required by oversight agencies concerning safety of participants.

If you do not wish to be in this study, or leave the study early, or if the study closes at any time, for any reason, you will not lose any of the benefits to which you are entitled. If you don't take part or withdraw, you can still receive all the usual care that is available to you. Your decision not to take part will not affect the relationship you have with your doctor or other staff, and it will not affect the usual care that you receive as a patient.

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You may be asked whether you are willing to continue limited participation in the study. This means if you consent to provide information on a less active level such as allowing study personnel to review your medical record to determine your medical status or by agreeing to limited phone contact.

If you wish to withdraw from this study, you may do so by submitting your request in writing to: CSPCC (151-A), VA Connecticut Healthcare System, 950 Campbell Avenue, West Haven, CT 06516; ATTN: CSP#592. The study team at this site can provide you with a Withdrawal Form as a convenience.

RIGHT OF INVESTIGATOR TO TERMINATE PARTICIPATION

The investigator reserves the right to terminate your participation if, in the judgment of the investigator, your continued participation represents a potential for harm. Reasons for this may include your inability to comply with the study, or early stoppage of the study due to safety concerns, benefit or insufficient number of participants.

PERSONS TO CONTACT ABOUT THIS STUDY

If you have questions, complaints, or concerns about this research, you can call the National Study Coordinator at 1-202-745-8000 x 54087 or your VA medical center patient advocate(s): _____at _____.

If you have questions about your rights as a study participant, or you want to make sure this is a valid VA study, you may contact the VA Central Institutional Review Board (IRB). This is the Board that is responsible for overseeing the safety of human participants in this study. You may call the VA Central IRB toll free at 1-877-254-3130 if you have questions, complaints or concerns about the study or if you would like to obtain information or offer input.

SIGNIFICANT NEW FINDINGS

Sometimes during a research study, new information becomes available about the treatments that are being studied that might change a person's decision to stay in the study. If this happens, your research study team will tell you about it and discuss with you whether you want to continue in the study. If you decide to continue in the study, you might be asked to sign an updated informed consent form. Your research study team may also decide it to be in your best interests to withdraw you from the study. If so, the reasons will be explained and your usual clinical care will not be affected.

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Participant Name: _____ Date: _____

Title of Study: VA Cooperative Studies Program #592: Efficacy and Safety of Implantable Cardioverter Defibrillator (ICD) Implantation in the Elderly

Local Site Investigator: _____ VA Facility: _____

Principal Investigator for Multisite Study: Steven Singh, MD

AGREEMENT TO PARTICIPATE IN THE RESEARCH STUDY

A study team member has explained the research study to you. You have been told of the risks or discomforts and possible benefits of the study. You have been told of other choices of treatment available to you. You have been given the chance to ask questions and obtain answers.

You voluntarily consent to participate in this study. You also confirm that you have read this consent, or it has been read to you. You will receive a copy of this consent after you sign it. A copy of this signed consent will also be put in your medical record if applicable.

I agree to participate in this research study as has been explained in this document.		
_____ Participant's Name	_____ Participant's Signature	_____ Signature Date
_____ Name of person obtaining consent	_____ Signature of person obtaining consent	_____ Signature Date

FOR RESEARCH STAFF

☐ In-person

☐ Telemedicine

☐ Telephone

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Official Title: Efficacy and Safety of Implantable Cardioverter-Defibrillator (ICD) Implantation in the Elderly (I-70)

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Document Type: Statistical Analysis Plan

Document Date: 2/19/2016

VA Cooperative Study No. 592

Efficacy and Safety of ICD Implantation in the Elderly (the "I-70 Study")

Statistical Analysis Plan

February 19, 2016
v1.2

PRIVILEGED AND CONFIDENTIAL
Not for Dissemination Beyond the Official Study Function and Use

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
AR1	Autoregressive Covariance Structure
ATP	Antitachycardia Pacing
BMI	Body Mass Index
CI	Confidence Interval
CMS	Center for Medicare and Medicaid Services
CSP	Cooperative Studies Program
CS	Compound Symmetry
CSPCC	Cooperative Studies Program Coordinating Center
CSPCRPCC	Cooperative Studies Program Clinical Research Pharmacy Coordinating Center
DMC	Data Monitoring Committee
ECG (EKG)	Electrocardiogram
ICD	Implantable Cardioverter Defibrillator
LRT	Likelihood Ratio Test
LVEF	Left Ventricular Ejection Fraction
MI	Myocardial Infarction
MITT	Modified Intention to Treat
MLHF	Minnesota Living with Heart Failure
NDI	National Death Index
OMT	Optimal Medical Therapy
PDF	Portable Document Format
SAP	Statistical Analysis Plan
SAS	Statistical Analysis Software
SCD	Sudden Cardiac Death
QOL	Quality of Life
VA	Department of Veterans Affairs

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1. Introduction

1.1 Overview

1.1.1 Motivation of the Statistical Analysis Plan

This Statistical Analysis Plan (SAP) is intended to be a comprehensive and detailed description of the strategy, rationale, and statistical techniques that will be used in the monitoring and analysis of the data collected in this study.

1.1.2 Motivation of CSP#592

Sudden cardiac death (SCD) is the second greatest cause of death in the United States, after all cancers combined. The implantable cardioverter defibrillator (ICD) has shown great efficacy in reducing all-cause mortality, and specifically SCD, by continuously monitoring the electrophysiological signatures of the heart, and intervening with a therapeutic shock in case of a detected arrhythmia. However, whereas the landmark clinical trials demonstrating ICD efficacy have included primarily middle-aged patients, there is little known of the impact of the ICD on older patients; clinicians often treat the elderly based on empiric judgments, rather than robust clinical evidence. There is an emergent need to study both efficacy and safety of the ICD in patients with advanced age.

The overall aim of CSP#592 is to study the safety and efficacy of ICD implantation as a primary prevention strategy of SCD in patients 70 years and older. In particular, this study is designed to determine the comparative effectiveness of ICD, in addition to optimal medical therapy (OMT), in reducing all-cause mortality, versus OMT alone. OMT includes standard intervention for chronic heart failure patients, i.e. lifestyle modification, disease management, adoption of healthy diet and exercise practices,

etcetera. One particularly important secondary objective is to assess treatment efficacy under the conditions of high versus low co-morbidity burden.

1.2 Study Objectives and Hypotheses

1.2.1 Primary Objectives

The primary objective of CSP#592 is to determine whether a primary prevention strategy with ICD implantation in addition to optimal medical therapy (OMT) is effective in reducing all-cause mortality compared to OMT alone in patients ≥70 years of age who are eligible for ICD therapy according to current Centers for Medicare & Medicaid Services (CMS) criteria. The primary hypothesis of CSP#592 is that implantation of an ICD plus optimal medical therapy will reduce all-cause mortality in patients ≥70 years of age versus optimal medical therapy alone.

1.2.3 Secondary Objectives

1.2.3.1 Co-morbidity Burden

A secondary objective of this study is to ascertain whether age, co-morbidity burden, or age and burden together, are determinants in mortality outcomes in the OMT versus ICD + OMT group.

1.2.3.2 Quality of Life

An additional secondary objective of the study is to determine the effect of ICD implantation plus optimal medical therapy on QoL among elderly patients compared with optimal medical therapy.

1.2.4 Exploratory Analyses

1.2.4.1 Prevention of Sudden Cardiac Death

This study will also ascertain whether –irrespective of the effect of ICD on all-cause mortality– the ICD is effective in its designed mechanism of action, i.e. preventing sudden cardiac death.

1.2.4.2 Reduction in All-Cause Hospitalization

As an additional exploratory analysis, CSP#592 will test whether there is a significant difference in the number of hospitalizations among participants randomized to ICD + OMT versus those randomized to optimal medical therapy alone.

1.3 Outcome Measures

1.3.1 Primary Outcome Measure

The primary outcome measure for this study will be death from any cause analyzed as time to event. The date of randomization will be used as the time origin. VA Vital Status File will be used to determine the vital status of all study participants who are lost to follow-up at study exit. The VA Vital Status File has been shown to be highly accurate compared to the National Death Index (NDI)[1]. As cause of death is not available from the VA Vital Status File, a NDI Plus database search will be performed for all participants who are found to have died through the database search in order to adjudicate the cause of death for secondary outcomes.

1.3.2 Secondary Outcome Measures

1.3.2.1 Quality of Life

Among the cardiac-specific quality of life (QoL) instruments, the Minnesota Living with Heart Failure questionnaire (MLHF) is considered to be among the best[2]. It has been widely validated[3–5], and it is more sensitive than the generic QoL measures in detecting clinically important changes over time in patients with heart failure[6,7]. The MLHF was

also chosen as the QoL measure for this study because it is simple, inexpensive, short, easily understood by ill and elderly individuals, and easy to score [8–15].

The MLHF questionnaire is designed to specifically assess the impact of heart failure on QoL. It consists of 21 questions that measure the effect of symptoms specifically related to heart failure and its treatment in adults[16]-[17] The response to each question is scored on a 6-point Likert scale (0-5). There are two subscales to MLHF: physical and emotional. The effect size outcomes of several studies employing QoL are summarized in the following table.

Table 1 Effect sizes reported using Minnesota Living with Heart Failure survey *.		
Effect Size	Interpretation	Source
1	Not significant	Rector, 1992 [15]
1.6	Not significant (P=0.33)	Kasper, 2002 [14]
4	P<0.001	Rector, 1992 [15]
5	Not significant	Owen, 2000 [12]
6.6	P=0.0006	Kasper, 2002 [14]
6.7	Not significant (P=0.41)	Curiati, 2005 [18]
9.6	P=0.01	Kasper, 2002 [14]
11.6	P=0.02	Curiati, 2005 [18]

MLHF on 105-point scale, including their calculated significance. Original references listed.

A disease-specific instrument was chosen in favor of a broader (“generic”) QoL assessment for the reason that questionnaires with greater emphasis on ICD-specific and arrhythmia-specific measures may be more sensitive to changes in outcome, and would be more impactful in addressing ICD as a treatment choice for life threatening

arrhythmias[19]. The Minnesota Living with Heart Failure is designed to capture both physical and emotional (anxiety or distress) dimensions of patient well-being and is considered an effective and efficient instrument [20].

1.3.2.2 Co-Morbidity Burden

One of the primary reasons for doing a study like CSP#592 is to determine whether there are differential risk-benefit issues in the elderly: in patients with declined health status, the likelihood of surviving long enough to derive benefit from device implantation may be decreased. This study will test whether poor general health status shifts the risk-benefit profile. In this way, the Charlson Co-Morbidity Index is the most practical tool for incorporation into CSP#592, as it is an extensively validated method of measuring the prognostic impact of co-morbid disease [20,21]

1.3.2.3 Sudden Cardiac Death

Sudden cardiac death will include deaths that occur unexpectedly that are not preceded by an acute myocardial infarction. SCD will include the following events [22]:

- Death witnessed and instantaneous without new or worsening symptoms;
- Death witnessed within 60 minutes of the onset of new or worsening cardiac symptoms, unless the symptoms suggest an acute myocardial infarction;
- Death witnessed and attributed to an identified arrhythmia, e.g., captured on an electrocardiographic (ECG) recording, witnessed on a monitor, or unwitnessed but found on implantable cardioverter-defibrillator review;
- Death after unsuccessful resuscitation from cardiac arrest;

- Death after successful resuscitation from cardiac arrest and without identification of a non-cardiac etiology (Post-Cardiac Arrest Syndrome); and
- Unwitnessed death without other cause of death (information regarding the participant's clinical status preceding death should be provided, if available).

General considerations for SCD are that a subject seen alive and clinically stable 12-24 hours prior to being found dead without any evidence or information of a specific cause of death should be classified as SCD. Deaths for which there is no information beyond "Patient found dead at home" may be classified as "death due to other cardiovascular causes" or "undetermined cause of death" [22]. Cause of death determination will be National Death Index (National Center for Health Statistics); the NDI *Plus* database has been shown to be highly accurate in resolving cause of death [21]; an Adjudication Committee may be assembled if deemed necessary by the Executive Committee.

1.3.2.4 All-Cause Hospitalization

Hospitalization information will be captured by participant self-report and medical record review. Self-report is valid and reliable, especially with inpatient care and recall periods less than one year[23]; however, hospitalization data will also be collected from VA electronic medical records, and where feasible: access of non-VA medical records. Specifically, this study will test whether the total number of days of hospitalization are different between the two treatment arms.

1.3.2.5 ICD Device Data

ICDs monitor and store data on a wide range of parameters including battery and lead function, patient activity, heart rate, frequency of pacing, and most importantly tachyarrhythmia events. The ICD stores extensive data on all tachycardia events that trigger therapy including beat to beat intervals that met the programmed criteria for ICD therapy, electrograms from before, during, and after ICD therapy, the types of ICD therapy employed including shocks and anti-tachycardia pacing (ATP), the results of each therapy attempt, and the final results of ICD treatment. This data can be accessed in clinic using a device called a programmer which interrogates the defibrillator and then displays the results and allows the results to be saved as a PDF file. This data can also be retrieved "remotely" in the patient's home using a home monitoring device that is available to all newly implanted ICD patients. These home monitoring systems interrogate the ICD on a programmable schedule and transmit the data to secure servers via either land line or cell phone systems on a routine usually every 3 month basis and when certain programmable criteria for unscheduled transmissions are met. "On demand" transmissions can also be initiated by patients if they feel they are having a problem or are instructed to do so by their provider. The VA National Cardiac Device Surveillance Center manages the data flow from this remote monitoring and posts PDF files of all transmissions on their web site and alerts providers if there are urgent findings on a transmission. Remote monitoring provides significant benefits to the Study Team, as it 1) provides accurate, objective, and timely record of therapeutic events, and 2) provides a platform for assessing protocol adherence with regard to device programming, and 3) reduces loss to follow-up. Registration for this database is expected of all CSP#592 study

participants; failure to register within 30 days of implantation will be considered a protocol deviation.

Files documenting all in clinic interrogations will be accessed by the Study Team in a separate and independent transaction from that conducted by the care provider as part of routine clinical practice. These files will be used most importantly as source documentation for exploratory analyses of ICD therapy events including the frequency of ICD therapy, the appropriateness of ICD therapy, the rhythms that trigger ICD therapy and the overall number of shocks experienced by participants with ICDs. These files could also be used for other exploratory analyses focusing on other aspects of ICD function. The data contained within these files may be the result of direct interrogation of the device, or a filtered dataset exported from a larger database used in order to increase the efficiency of data analysis.

Lastly, every effort will be made to interrogate the device upon death. This is standard clinical practice and is often impactful in facilitating determination of the cause of death.

1.4 Patient Characteristics

1.4.1 Screened Population

This study will recruit within the electrophysiology service, heart failure clinics, gerontology, and general practice. A broad outreach effort will be undertaken in an effort to ensure adequate enrollment and from a diverse patient pool. All individuals identified in the site screening logs as potential participants who referred to the study for screening, or for whom referral was sought through a treating clinician, or for whom there appeared to be evidence of study eligibility will be noted. De-identified data from these screening logs will be transmitted from the sites to the centralized members of the Study Team

(Chair's Office and Coordinating Center). This population may include many patients who are ineligible for the study; Eligibility criteria will be clearly noted within this screening log

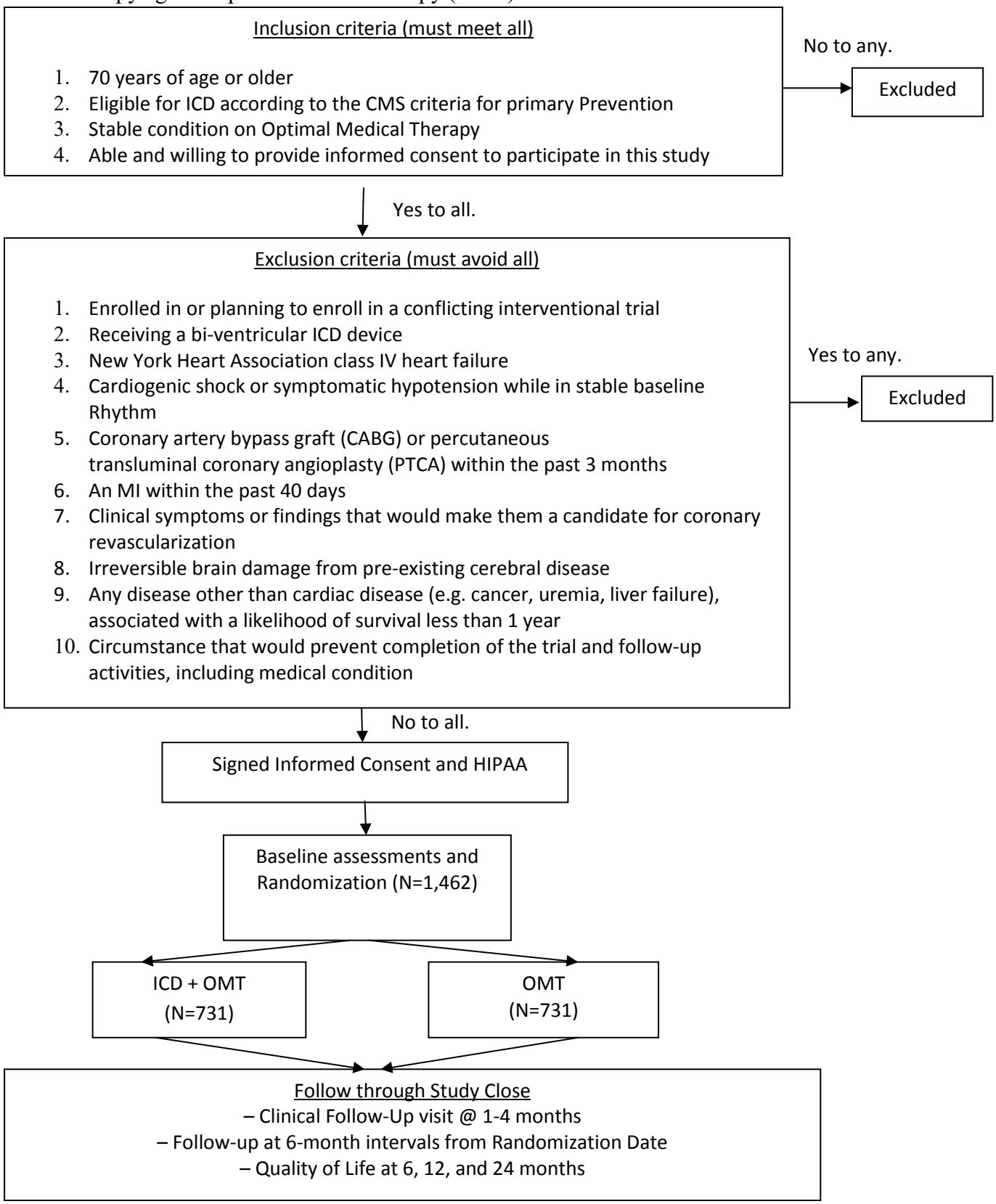
1.4.2 Enrolled Population

Participants enrolled in CSP#592 will have been introduced to the study and its risk and benefits, and provided informed consent to be randomized to either study arm (OMT + ICD, or OMT without implantation). Provision of informed consent permits the collection of baseline data, which will be useful in confirming eligibility to be randomized. This population may still include patients who are ineligible for the study.

1.4.3 Randomized Participants

Participants qualified to be randomized within CSP#592 must meet all eligibility criteria, and may not meet any of the exclusion criteria. The Inclusion and Exclusion criteria are exhaustively detailed in the Study Protocol and Operations Manual, and are summarized as follows (Figure 1).

Figure 1: CSP #592, multi-site, prospective, randomized clinical trial comparing ICD therapy against optimal medical therapy (OMT).



2. Statistical Approaches

2.1 Study Design Summary

The primary outcome of CSP#592 is all-cause mortality analyzed as time to event. The primary hypothesis is that the ICD arm will have a 25% reduction in the hazard ratio (HR=0.75) (23.5% relative risk reduction in the annual mortality rate). The sample size calculation assumes a 15% annual mortality rate in the control arm. The cumulative event rate by the end of the 5-year trial (3.6 years average follow-up[1]), taking into account administrative censoring, loss, drop-in, and drop-out, is projected to be 42.0% in the control arm versus 34.1% in the ICD arm. The following assumptions were used for the sample size calculation:

- Two-sided Type I error of 0.05
- Pilot stage with uniform recruitment over 1 year, with uniform follow-up of 5 years for all participants; 17 participants per site at 6 sites, i.e. 102 × 5 = 510 patient follow-up years
- Full-scale stage with uniform recruitment over 3 years (minimum follow-up = 2 years, maximum follow-up = 5 years, median follow-up = 3.5 years)
- Annual event rate of 15% in the control arm
- Hazard ratio of 0.75 (relative risk reduction =23.5%)
- Allocation ratio of 1:1 for the treatment groups
- Annual drop-in rate of 2.5% from the control group to the ICD group

[1] Five years follow-up for Pilot Study participants (N=102), plus 3.5 years average follow-up for participants in Stage II (N=1360): (5×102 + 3.5×1360) ÷ (102+1360) = 3.6 average years of follow-up.

- Drop-out rate of 1% from the ICD group to the control group in year 1 only.
- Annual loss-to-follow-up of 1%

Because the VA Vital Status File will be searched for all deaths, loss-to-follow-up for the primary endpoint is considered to be very negligible and was therefore not accounted for in the sample size calculation. Based on a 15% annual event rate in the control arm and a hazard ratio of 0.75, and the other assumptions listed above, a sample size of 1,462 (565 total primary outcome events) will be needed in order to achieve 90% power with a 2-sided Type I error rate of 0.05.

The secondary objectives for this trial are to test the treatment interactions by co-morbidity level, and to test the change from baseline in the Minnesota Living with Heart Failure score. Neither secondary analysis will require adjustment for type I error, i.e. no "multiple testing" corrections: adjustments for multiple comparisons are required in confirmatory whenever results from multiple tests have to be combined in one final conclusion and decision; in studies with a single primary endpoint, all other endpoints are considered subsidiary and their results can only have an exploratory rather than a confirmatory interpretation – multiplicity corrections are not required[24].

2.2 Statistical and Analytical Plans

2.2.1 Randomization Scheme

Veterans who satisfy all of the study eligibility criteria, provide written informed consent and complete the necessary baseline assessments will be randomized to one of two treatment strategies: ICD therapy + optimal medical therapy, or optimal medical therapy alone. The treatment assignment will be provided through a web-based randomization platform or over the telephone to the site investigator or coordinator. The treatment allocation ratio for the two treatment regimens will be 1:1 within each stratum; participants will be stratified both by medical center and by Charlson score (Charlson <3, and Charlson ≥3), using a random permuted block scheme with randomly varying block size. The random treatment scheme has been generated by CSPCC. When a subject is to be randomized, the Study Coordinator or Local Site Investigator will complete the eligibility and baseline forms. If all eligibility criteria are satisfied and informed consent has been obtained, a new randomization will be assigned. This procedure has been tested and validated before enrollment began.

The CSPCC will review the overall and by-site randomization at least weekly during the enrollment phase of the study, and will be monitoring the randomization transactions with equal or greater frequency. The participant's unique study ID number will be linked in the randomization file to the treatment assignment for each individual. The randomization file data will remain separate from the rest of the study data on the central database.

Randomization may occur on the same day the patient has completed the necessary portions of the Screening and Baseline assessments and is judged eligible for

randomization. Delay in randomization due to participant or medical circumstances are permitted up to a maximum of 30 days past baseline data collection; if randomization is delayed further, baseline data must be collected anew. When a new participant has been enrolled, his/her electronic medical record will be updated indicating participation in the study. Source documentation for eligibility criteria and randomization will be kept at the site with the participant's study folder.

2.2.2 Baseline Comparability

Because of the size of this study, we expect that the randomization process will produce reasonably comparable groups of participants. However, the adequacy of the randomization will be assessed by comparing the distribution of baseline assessment. The baseline assessment includes demographics and military history, clinical history, laboratory measurements, EKG, physical examination, six-minute walk test, medication use, and Minnesota Living with Heart Failure Questionnaire score. Specifically, continuous variable (e.g. age and BMI) will be examined for skewness and outliers , both quantitatively and by graphical means such as side-by-side histograms, boxplots, and normal quartile plots. The summary statistics will also be calculated including means, medians, quartiles, etc. The difference in the means for continuous variable will be tested through two-sample *t* test. F tests for equality of variances will be used to guide the selection of the appropriate statistical tests for continuous measures. For the variables that are not normally distributed, a nonparametric method, such as Wilcoxon rank-sum test will be used to test the difference between the two groups. Categorical variables will be examined by calculating frequency distributions. Chi-square test or Fisher's exact test

(when expected cell counts are less than 5) will be used for comparing the distribution between treatment groups.

2.2.3 Analysis of the Primary Outcome

For all the endpoints (primary, secondary, and exploratory) we will present summary information, as well as estimated result with p-value from an appropriately selected hypothesis test. The number of participants reaching the primary endpoint will be summarized in terms of total number participants as well as percent by treatment arm and treatment stratified by health stratum.

Treatment effect on the primary outcome, all-cause mortality, will be analyzed as time to event and tested by the stratified log rank statistic (stratified by Charlson score <3 versus ≥3), with a type I error of 0.05 (2-sided). Cumulative survival rates will be calculated using the method of Kaplan-Meier. The treatment effect will be estimated from a Cox proportional hazards model, adjusted by Charlson score and provided as a hazard ratio (ICD versus optimal standard of care) with a 95% confidence interval. The start time for all time-to-event analyses will be defined as the date of randomization and participants who do not experience an event will be right-censored at the date of last contact, date withdrawn, or date of study exit. VA Vital Status File will be used to determine the vital status of all study participants who are lost to follow-up at study exit.

Prior to Cox model fitting, the assumption of proportionality will be tested via treatment by time interaction term. If the assumptions of proportionality are not fulfilled, there will be no impact on the primary hypothesis test since we apply log-rank test on the primary

hypothesis test. We may estimate the hazard ratio by introducing interactions of treatment with function of time in the model. In addition, we will also test the treatment and Charlson stratum interaction in the Cox proportional hazards model[25]. Breslow's approximation, which is the default in PROC PHREG in SAS, will be used to handle tied event times when ties are relatively few[26]. If data are moderately- or heavily tied, we will use Efron's method, which gives closer results to the exact results than Breslow's approximation[27,28].

2.2.4 Exploration of a Modified Intention to Treat Approach

The primary analysis uses an intention to treat approach, with time to event according to time from randomization to exit/death. As we anticipate that there will be some delay between randomization and ICD implantation, we will perform a sensitivity analysis on the primary outcome using a modified intention to treat (MITT) approach without adjusting the type I error. In the MITT sensitivity analysis, we will first calculate the average time from randomization to implantation τ. Then, the start time for participants in the OMT arm will be adjusted by τ, in order to calibrate the time of treatment; the time for participants randomized to ICD will be taken from time of implantation. In a situation where a participant dies before implantation (OMT+ICD arm) or τ (OMT arm), he/she will be excluded from the MITT analysis[29]. The survival analysis for MITT will be the same as the primary analysis.

Similar sensitivity analysis will be applied to other mortality endpoints, such as sudden cardiac death.

2.2.5 Supportive Co-Variate-Adjusted Analysis

Adjustment for significant treatment imbalances in baseline covariates will not be done in the primary analysis because this approach can be biased [30,31]. Instead, exploratory analyses examining the treatment effect will be conducted using a model adjusted for a predefined set of important clinical covariates known to moderate or mitigate outcomes. The model will include factors that are known to increase risk in ICD patients, such as age at randomization, number of previous myocardial infarctions (MI), and baseline left ventricular ejection fraction (LVEF).

2.2.6 Analysis of the Secondary Outcomes

The overall type I error for the secondary outcomes will be 0.05 (2-sided) without adjustment for multiple comparisons. We will apply the same analysis to the secondary outcome as the primary outcome.

2.2.6.1 Treatment Interactions by Co-Morbidity

The primary analysis of the treatment interaction with co-morbidity will take the form of a time to event, and will be analyzed using the same methodology (log-rank test) described for the primary outcome at a 0.05 2-sided significance level. The treatment effect will be summarized as a hazard ratio with 95% confidence interval. A test of treatment interaction by Charlson score <3 versus ≥3 (alternative subgroups) will also be performed.

In the study, the original Charlson score is a continuous variable. It is known that dichotomizing a continuous outcome into low or high values leads to a loss of information[32,33]. Therefore, to keep the statistical power of the analysis, the testing of interaction will also be conducted by treating Charlson score as a continuous measure, via the Cox model, cf. the log-rank rest for dichotomous formulation. The results from the above two methods will be compared, and they should be similar. In addition, a forest plot and treatment effects will be examined for each type of co-morbidity.

2.2.6.2 Quality of Life

The QoL will be measured by the Minnesota Living with Heart Failure questionnaire (MLHF), which contains 21 items that evaluate patients' perception of the effects of heart failure on their daily lives. In the questionnaire, each question is rated on a scale of 0 to 5, producing a total score between 0 and 105. The higher the score, the worse the quality of life. The total score will be treated as a continuous variable. The change in MLHF score at 12 months post-randomization relative to baseline will be calculated and tested for normality. If the distribution appears sufficiently normal, two sample t-test will be used to compare the difference between the two treatment groups. If not, a non-parametric method, such as the Wilcoxon rank-sum test will be used.

2.2.7 Exploratory Analysis

2.2.7.1 Quality of Life

The QoL score at each time point will be summarized in terms of mean and standard deviation by treatment arm and treatment by stratified health status.

Early effects (QoL at 6 months), late effects (QoL at 24 months), and longitudinal effects (effect over 24 months) for the Minnesota Living with Heart Failure QoL data will also be assessed by a longitudinal repeated measures mixed effects analysis.

The outcome variable in the mixed models will be the change in the MLHF QoL score at each follow-up visit relative to baseline, which is a continuous variable. Model building methods will be used to first determine the most parsimonious covariance structure for the data. The model will first be fit with an unstructured covariance matrix with time treated as a categorical variable. The mixed model will include the following covariate: baseline MLHF score (continuous variable), site as a random effect, and general health status (Charlson co-morbidity index) as a fixed effect and time, along with a time and treatment interaction term. A second model will be fit with an unstructured covariance matrix with time treated as a linear trend. The model will include treatment, time, and the treatment by linear time interaction plus the pre-determined covariates. A likelihood ratio test (LRT) will then be performed to determine if the linear trend (plus its interaction with treatment) is consistent with the data. If the simpler model with time as linear is sufficient, time will be treated continuously. If the fit is significantly improved with time as a categorical effect, then time will be included in the model as a categorical variable.

Once the mean structure of the model is determined, a LRT will be performed to determine whether a more parsimonious covariance structure e.g. autoregressive covariance structure 1 (AR1) or AR1 or compound symmetry (CS), will fit better. Once the mean and covariance structure are identified for this model, a treatment by time interaction will be examined. If the interaction term is not significant, it will be removed

from the model. If the treatment by time interaction is significant, then pairwise treatment comparisons will be performed at each time point separately.

As discussed previously, the Charlson score is originally a continuous variable. We will also perform the mixed model analysis without dichotomizing general health status. In addition, graphical methods will used to summarize the estimates of least square means and standard deviation, with pairwise comparisons at each time point.

2.2.7.2 All-cause Hospitalization

Total hospitalizations, total number of days of hospitalization, and the proportion of participants who require at least one hospitalization during the follow-up period will be summarized by treatment and compared between treatment groups at a 0.05 significance level. No adjustment will be made for multiple testing for tertiary outcomes because they are considered exploratory in nature.

The total hospitalizations and total days of hospitalization will be analyzed using generalized Poisson or negative binomial regression models. If extra zero counts are observed in the above, a zero inflated Poisson model will be used[34]. In the generalized mixed model, covariates will include site as a random effect, and general health status (Charlson <3 versus ≥ 3, or as continuous variable) as a fixed effect. Proportion of participants requiring at least one hospitalization will be analyzed using a chi-square test statistic.

Considering informative censoring due to death if there is a treatment effect, we will also summarize hospitalization rate and days of hospitalization based on total active follow-up time. Similar tests as described above will be processed.

2.2.7.3 Sudden Cardiac Death

Time to event for sudden cardiac death will be analyzed using the same methodology described for the primary outcome at a 0.05 2-sided significance level. VA Vital Status File will be used to determine the vital status of all study participants who are lost to follow-up at study exit. VA Vital Status File search plus a NDI Plus database search for all participants who are found to have died through the VA database search will be performed in order to adjudicate the cause of death (Table 23).

2.2.7.4 Informed Consent Questionnaire

Additionally, data from the Informed Consent Questionnaire will be used for exploratory analysis of the association between perceived and actual participant understanding of the study. The goal of this analysis is to measure which study nuances are most easily understood. The first part (Items 1-11) of Informed Consent Questionnaire measures the patients' perception/knowledge of the study. The total number and proportion of correct responses per each item will be calculated for each subject. Mean and standard deviation will be calculated for each group.

The second part (Question 12-15) comprises validated items that measures patients' perceived understanding of the study[35], which are subjective patients' reports of their own understanding. The perceived understanding is scored on 0 to 3 scales with total

score of 0 to 9. Higher scores indicate greater perceived understanding. The association between perceived and actual participant understanding of the study can be measured by agreement analysis between part 1 and part 2. In addition, the association between patients' perceived understanding and the probability of patients' withdrawal and other factors in baseline, such as patients' age will also be studied. We note that because these data are collected during the consenting procedure, there is no plan to analyze by treatment group.

2.2.8 Device Data

ICDs are capable of delivering information related to a wide range of parameters including activity level, heart rate variability, as well as data related to the delivery and cessation of arrhythmic therapy. The device data will be collected during study follow-up visits for participants in the ICD arm and followed by remote monitoring where possible. Descriptive analysis will be used to summarize the ICD device data. The analysis will be focused on three activities in particular:

(1) Routine assessment of device activations to assess shock events. The shock events will be summarized and grouped in relevant categories, e.g. by year, by age, by health status, by cause, and by resolution/outcome, and whether appropriate or inappropriate shock[36]. Subjects with no recorded events will also be noted.

(2) The risk of death after shock will be analyzed for both appropriate shock and inappropriate shock

(3) Analysis of device data at follow-up appointments as is done in standard clinical practice.

ICD therapy will be defined as either antitachycardia pacing (ATP) or ICD shock. Any ICD therapy not delivered for VT or VF will be deemed inappropriate, and the rhythm triggering therapy categorized as: atrial fibrillation or atrial flutter (AF), supraventricular including sinus tachycardia (SVT), or inappropriate sensing using published criteria. An episode's termination will be defined by the ICD re-detecting sinus rhythm and thus could include more than 1 shock (and/or ATP bursts). As done previously in the AVID (Antiarrhythmics Versus Implantable Defibrillators) study, a subsequent episode beginning <5 min after episode termination will be ignored for this analysis. Thus, an inappropriate shock episode will be defined as an episode during which one or more inappropriate shocks occurred; a separate ICD episode of the same type (inappropriate or appropriate) occurring <5 min later will not be counted.

Descriptive statistics will be used to summarize all clinical characteristics. The Kaplan-Meier life-table method will be used to graphically display the time to first shock event and calculate the cumulative event rates for each group. The results will be compared using the log-rank statistic.

Among the patients who have an active ICD, we will use a Cox regression to evaluate what factors are associated with time to inappropriate shock where time to the first inappropriate shock will serve as the dependent variable, and subjects who never experience a shock or experience only appropriate shocks will be censored at the last time of follow-up. In a similar way, we will evaluate the association of inappropriate, appropriate shock with mortality where time to death will serve as dependent variable and inappropriate shocks, appropriate shocks and other related clinical variables will be

included as time-dependent co-variates. These analyses may provide insights in understanding how the device shock therapies are utilized and affect the study outcomes.

2.2.9 Analysis of Safety Data

New Adverse Events (AEs) will be collected for only 30 days post-randomization (OMT arm) or 30 days post-implantation (ICD arm); these events will be followed throughout the study until study close or AE resolution, but new AEs will not be collected after this period. All reportable non-serious and serious adverse events will be coded by one or more AE specialist. The total number of AE/SAE, and total number of participants experiencing an event will be summarized by treatment. The proportion of participants experiencing an AE/SAE will be calculated for each treatment group. A chi-square test for the difference in the proportion of SAEs will be used to compare treatment groups over all at the 0.05 level. Treatment comparisons will be made for the number of participants experiencing SAE, the number of treatment-related SAE, and for the number of non-serious adverse events.

In addition, the adverse events will be summarized according to the Medical dictionary for Regulatory Activities (MedDRA)[37], in terms of system organ class and preferred terms, by treatment and as overall (Tables 17 and 20).

2.2.10 Consenting Rates

Whereas there are no known published data on the willingness of elderly patients to consent into a study of this nature, it is incumbent on CSP#592 to measure and report the rates of consent among patients deemed so eligible. Data collected from patients found

eligible for entry into the study will be analyzed. The total number of patients meeting ICD eligibility criteria, and the total number and percent of patients meeting each exclusion criterion will be calculated. Among the eligible patients, we will summarize the percentage of those enrolled and –as applicable– reasons for non-enrollment. Both the raw percentage and exclusive percent (pick the first exclusion for each subject) will be reported (Tables 3 and 4). This activity contributes substantially to the knowledge base for the design of future clinical trials both in the study of the elderly, and in device-based trials.

2.3 Interim Monitoring and Analysis

2.3.1 Overview

Interim monitoring of both the pilot study and the full scope study will be performed by the CSPCC. The first phase of the study will be a one-year Pilot study with six participating sites. The objective of the Pilot study is to determine feasibility of recruitment for the full study phase. The interim monitoring within the Pilot study will focus on recruitment and safety. The interim monitoring within the whole study will focus on recruitment (overall and by site), baseline comparability of treatment groups, protocol adherence, completeness of data, accrual of primary endpoint events (i.e., information accrual), safety, and treatment efficacy. Recruitment and completeness of data will also be monitored for purposes of daily trial operations and quality assurance. The CSPCC monitoring provides the basis for reporting to the Data Monitoring Committee (DMC).

2.3.2 Monitoring Recruitment

The CSPCC will monitor all steps in the recruitment process to assure early recognition of inadequate performance and to identify reasons for inadequate performance at each recruitment site and for the trial overall. To assist in this process, the CSPCC will produce weekly data monitoring reports (Table 1 and 2). These reports will include number of screening forms completed, reasons for non-matriculation into study, number of informed consent documents signed, and number of randomizations overall and by medical center. The same reports will be made available to the DMC at each of its meetings. Predicted total patient accrual for the full study will be calculated using both direct extrapolation.

In CSP#592 we may test an alternative accrual assessment approach via multicenter Bayesian method[38] , using the recruitment goal of 17 patients per site per year as prior and the data from the Pilot study. The Bayesian prediction methods will extend the direct extrapolation method by providing a credible interval for the prediction of the recruitment which considers the uncertainty and variation during the process. The purpose of this analysis is to pursue new and different techniques for projecting study enrollment rates.

2.3.3 Monitoring Safety

Trial safety will be monitored by CSPCC and the CSPCRPCC, throughout the study, both in Pilot and full study. Safety reports will be submitted to the DMC approximately every 6 months after enrollment begins, or more frequently, if requested by the DMC. For reports to the DMC closed session, serious adverse events will be summarized by treatment groups, and relatedness to the assigned interventions.

The proportion of participants experiencing an SAE in each treatment group will be calculated. If the DMC finds the proportion of SAEs unacceptably higher in one

treatment group compared to another, the DMC may consider recommending that the trial be stopped or that the protocol be modified.

2.3.4 Monitoring Outcomes

Two interim analyses of the treatment effect on the primary endpoint of all-cause mortality will be performed when approximately half and three quarters of the events are accumulated (~280 and 420, anticipated at approximately years 3 and 4). However, the DMC will have discretion to request additional or different timing of interim analyses. A Haybittle-Peto type stopping boundary ($p<0.001$) will be used for monitoring the study for early efficacy[39].

A futility analysis for the primary endpoint is also planned at the time of the interim analysis. If the analysis shows that the primary endpoint crosses the internal boundary for futility, it would indicate that the observed effect size is much smaller than anticipated and that the trial has very low conditional power to detect the estimated treatment effect for the primary outcome. The proposed stopping boundary for futility is a hazard ratio of between 1.02 and 0.98 (approximate p-value of 0.80).

In addition to these futility analyses, the observed primary outcome event rate and rate of information accrual (number of events) is monitored from the initiation of the trial and compared with the expected rates. Based on these rates, an estimated time for study completion (i.e. time to reach 565 events) and the estimated number of events that will be reached by the scheduled end of the trial will be presented to the DMC. When considering the futility analyses and rate of information accrual, the DMC may also consider other internal or external evidence of futility (i.e., secondary outcomes) and has the option of recommending early termination of the trial for futility, or continuing with a

possible adjustment to sample size. As there will not be enough events for analysis of efficacy, we will not monitor outcomes in a meaningful way in the Pilot study.

2.3.5 Monitoring Protocol Adherence

Protocol adherence will be monitored to assure early identification of poor performance at individual sites and in the trial overall. Periodic reports will be provided to the Executive Committee and to the DMC at each of its meetings. Specific parameters to be monitored include:

• Randomization of ineligible participants

• Treatment allocation errors

• Failure to complete required follow-up assessments on time

• Loss and withdrawal rates

• Treatment adherence

2.3.6 Sample Size Re-estimation

CSP#592 is designed as an event-driven trial. Therefore, the sample size assumptions regarding the control group event rate and the crossover rate will be re-evaluated at between 6 and 12 months after initiation of the Pilot study, and again approximately six months prior to the end of Full study recruitment to determine whether the estimated sample size and projected follow-up time are sufficient to achieve the target number of events. This will be done blinded to the treatment effect. If necessary, the sample size will be re-estimated based on the accumulated data but under the original hypothesized treatment effect to preserve the Type I error. This information will be presented to the DMC who will make a recommendation to the CSP on whether the sample size for the trial and/or the length of follow-up should be increased to achieve the study objectives.

Efficacy and futility analyses, as described above will not be performed until the sample size re-estimation has been completed.

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3. Ground Rules and Data Handling Conventions

3.1 Baseline Definitions or Conventions

Baseline will be defined as the last assessment taken prior to randomization and the assignment of study treatment. These assessments could have been taken at either the screening visit or the baseline visit, or at a later visit meant to recapture baseline data (e.g. if the extant baseline data are older than the limit specified in the Protocol).

3.2 Time Points, Day Ranges, and Phasing of Study Periods

The time points for analysis will follow the visit schedule presented in the Protocol. Visit windows are defined in the operations manual and the patient scheduling program and shown below. Follow-up visits are to be scheduled within the visit window based on the days from date of randomization. If the visit occurred early or late outside of the visit window, the visit is still identified as targeted for that month and included in the analyses for that time point, but study team members are strongly encouraged to adhere to the ± 30 days window. The number of days the actual follow-up visit occurred from the scheduled visit date will be tracked and the number of times and number of days the visits occurred outside the allowable window will be reported.

If a follow-up visit is missed, then the assessments from the next completed follow-up visit will be used as the next consecutive visit. A missed visit will also be reported as a protocol deviation, so long as proper contacting procedures were followed per the Operations Manual.

In this study, the 1-4 month follow-up cannot be sooner than 30 days since day of randomization, or later than 120 days following randomization (both treatment groups).

Additionally, so as to mirror clinical practice, among the ICD group, this visit cannot be sooner than 30 days following implantation and cannot be later than 120 days post implantation.

3.3 Handling of Missing Data

For data summaries, descriptive statistics will be calculated based on available data. The number of missing data values will be reported for major data items and be made apparent by reporting the number of values that were available and/or the number of missing responses. Missing data can occur through loss to follow-up, or missed visit, etc. For the survival outcome, such as all cause mortality, sudden cardiac death, cardiovascular death, there should be no missing data since we perform a time to event analysis. Quality of life will be measured at four different time points. A longitudinal mixed model will be used for the analysis. For this analysis, missing data can be handled through a slope analysis or some imputation method. Overall, missing data is not a big concern in the current study.

3.4 Description of Protocol Violations

The frequency of protocol deviations will be tabulated by protocol deviation category and treatment group. The number and category of protocol deviations will also be summarized by site.

3.5 Datasets/Programs/Variables

Raw Datasets: Raw datasets will be created for each study case report form. CRFs are transmitted to CSPCC via a fax server and will be processed through the Teleform Reader optical character recognition (OCR) program. Each CRF is then exported to our

local server as a CSV file. CSV files will be read by SAS programs to create SAS datasets for each CRF. The CSPCC data management utility tools are used to create and manage the updating and checking of these datasets.

Analysis Datasets: Programs will be developed to create analysis datasets that will facilitate production of tables and figures for interim reports and final analyses. These files include:

- Pre-screening Activities — PreScreening.sas7bdat
- Demographic, Baseline and Subject Status — Demo.sas7bdat
- Regular Follow-up — RegFollowUp.sas7bdat
- ICD Follow-up — ICDFollowUp.sas7bdat
- Safety (Adverse Events) — safety.sas7bdat
- Consent and HIPAA — hipaavsicf.sas7bdat
- Accrual — intakebymonthbysite.sas7bdat

DEMO: Demographic, Baseline Data and Subject Status dataset – One record per enrolled participant. Includes screening data (Form 1 Screening) for all enrolled participants, and baseline data (Baseline Forms 4 – 9, Form 11 QoL (at baseline only), randomization (Randomization Report from Albuquerque and Form 12 ICD Implantation) and termination data (Form 25 Exit) for all randomized patients.

REGULAR FOLLOW-UP: Data collected at regular follow-up visit – One record per regular follow-up visit for each randomized participant, therefore, multiple records per randomized participant. Follow-up data includes Form 10 Medication Use, Form 11 QoL (all except baseline), and Form 13 Follow-Up.

ICD FOLLOW-UP: ICD Therapy Events Analysis File – Multiple records per randomized participant. ICD follow-up data includes Form 12 ICD Implantation, Form 14 ICD Follow-up, and Form 15 ICD Therapy Event.

SAFETY: Adverse Event dataset that includes all reported adverse events. There is one record per adverse event record including the initial report and all follow-ups (Forms 17 and 18). Value added fields include time from randomization/implantation to onset of the event, and MedDRA coding terms. ACCRUAL: Intake by month and by site. Targeted randomization versus actual randomization.

3.6 Programming Specifications and Software

Programming for data summaries and analyses will be primarily performed using SAS v9.1 or v9.3 on the UNIX AIX platform. Programming specifications and documentation will be completed according to the study data management plan and the Center work instructions.

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5. Reporting Tables

Table 1: Cumulative Number of Subjects Pre-screened, Enrolled, and Randomized by month

Date	Number of Patients pre-screened	Number of Participants Enrolled	Number of Participants Randomized	Expected Number of Randomizations
05/2015				
06/2015				
07/2015				
08/2015				
⋮				

Table 2: Total Number of Subjects Pre-screened, Enrolled and Randomized by Site

Site	Number of Patients Pre-screened	Number of Participants Enrolled	Number of Participants Randomized	Expected Number of Randomizations
Gainesville, FL(573)				
Minneapolis, MN (618)				
Nashville, TN (626)				
Palo Alto, CA (640)				
Portland, OR (648)				
Washington, DC (688)				

Table 3: Summary of Inclusion and Exclusion Criteria and Pre-Screening Status – All Pre-Screened Subjects with Age ≥70, eligible for implantation and with OMT

	N (%)
No. of Pre-Screened Subj who meet Inclusion Criteria and Eligibility determined	
No. of Pre-Screened Subj. who meet Inclusion Criteria but not eligible	
Enrolled in or planning to enroll in a conflicting trial	
Receiving a bi-ventricular ICD device	
NYHA class IV heart failure	
Cardiogenic shock or symptomatic hypotension while in stable baseline rhythm	
Coronary artery bypass graft (CABG) or percutaneous transluminal coronary angioplasty (PTCA) within the past 3 months	
An MI within the past 40 days	
Clinical symptoms or findings that would make them a candidate for coronary revascularization	
Irreversible brain damage from pre-existing cerebral disease	
Any disease other than cardiac disease (e.g. cancer, uremia, liver failure), associated with a likelihood of survival less than 1 year	
Circumstance that would prevent completion of the trial and follow-up activities, including medical condition	
No. of Pre-Screened Subj who meet Inclusion Criteria and are Eligible	
Final: Enrolled in study	
Final: Eligible but will not enroll	
Ongoing: Eligible & planning to enroll;	
Ongoing: Eligible & contacted but not final	
Ongoing: Eligible but not yet contacted	
Other	
Missing	

Table 4: Summary of Inclusion and Exclusion Criteria and Reasons for Non-Randomization – All Enrolled Participants

	N (%)
No. of Enrolled Participants	
No. of Randomized Participants	
Inclusion Criteria	
Veteran Aged 70 Years or Older	
Eligible for ICD per CMS Criteria for Primary Prevention	
Stable Condition on Optimal Medical Therapy	
Able and Willing to provide ICF	
Exclusion Criteria	
Enrolled in a Conflicting Trial	
Candidate for bi-ventricular ICD device	
NYHA class IV heart failure	
Cardiogenic shock or symptomatic hypotension	
CABG/PTCA within past 3 months	
I within the past 40 days	
Candidate for coronary revascularization	
Irreversible brain damage	
Likelihood of survival less than 1 year	
Inability to complete follow-up	
No. of Enrolled Participants who exited prior to Randomization	
Physician refused entry	
Participant wants to choose his/her own therapy	
Participant died	
Participant lost to follow-up	
Other reason for non-randomization	

Table 5: Summary of Stratification – All randomized participants

	Treatment 1	**Treatment 2**	**All**
	N (%)	**N (%)**	**N (%)**
Charlson Score <3			
Charlson Score ≥3			

Table 6: Frequency of Total Charlson Score among Randomized Participants

	Treatment 1	**Treatment 2**	**All**
	N (%)	**N (%)**	**N (%)**
No. of Randomized Participants			
Charlson Score			
1			
2			
3			
4			
5			
6			
7			
8			
9			
10+			
N			
Median			
Mean			
Std			
Subtotal Charlson <3			
Subtotal Charlson ≥3			

Table 7: Frequency Table by Charlson Item

	Treatment 1 (N = ##)	**Treatment 2 (N = ##)**	**All (N = ##)**
No. of Randomized Participants			
Charlson Score Items			
1. Myocardial Infarction			
2. Congestive Heart Failure			
3. Peripheral Vascular Disease			
4. Cerebrovascular Disease			
a. Stroke			
b. TIA			
c. Other			
5. Dementia			
6. Chronic Pulmonary Disease			
7. Rheumatologic Disease			
8. Peptic Ulcer Disease			
9. Mild Liver Disease			
10. Diabetes without Complications			
11. Diabetes with Complications			
12. Hemiplegia or Paraplegia			
13. Renal Disease			
14. Any Malignancy			
15. Moderate/Severe Liver Disease			
16. Metastatic Solid Tumor			
17. AIDS			

Table 8: Completeness of Data Forms by Site-All Enrolled Participants

	Form **			**Form ****			**Form ****		
	Rec*	**Exp****	**%**	**Rec***	**Exp****	**%**	**Rec***	**Exp****	**%**
Gainesville, FL (573)									
Minneapolis, MN (618)									
Nashville, TN (626)									
Palo Alto, CA (640)									
Portland, OR (648)									
Washington, DC (688)									

Table 9: Reason for Exit for before and after Randomization – All Enrolled Participants

			All
			N (%)
No. Enrolled Participants			
No. of Enrolled but not yet Randomized Participants			
No. Exit Study Before Randomization			
Reason for Exit During			
Death			
Participant voluntarily withdrew			
Lost to follow up			
Due to AE/SAE			
Withdrew consent			
Unknown			
Other			
LSI withdrew participant			
Withdrew for safety reasons			
Participant lost capacity to consent			
Other			
	Treatment 1	**Treatment 2**	
	N (%)	**N (%)**	
No. of Randomized Participants			
No. of Randomized Participants who exited study			
Reason for Exit After Randomization			
Study Ended			
Death			
Participant voluntarily withdrew			
Lost to follow up			
Due to AE/SAE			
Withdrew consent			
Unknown			
Other			
LSI withdrew participant			
Withdrew for safety reasons			
Participant lost capacity to consent			
Other			

Table 10: Baseline Demographic Characteristics - All Randomized Participants

	Treatment 1		Treatment 2		All	
	N	%	N	%	N	%
No. of Randomized Participants						
Age						
N						
Mean						
Median						
Std						
Min						
Max						
Gender						
Male						
Female						
Race						
White						
Black or African-American or Negro						
American Indian or Alaskan Native						
Asian Indian						
Chinese						
Japanese						
Filipino						
Korean						
Vietnamese						
Other Asian						
Native Hawaiian						
Gaumanian or Chamorro						
Samoan						
Other Pacific Islander						
Other						
Refused to Answer						
Ethnicity						
Not Hispanic						
Mexican, Mexican American,						
Puerto Rican						
Cuban						
Other Spanish, Hispanic or Latino						
Refused to Answer						

Table 11: Military Service History-All Randomized Participants

	Treatment 1	**Treatment 2**	**All**
	N(%)	**N(%)**	**N(%)**
No. Participants Randomized			
Service U.S. Military			
Yes, Active Duty			
Yes, Reserves Only			
No			
Time Served			
Prior to December 1941			
World War II			
January 1947 – June 1950			
Korean Conflict (July 1950 – January 1955)			
February 1955 – July 1964			
Vietnam Conflict (Aug 1964 – April 1975)			
May 1975 – July 1990			
Persian Gulf War (August 1990 – February			
February 1991 – September 2001			
Afghanistan/Iraq Conflict (October-present)			
Served Outside U.S.			
Yes			
No			
Branch of Service			
Army			
Navy			
Marine Corps			
Coast Guard			
Air Force			
National Guard			
Merchant Marines			
National Oceanic and Atmospheric Adm.			
Public Health Services			

Table 12: Baseline Clinical History - All Randomized Participants

	Treatment 1		Treatment 2		All	
	N	Mean (SD) Or %	N	Mean (SD) Or %	N	Mean (SD) Or %
No. Of Randomized Participants						
Qualifying Ejection Fraction						
N						
Mean						
Std						
Cardiomyopathy (N %)						
No						
Ischemic (N %)						
Non-ischemic (N %)						
Arrhythmias (N %)						
Atrial fibrillation/atrial flutter (N %)						
Paroxysmal						
Persistent						
Permanent						
Clinically significant SVT (N %)						
Sick Sinus Syndrome						
Ablation						
Syncope						
Shortness of Breath						
Paroxysmal Nocturnal Dyspnea						
Dizziness						
Palpatations						
Hypertension						
Smoking Status						
Current Smoker						
Former Smoker						
Non-Smoker						
Alcohol Consumption						
More than moderate drinker						
Moderate Drinker						
Non-drinker						
NYHA Functional Class						
I						
II						
III						

Table 13: Baseline Laboratory Assessments – All Randomized Participants

	Treatment 1		Treatment 2		All	
	N	**Mean (SD) Or %**	**N**	**Mean (SD) Or %**	**N**	**Mean (SD) Or %**
No. of Randomized Participants						
BUN (mg/dL)						
Serum Creatinine (mg/dL)						
Glucose (mg/dL)						
Total Cholesterol (mg/dL)						
Hemoglobin (g/dL)						
Hematocrit (%)						
Platelet Count (K/mm3)						
BNP (pg/mL)						
NT-proBNP (pg/mL)						

Table 14: Baseline Physical Examination – All Randomized Participants

	Treatment 1		Treatment 2		All	
	N	**Mean (SD) Or %**	**N**	**Mean (SD) Or %**	**N**	**Mean (SD) Or %**
No. of Randomized Participants						
Weight (lbs)						
Height (inches)						
SBP (mmHg)						
DBP (mmHg)						
Heart Rate (beats/min)						
Respiration Rate (breaths/min)						

Table 15: Summary of Adverse Events occurring 30 days of Randomization (OMT) or Implantation (OMT+ICD)* – All Randomized Subjects after Randomization

	Treatment 1	**Treatment 2**	**All**
	N(%)	**N(%)**	**N(%)**
No. Subjects Randomized			
Subject-Months of Treatment Exposure			
No. Adverse Events within 30 days			
No. Subjects with Adverse Events			
AE Criteria			
Emergency room or unscheduled clinic visit for heart failure			
Persistent painful implant site			
New symptomatic dizziness			
New symptomatic fatigue			
Psychological distress			
Other			
Severity of this AE			
Mild			
Moderate			
Severe			
AE Attribution to ICD device			
Not Attributed			
Possibly Attributed			
Yes, Attributed			
AE Attribution to OMT			
Not Attributed			
Possibly Attributed			
Yes, Attributed			
Outcome of AE			
Ongoing, Recovering/Resolving			
Recovered/resolved			
Recovered/resolved with sequelae			
Ongoing, not recovered/not resolved			
Unknown			

* For the control arm, it is within 30 days of randomization.

Table 16: Summary of Adverse Events– All randomized subjects after randomization

	Treatment 1	**Treatment 2**	**All**
	N(%)	**N(%)**	**N(%)**
No. Subjects Randomized			
Subject-Months of Treatment Exposure			
No. Adverse Events			
No. Subjects with Adverse Events			
AE Criteria			
Emergency room or unscheduled clinic visit for heart failure			
Persistent painful implant site			
New symptomatic dizziness			
New symptomatic fatigue			
Psychological distress			
Other			
Severity of this AE			
Mild			
Moderate			
Severe			
AE Attribution to ICD device			
Not Attributed			
Possibly Attributed			
Yes, Attributed			
AE Attribution to OMT			
Not Attributed			
Possibly Attributed			
Yes, Attributed			
Outcome of AE			
Ongoing, Recovering/Resolving			
Recovered/resolved			
Recovered/resolved with sequelae			
Ongoing, not recovered/not resolved			
Unknown			

Table 17: Summary of Adverse Events after Randomization by System Organ Class and Preferred Term – All Randomized Participants

	Treatment 1		**Treatment 2**		**All**	
	N	**%**	**N**	**%**	**N**	**%**
System Code						

Table 18: Summary of Serious Adverse Events occurring 30 days of Randomization (OMT) or Implantation (OMT + ICD) – All randomized subjects after randomization

	Treatment 1	**Treatment 2**	**All**
	N(%)	**N(%)**	**N(%)**
No. Subjects Randomized			
Subject-Months of Treatment Exposure			
No. Serious Adverse Events within 30 days			
No. Subjects with Serious Adverse Events within 30 days			
SAE Criteria *			
Death			
Life Threatening			
Congenital anomaly/birth defect			
Disability-incapacity			
Hosp/Prolongation of Hosp			
Other			
SAE being reported			
Bleeding/Hematoma			
Infection: ICD pocket or lead			
Infection: other			
Pacing parameters required lead replacement or revision			
Pnuemothorax			
Myocardial infarction (MI)			
New onset Atrial Fibrillation/Atrial Flutter			
Stroke			
Other			
SAE Attribution to ICD device			
Not Attributed			
Possibly Attributed			
Yes, Attributed			
SAE Attribution to OMT			
Not Attributed			
Possibly Attributed			
Yes, Attributed			
Outcome of SAE			

Fatal			
Ongoing, Recovering/Resolving			
Recovered/resolved			
Recovered/resolved with sequelae			
Ongoing, not recovered/not resolved			
Unknown			

Table 19: Summary of Serious Adverse Events – All randomized subjects after randomization

	Treatment 1	Treatment 2	All
	N(%)	N(%)	N(%)
No. Subjects Randomized			
Subject-Months of Treatment Exposure			
No. Serious Adverse Events			
No. Subjects with Serious Adverse Events			
SAE Criteria *			
Death			
Life Threatening			
Congenital anomaly/birth defect			
Disability-incapacity			
Hosp/Prolongation of Hosp			
Other			
SAE being reported			
Bleeding/Hematoma			
Infection: ICD pocket or lead			
Infection: other			
Pacing parameters required lead replacement or revision			
Pneumothorax			
Myocardial infarction (MI)			
New onset Atrial Fibrillation/Atrial Flutter			
Stroke			
Other			
SAE Attribution to ICD device			
Not Attributed			
Possibly Attributed			
Yes, Attributed			
SAE Attribution to OMT			
Not Attributed			
Possibly Attributed			
Yes, Attributed			
Outcome of SAE			
Fatal			

Ongoing, Recovering/Resolving			
Recovered/resolved			
Recovered/resolved with sequelae			
Ongoing, not recovered/not resolved			
Unknown			

Table 20: Summary of Serious Adverse Events after Randomization by System Organ Class and Preferred Term – All Randomized Participants

	Treatment 1		**Treatment 2**		**All**	
	N	**%**	**N**	**%**	**N**	**%**
System Code						

Table 21: Listing of Serious Adverse Events after Randomization – All Randomized Participants

Rand. Date	SAE Preferred Term	SAE Onset Date	SAE Event No.	SAE Report Type	SAE Criteria	Attribution		SAE Outcome
						OMT	ICD	

Table 22: Summary of Mortality by Preferred Term-All Randomized Participants after Randomization

	Treatment 1	**Treatment 2**	**All**
No. Subjects Randomized			
No. of Deaths			
Preferred Term	**N (%)**	**N (%)**	**N (%)**

Note: After Randomization - From the date of randomization to the end or exit from the study.

Table 23: Summary of the Cause of Mortality -All Deaths Occurring after Randomization

	Treatment 1	**Treatment 2**	**All**
No. Subjects Randomized			
No. of Deaths			
Primary cause of death on the available documentation	**N (%)**	**N (%)**	**N (%)**
Sudden Death			
Other factors			
Cardiovascular death			
Due to an arrhythmic event			
Due to congestive heart failure			
Due to stroke			
Other			
Death due to complications from implantation			
Death due to infection			
Death due to trauma			
Death due to cancer			
Death due to another cause			

Table 24: Primary Outcome: All-cause Mortality by Treatment Assigned

Primary Outcome (No. of Death)	**Treatment 1**		**Treatment 2**		**Overall**	
	R/N	**%**	**R/N**	**%**	**R/N**	**%**
No. of Randomization						
No. of Death (all-cause)						
Hazard Ratio (95% CI)	NA	NA	NA	NA	x.xx	(x.xx, x.xx)

Table 25: Secondary Outcome: Cardiovascular Death by Treatment Assigned

Secondary Outcome (No. of Death)	**Treatment 1**		**Treatment 2**		**Overall**	
	R/N	**%**	**R/N**	**%**	**R/N**	**%**
No. of Randomization						
No. of Death (all-cause)						
Hazard Ratio (95% CI)	NA	NA	NA	NA	x.xx	(x.xx, x.xx)

Table 26: QoL MLHF Score by Time Point and Treatment Assigned – All randomized participants

QoL MLHF Score	Treatment 1		Treatment 2		Overall	
	Mean	Std	Mean	Std	Mean	Std
No. of Randomized Participants						
Baseline						
6 Months						
12 Months						
24 Months						

Table 27: Sudden Cardiac Death by Treatment Assigned

Secondary Outcome (No. of Sudden Cardiac Death)	Treatment 1		Treatment 2		Overall	
	R/N	%	R/N	%	R/N	%
No. of Randomization						
No. of Death (all-cause)						
Hazard Ratio (95% CI)	NA	NA	NA	NA	x.xx	(x.xx, x.xx)

Table 28: Summary of ICD reports

	Total	Median (IQR) per participant	Mean (SD) per participant
N Participants yielding at least 1 report		–	–
N Reports			
N Days between implantation and first report			
N Missed Days		–	–
Interval between implantation and 1st report			
Intervals between reports			
N Reports containing at least 1 therapy		–	–
N Events			
Median (IQR) per subject			
Mean (SD) per subject			
Programming status			
Not changed			
Changed to return to protocol settings			
Changed to accommodate SVT			
Changed to accommodate Syncope			
Changed to accommodate Near-Syncope			
Changed to accommodate Heart Block			
Changed to accommodate Sick Sinus			
Changed for unknown reasons			
Changed for other reason			
TOTAL Programming Status Change			

Table 29: ICD Therapy Event Frequency Table

N Participants randomized to ICD				
N Participants yielding at least one report				
N Events				
	Number of participants with at least 1 event	**Per-cent**	**Total Number of events**	**Per-cent**
ATP Pacing Events				
No Change				
Acceleration without termination				
Acceleration, termination into additional therapy				
Termination, with tachycardia restart into additional therapy				
Termination				
NA				
Unknown				
TOTAL				
Shock Events				
No Change				
Acceleration without termination				
Acceleration, termination into additional therapy				
Termination, with tachycardia restart into additional therapy				
Termination				
NA				
Unknown				
TOTAL				

Table 30: Summary Rhythm at Time of Detection

N Participants randomized to ICD				
N Participants yielding at least one report				
N Events				
	Number of participants with at least 1 event	**Per-cent**	**Total Number of events**	**Per-cent**
Oversensing				
EMI				
T-wave over-sensing				
Lead Fracture				
Myopotentials				
Other				
Atrial Fibrillation				
Supraventricular Tachycardia				
Ventricular Tachycardia				
Non-sustained Ventricular Tachycardia				
Ventricular Fibrillation				
Non-sustained Ventricular Fibrillation				
Unknown				
No egram available				
No RR data				
Conflicting data				
TOTAL				

Table 31: Summary of Rhythm at end of episode

N Participants randomized to ICD				
N Participants yielding at least one report				
N Events				
	Number of participants with at least 1 event	**Per-cent**	**Total Number of events**	**Per-cent**
Normal Sinus Rhythym/Sinus Tachycardia/Atrial pacing				
Atrial Firbillation				
New				
Pre-Existing				
Unknown				
Ventricular Pacing				
Supraventricular Tachycardia (other than AF)				
Ventricular Tachycardia				
Ventricular Fibrillation				
Accelerated Idioventricular Rhythm				
Unknown				
No egram available				
No RR data				
Conflicting data				
Other				
TOTAL				