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The latest SCD-HeFT Directory can be seen at the SCD-HeFT web site. For more information on accessing the web site, see Section 22.

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1. Specific Aims

1.1 Background: Congestive heart failure is a common and lethal disease. A new diagnosis of congestive heart failure (CHF) is made in 400,000 Americans each year. Those with moderate left ventricular dysfunction have a substantial risk of premature death, approximately 25% over 2.5 years. Fifty percent of these deaths are thought to be sudden, due to arrhythmias, and may be preventable. As a consequence, CHF patients represent the largest single identifiable population of patients that can be targeted for primary prevention of sudden cardiac death (SCD.)

1.2 Hypothesis: The central hypothesis of this study is that amiodarone or an implantable cardioverter-defibrillator (ICD) will improve survival compared to placebo in patients with NYHA Class II and Class III CHF and reduced left ventricular ejection fraction ($\leq$ 35%.)

1.3 Specific Aims: The principal goal of this three arm, randomized, primary prevention trial is to identify therapy that will significantly reduce death rates in patients with CHF resulting from ischemic cardiomyopathy or nonischemic dilated cardiomyopathy. We will attempt to achieve this goal by reducing arrhythmic deaths in patients with CHF and a reduced ejection fraction ($\leq$ 35%) and no record of sustained ventricular tachycardia (VT) or ventricular fibrillation (VF.)

The study will be a prospective, clinical trial with 2,500 patients randomly allocated in equal proportions to three different treatment arms over 2.5 years. **The first arm** of the study will be a control arm that consists of conventional heart failure therapy and placebo. Conventional CHF therapy will require the use of appropriate dose angiotensin converting enzyme (ACE) inhibitors. Nitrates and hydralazine, and especially losartan, have not been proven to be of similar value, and should only be used if the patient is absolutely intolerant to ACE inhibitors. Digoxin, diuretics, beta-blockers, warfarin and/or aspirin may be used at the discretion of the managing physician. **The second arm** of the study will combine conventional therapy, as defined above, with the use of amiodarone. In the first and second arms of the study, placebo and amiodarone will be delivered in a double-blind fashion. **The third arm** of the study will employ conventional therapy together with a single lead, pectoral ICD that can be inserted on an outpatient basis. Treatment arms will be compared using an intention-to-treat analysis.

By using readily available clinical measures of CHF and eliminating the need for specialized screening tests to identify subjects, the study is designed to facilitate ease of enrollment and to be broadly applicable as a primary prevention strategy implemented on an outpatient basis. The study will carry the acronym of ***SCD-HeFT***, for ***S***udden ***C***ardiac ***D***eath in ***He***art ***F***ailure**:** ***T***rial of prophylactic amiodarone or implantable defibrillator therapy v. placebo.

We have one primary specific aim**:**

1. To compare all cause mortality based on a minimum of 2.5 years of follow-up in the three arms of the study.

We have five secondary specific aims**:**

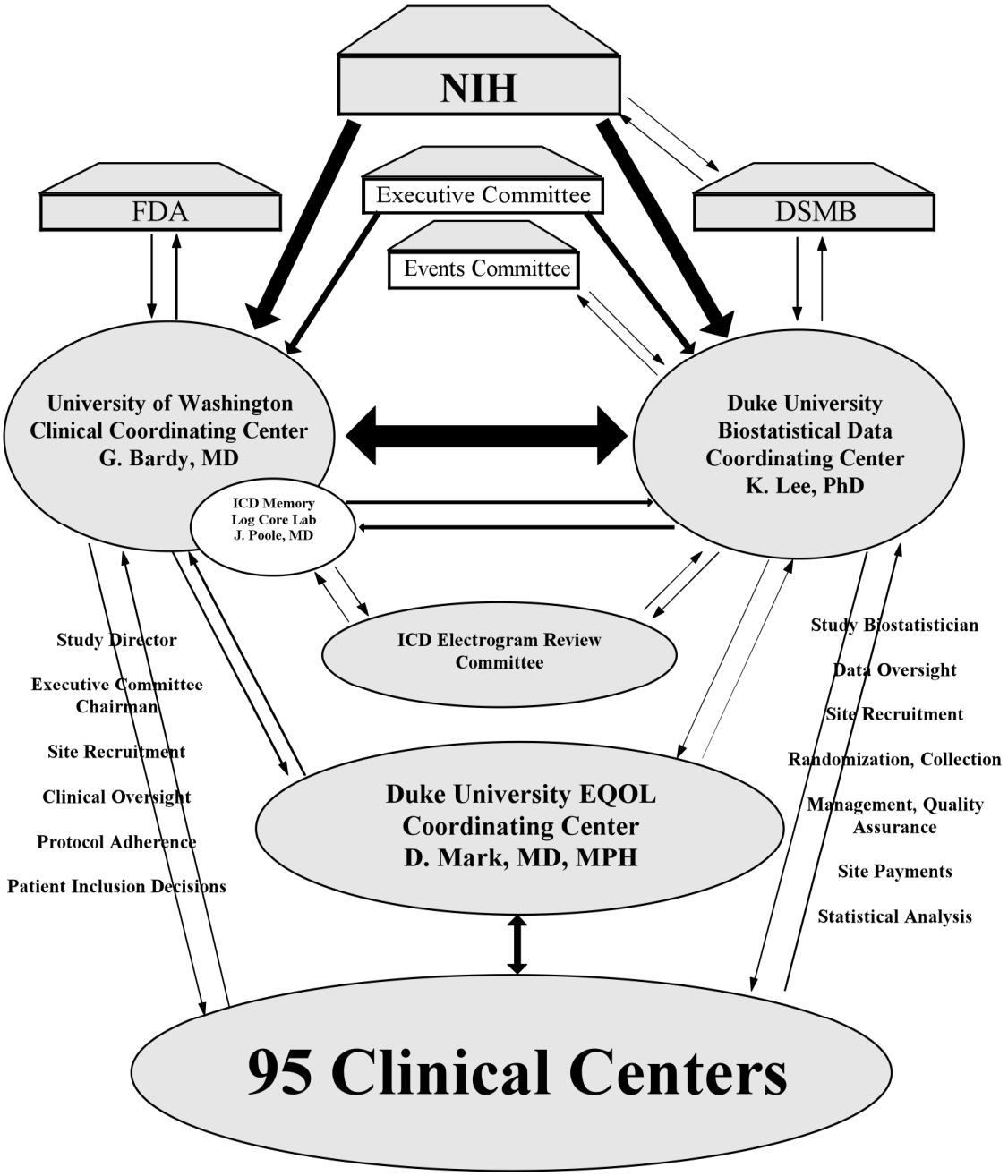
1. To compare arrhythmic cardiac mortality in the three arms of the study.
2. To compare non-arrhythmic cardiac mortality in the three arms of the study.

3. To compare morbidity in the three arms of the study, defined as all cause mortality and re-hospitalization for congestive heart failure.
4. To compare health-related quality of life in the three arms of the study.
5. To compare cost of care for each treatment group and calculate incremental cost-effectiveness ratios for the two intervention arms.

We also intend to determine the incidence of VT/VF and profound bradyarrhythmias (rates $\leq$ 34 bpm) in CHF patients in the ICD arm via the ICD memory log.

1.4 Operations: The study will be performed at 95 North American Institutions. The pilot study was done at 10 of these institutions. The Clinical Coordinating Center (CCC) is the University of Washington in Seattle and the Biostatistical and Data Coordinating Center (DCC) and the Economics and Quality-Of-Life (EQOL) Coordinating Center are at Duke University. The ICD Memory Log Core Laboratory is a subunit of the Clinical Coordinating Center focusing on ICD memory analysis. The organization of the study is shown below.

SCD-HeFT Organization



2. Background and Significance

2.1 Statement of the problem:

Congestive heart failure has a profound effect on public health and use of health care resources. Approximately 1-2 million people in the United States have CHF with 400,000 new cases occurring annually [McFate-Smith 1985; Francis 1986; Parmley 1991; Schocken 1992.] Heart failure is the most common cardiovascular discharge diagnosis in elderly patients. Its incidence more than doubles each decade after age 45. In 1989, it accounted for approximately 5 million person-days of hospitalization [Graves 1991.] In light of this, with the aging of the US population, its prevalence is anticipated to increase markedly.

Although the use of angiotensin converting enzyme inhibitors has improved survival, patients with moderately symptomatic heart failure still have at least a 25% probability of dying over two and one-half years. One half of these deaths occur suddenly and without warning and are probably caused by ventricular arrhythmias or, less commonly, bradyarrhythmias. Therefore, developing an effective primary prevention strategy for SCD in CHF patients should result in a significant reduction in death rates in this large patient population.

2.2 Relevant studies on the relationship of sudden cardiac death and left ventricular dysfunction:

SCD, like CHF, is a major public health problem in the United States, affecting 200,000-400,000 Americans each year [Gillum 1989; Gordon 1971,1975; Kuller 1966, 1989; N.C.H.S. 1981.] The relationship between SCD and CHF is inextricable. Epidemiological studies of SCD [Ritchie 1985; Myerburg 1980; Greene 1990] have shown that the most important pre-existing condition in cardiac arrest victims is left ventricular dysfunction due to coronary artery disease or primary cardiac muscle disease. Left ventricular dysfunction is known to be the strongest predictor of SCD [Bigger 1984; Cupples 1992; Hammermeister 1979; Mukharji 1984; Schlant 1982.] Thus, patients with CHF represent a prime target population in which to undertake a primary SCD prevention trial.

2.3 Relevant studies on total mortality and mechanism of death in CHF:

The natural history of heart failure has been thought to be characterized by an inexorable deterioration in ventricular function, with death occurring from progressive pump failure, ventricular tachyarrhythmias or bradyarrhythmias. Several moderate sized randomized multicenter trials [CONSENSUS 1987, V-HeFT II (Cohn 1991,) and SOLVD 1991] have confirmed that ACE inhibitors reduce mortality in patients with moderate and severe congestive heart failure. The definitive mechanisms by which ACE inhibitors reduce mortality are not known, but ACE inhibitors presumably do so by reducing death from pump failure [CONSENSUS; SOLVD] and may reduce the risk of sudden cardiac death [V-HeFT II.] However, despite the beneficial effect of ACE inhibitors, patients with moderate CHF treated with ACE inhibitors continue to have a significantly increased risk of dying [SOLVD 1991; V-HeFT II 1991; CHF-STAT:Singh 1995.]

Survival data from the ACE inhibitor treatment arms of three recent trials, SOLVD, V-HeFT II and the recently completed VA study of amiodarone v. placebo, CHF-STAT, [Singh 1995] best reflect the prognosis of patients with congestive heart failure of moderate severity, i.e., those most pertinent to SCD-HeFT. The 2.5 year mortality rate in the ACE inhibitor treatment groups was approximately 27% in SOLVD, 25% in V-HeFT II, and 36% in CHF-STAT.

In SOLVD, V-HeFT II, and CHF-STAT, historical information was used to characterize the mechanism of death. In SOLVD, 23% of deaths were characterized as "arrhythmic without worsening CHF." In V-HeFT II, 31% of deaths were characterized as "sudden with no warning symptoms" and 43% of deaths were "sudden with or without warning symptoms." In CHF-STAT, 52% of the deaths in the control population were characterized as sudden. These data suggest that up to half of the deaths in patients with CHF may be preventable with effective prophylaxis against tachyarrhythmias and, possibly, bradyarrhythmias.

The mortality data from the V-HeFT trials provides information about the natural history of patients with congestive heart failure [Goldman 1993.] First, sudden deaths tended to occur earlier than pump-failure deaths. Second, total mortality, and both pump failure death and sudden death were related to the severity of left ventricular dysfunction measured by ejection fraction, plasma norepinephrine levels, or the severity of functional impairment measured by peak exercise oxygen consumption. Third, sudden death occurred at similar rates in patients with ischemic cardiomyopathy versus nonischemic dilated cardiomyopathy. Fourth, the presence of ventricular arrhythmias on Holter monitoring was associated with a higher overall mortality but not an increased proportion of sudden versus pump failure deaths. V-HeFT data did not identify a clinical marker specific for sudden death. Rather, sudden death and pump failure death were both predicted by the severity of left ventricular dysfunction and functional impairment. These findings have direct pertinence to the SCD-HeFT trial design. The data suggest that we can not predict which patients with heart failure will succumb to cardiac arrhythmias. As a consequence, we believe that SCD-HeFT can remain unencumbered by screening and risk stratification tools of unproven value. This approach fosters the development of a broadly applicable prevention strategy based on easily identifiable clinical measures of left ventricular dysfunction. In turn, the cost and complexity of the study will be minimized and enrollment will be facilitated.

2.4 The role of amiodarone in SCD prevention:

In patients resuscitated from VF, empiric amiodarone has been shown to be more effective in the prevention of recurrent cardiac arrest and death than conventional antiarrhythmic drug therapy guided by electrophysiologic studies or Holter monitoring [Greene 1993, CASCADE.] These data, together with its favorable history in preventing death in other studies like BASIS [Pfisterer 1992], the Polish post-MI study [Ceremuzynski 1992], and in meta-analyses [Teo 1993], make amiodarone the most promising antiarrhythmic agent for sudden death prevention in CHF patients. Sotalol was considered as an alternative to amiodarone, but the recent disclosure of increased mortality in patients treated with the d-isomer over placebo in the SWORD study [Waldo 1995] has raised concerns about its efficacy. The negative inotropic effect of the racemic form of sotalol will also limit its use in patients with CHF. Finally, sotalol is difficult to use without in-hospital monitoring because of its tendency to prolong the QT interval with its relatively high incidence of proarrhythmia. Consequently, it is a much less suitable agent for SCD-HeFT than amiodarone and will not be considered further in this study.

The two most relevant studies on the use of amiodarone in patients with CHF are CHF-STAT [Singh 1995], with 674 patients, and GESICA [Doval 1994], with 516 patients. CHF-STAT was a placebo controlled, double-blind study of the effect of moderate dose amiodarone (300-400 mg qd) on total mortality in patients with Class II-IV CHF treated with ACE inhibitors or vasodilators having left ventricular ejection fractions $\leq$ 40% and > 10 VPDs/hour. This study found no difference in mortality in the amiodarone treatment arm compared to the placebo arm. Mortality from all causes at 3 years was

42% for both arms. Sudden death rates estimated from historical information were also similar in both groups, 52 % of the deaths in the placebo group and 49% of the deaths in the amiodarone group.

CHF-STAT is the only placebo controlled study in heart failure patients to suggest that amiodarone ***does not*** have a favorable affect on survival. As such, its findings are contrary to our experience with amiodarone for secondary prevention of death in survivors of cardiac arrest [Herre 1989; Greene 1993.] It is possible, though, that the poor outcome with amiodarone in CHF-STAT is a consequence of the inclusion of Class IV patients in the study. Class IV patients appear to have more cardiac arrests associated with bradyarrhythmias than with ventricular tachyarrhythmias [Luu 1989.] Because amiodarone induces sinus bradycardia and slows atrioventricular conduction, it is logical to postulate that amiodarone may have promoted bradyarrhythmic deaths in CHF-STAT, especially in Class IV patients. At the same time, amiodarone may have decreased deaths from ventricular tachyarrhythmias. We speculate that the two effects may have canceled. In addition, CHF-STAT was a study of American Veterans, mostly male, and therefore did not represent the general population. It may be that women would fare better on amiodarone than men. Consequently, one can not yet dismiss amiodarone as a viable therapeutic alternative in a broad population of CHF patients, especially those with less severe cardiac dysfunction who are less likely to suffer bradyarrhythmic deaths.

In considering the role of amiodarone in primary SCD prevention, one must also examine the results of the GESICA study, the findings of which contradict those of CHF-STAT and argue in favor of prophylactic amiodarone [Doval 1994.] This smaller *un*blinded randomized study examined the benefit of prophylactic *moderate dose* amiodarone (300 mg qd) compared to conventional therapy in the prevention of death from any cause in patients with Class II, III and IV CHF, having enlarged hearts and/or left ventricular ejection fractions $\leq$ 35%. Cumulative mortality rates at 2 years were 33% in the amiodarone arm and 41% in the control arm, (p=0.024.) The percentage of deaths that were sudden was estimated from historical data to be identical, 37% in both arms. The limitations of this study are that it was *not* blinded and that the patient population was unusual: 32% were alcoholics and 9% had Chagasic cardiomyopathy. Thus, the findings of GESICA can not be used at the present time to advocate the use of amiodarone as a prophylactic agent in North American patients with mild to moderate CHF.

Although there remains no clear consensus regarding the prophylactic use of amiodarone for prevention of death in CHF patients, the apparent efficacy of this drug in preventing death in patients post-infarction or following resuscitated SCD, its ease of use, and its modest cost argue strongly that it be considered for further evaluation. The SCD-HeFT investigators therefore feel that it merits reexamination in a larger trial with a more representative population of patients with CHF.

2.5 The role of ICD therapy in SCD prevention:

The AVID, CASH, and CIDS trials of ICD therapy are directed toward patients who have already been resuscitated from VT or VF and, unlike SCD-HeFT, represent secondary prevention trials. Their results are pending. No prospective, placebo-controlled, randomized study has been done or is underway to evaluate ICD therapy for primary prevention of SCD in patients with CHF.

In several uncontrolled studies, ICD therapy appears promising for the secondary prevention of SCD. In patients resuscitated from cardiac arrest, survival rates have been reported to be 82-94% at 2 years [Bardy 1992,1993a; Powell 1993] even when older ICD technology has been used. Old ICD technology notwithstanding, survival rates of 82-94% at 2 years are very favorable in an otherwise high risk population. Consequently, we believe ICDs, especially easy to employ pacemaker-like ICDs, merit

investigation as the only other viable alternative to antiarrhythmic drug therapy for the population of patients addressed in SCD-HeFT.

SCD-HeFT also offers the first opportunity to evaluate the value of ICD therapy referenced to control. Unlike *secondary* SCD prevention trials, a control group is possible in SCD-HeFT because there are presently no ethical constraints to withholding antiarrhythmic drug or device therapy in this patient population.

Another unique feature of SCD-HeFT is the manner in which ICD technology and device programming is strictly controlled. This is an important design consideration not done in other ICD trials. SCD-HeFT employs the new paradigm for ICD therapy: easy to use, single lead, pectoral systems [Bardy 1993b, 1996a] that can be inserted on an outpatient basis. The SCD-HeFT investigators view the type of ICD used and the selection of detection and therapeutic algorithms to be comparable to the type and dosage of antiarrhythmic drugs. Just as all antiarrhythmic drugs are not alike, so is the case with ICDs and their programming. Previous ICD studies have treated the lead system, pulsing methods, detection and therapy algorithms under the rubric of a single therapeutic maneuver. Such an approach belies the multiple ways devices can be considered as therapeutic instruments. Representation of ICDs as a single therapeutic entity is an oversimplification, similar to calling all antiarrhythmic drugs the same. It would be inconceivable to design a study that allows indiscriminate use of and dosing of amiodarone, sotalol, disopyramide, propafenone, procainamide, quinidine, mexiletine, flecainide, diltiazem and beta-blockers in a prophylactic drug study. The SCD-HeFT investigators believe it is important to not make the parallel mistake with ICDs. Thus, SCD-HeFT is the first ICD clinical trial to control for the important clinical variables of ICD shock method and detection and therapy algorithms.

2.6 Philosophy of SCD-HeFT Trial Design:

Some have argued that SCD in CHF patients is a humane end for those with a limited lifespan due to an inexorable disease process. This attitude does not, however, accurately reflect the quality of life affordable to ambulatory patients with CHF using state-of-the-art heart failure management. A nihilistic approach may be understandable in Class IV patients who are not candidates for transplantation, especially in a time of fiscal constraint. However, such an approach is not reasonable in the majority of less severely ill CHF patients in whom a benefit from therapies directed toward SCD prevention might be achieved.

SCD victims do not represent, in any substantial numbers, the group of patients with end stage, Class IV CHF or those of advanced age where the SCD prevention strategies outlined here would probably be unwise as a broad national public health measure. It is important to recognize that most people who suffer SCD have been active and productive members of the community in the 55 to 65 year age range [Cobb 1980,1992.] The value of SCD-HeFT to the Nation's health, therefore, lies with our target population of ambulatory patients with CHF where a focused intervention of modest-to-moderate cost will be more acceptable.

We have intentionally excluded patients with Class IV heart failure from SCD-HeFT because of their limited prospects for long term survival [PROMISE (Packer 1991); CONSENSUS 1987.] Although event rates are higher in this population, therapies directed toward sudden death are less likely to meaningfully prolong life in these patients.

As an integral part of this study design, it is our opinion that any broad scale attempt to prevent SCD has to be within the conceptual and practical reach of general medical practitioners, not just electrophysiologists and heart failure experts. It is our firm opinion that the general medical community of family practitioners, internists, and general cardiologists have the most opportunity to easily identify those individuals at risk. SCD-HeFT then, has true public health importance in that a simple and broadly applicable identification strategy can be implemented on a comprehensive scale in the same manner as ACE inhibitors in CHF and beta-blockers after myocardial infarction. Thus, this study is designed to be reduced to practice by generalists rather than highly specialized electrophysiologists and heart failure experts, although someone skilled in pacemaker insertion would have to insert the ICD should this therapy prove useful. We do not view this as a major problem though, as almost every community of modest size has this capability. Consequently, if one of the two treatment arms of this study proves useful, then the primary physician need only determine heart failure Class and ejection fraction to make a decision about SCD prophylaxis and have it implemented with relative ease.

2.7 Economics and quality of life:

While the prevention of SCD is a major national public health goal, in the current era of restrained spending on health care, new therapies must not only produce evidence of efficacy but also must show that their extra or incremental health benefits are produced in proportion to their incremental costs (i.e., they must be cost effective) in order to be acceptable for large scale implementation [Mark 1993.] In this project, since the ICD therapy arm is associated with substantially greater costs than the other two arms, it must provide significant incremental quality-adjusted survival benefits if it is to be viewed as a viable prevention strategy for death in patients with CHF. It is also important to establish that any extra survival produced by the two investigational arms in this trial is not counterbalanced by significant morbidity resulting in diminished health-related quality of life. Thus, without careful prospective analysis of the economic and quality of life aspects of the investigational therapies being evaluated in SCD-HeFT, the mortality results of the trial would be insufficient to address the clinical and health policy questions about whether these therapies are “worthwhile.”

We feel that inclusion of both economic and quality of life data are a core requirement of the SCD-HeFT research effort. If postulated efficacy is demonstrated for the primary clinical endpoint (all-cause mortality,) then these data will clearly be pivotal in determining how the results of this study are viewed and whether the superior therapeutic strategy (or strategies) receive widespread implementation. We propose to use state-of-the-art methods for measuring cost and quality of life and for estimating cost effectiveness.

2.8 Significance of SCD-HeFT:

The significance of SCD-HeFT is fourfold.

1. This study tests two widely applicable SCD prevention strategies in otherwise functional individuals with CHF who have reasonable intermediate-term survival prospects and reasonable expectations for living productive lives. Enrollment of Class IV patients is specifically excluded in our study because these patients do not have these reasonable expectations of survival and productivity.

2. SCD-HeFT is unique in its ability among present ICD trials to define state-of-the-art ICD therapy **in reference to control**. In AVID, CASH and CIDS use of a control arm would be ethically untenable. Moreover, unlike these other studies, SCD-HeFT employs the pectoral, active can ICD system that can be used as an outpatient and therefore reflects **future practice styles**.

3. This study has the potential to define clinical mechanisms of death and teach us more about the natural history of CHF by virtue of the ICD electrogram and R-R interval memory log. Specifically, the relative incidence of bradyarrhythmic and tachyarrhythmic events will be determined in the 833 patients randomized to ICD therapy. This information will improve our understanding of SCD in patients with CHF and help us interpret the relative value of the two treatment arms in reference to control therapy. These data will also help in the design of future studies on CHF.

4. This study is designed to provide accurate economic and quality of life information for the three arms of the study. These data will have broad public health implications.

3. Preliminary Studies/Progress Report

3.1 Overview:

The preparation for SCD-HeFT has occurred over a four year period. The study was originally conceived in the fall of 1992 and has involved a total of nine half to full day investigator meetings for the development of the study protocol, arrangement of pilot study funding, and completion of the pilot. In addition to the participation of the principal investigators and colleagues from all three coordinating centers, the electrophysiologists and heart failure experts from the institutions participating in our pilot study and members of the Executive Committee have actively debated each aspect of the study design during our biannual meetings and conference calls. Two NHLBI scientific review committees, the NHLBI Council and the NHLBI appointed DSMB have reviewed and approved the protocol. Finally, the entire working group of participating sites for the main trial met 11/21/96–11/24/96 in Galveston, Texas to discuss and agree upon the working protocol. Thus, our study protocol represents the thoughtful considerations and reconsiderations of multiple clinical and research issues by many valued independent clinicians and investigators as well as by multiple NHLBI committees.

3.2 FDA oversight:

The FDA has granted a SCD-HeFT IND for amiodarone (#46,978) and a category B.3 IDE for ICD therapy (#G940194.)

3.3 Summary of SCD-HeFT Pilot Study:

The major objectives of the pilot trial were to:

(1) determine that patients meeting the enrollment criteria specified in the protocol would agree to participate in a randomized, controlled trial involving the three treatment arms to be compared in this investigation.

(2) determine that our projections were reasonable regarding the ability of participating sites to enroll patients at a rate that would allow the study to be completed in the timeframe outlined in the proposal, and

(3) "field test" all proposed systems and procedures for the study, including data forms and the procedures for randomization, data collection, data management, quality control, and patient follow-up.

We began the pilot study at the first three sites on May 19, 1995, and completed enrollment as of June 21, 1995. 52 patients were ultimately randomized from the 10 participating pilot sites. A summary of the pilot enrollment is provided in Table 1. We believe this rapid enrollment is an indication that the general medical community finds this a relatively facile study in which to enter patients.

During this pilot study enrollment period, we tested the mechanics of our enrollment and randomization processes and the clarity of our data forms. Most important, we demonstrated our ability to insert ICDs and initiate study drug therapy in an outpatient setting. All of these study components were accomplished without limitations.

A tabular summary of the SCD-HeFT patient demographic characteristics is contained in Table 2. Females and African-Americans constitute 19.2% and 19.2%, respectively, of the patients enrolled to date. The median age is 53.5 years. Although based on a relatively small sample, these characteristics (particularly the number of females and minorities) are consistent with our expectations for the main trial, given the particular populations from which these patients were drawn.

In terms of other baseline clinical characteristics, 61.5% of the pilot patients had NYHA Class II congestive heart failure at the time of study enrollment, with the remaining 38.5% exhibiting Class III symptoms. The median left ventricular ejection fraction is 25%. Atrial fibrillation occurred in 9.8% of the patients enrolled. A history of ischemic dilated cardiomyopathy was present in 44.2 % of the patients enrolled while 61.5% have a non-ischemic dilated cardiomyopathy and 11.8% had non-surgical valvular disease (some patients had combined disorders.) The percentages of the patients randomized to each of the three treatment arms are approximately equal.

In summary, we believe there are several important conclusions that emerge from the pilot phase of the trial.

(1) We have demonstrated that patients with Class II or Class III congestive heart failure and an ejection fraction ≤ 35% will agree to participate in a three-arm randomized, controlled trial involving conventional CHF therapy, conventional CHF therapy plus amiodarone, and conventional CHF therapy plus a single lead, pectoral ICD that can be inserted on an outpatient basis.

(2) Our projections regarding the rate at which sites can screen and enroll patients in this trial have been exceeded by the recruitment and enrollment experience to date. We are even more confident that the proposed number of centers and the time-frame specified in the study application will produce the desired number of randomized patients.

Table 1
Enrollment Summary

Enrolling Sites	Principal Investigator	Number of Patients Enrolled
University of Washington Medical Center	Wayne Levy, MD Peter Kudenchuk, MD	9
Mayo Clinic	Douglas Packer, MD Richard Rodeheffer, MD	3
Philadelphia Heart Institute	Francis Marchlinski, MD Mariell Jessup, MD	1
Oregon Health Sciences University	Blair Halperin, MD Ranae Ratkovec, MD	3
Sentara Norfolk General Hospital	John Herre, MD John Brush, MD	6
Cardiology of Tulsa, Inc.	John Swartz, MD Douglas Ensley, MD	9
Michigan Heart and Vascular Institute	Lorenzo DiCarlo, MD John Longabaugh, MD	1
University of Maryland Medical System	Michael Gold, MD Steve Gottlieb, MD	10
Midwest Heart Research Foundation	Andrew Rauh, MD Michael O'Toole, MD	9
Loyola University Medical Center	Brian Olshansky, MD Marc Silver, MD	1
	Total Enrollment as of June 21, 1995:	52

Table 2
Patient Demographics

Age (median, 25th, 75th)	53.5 (46,63.5)
Gender	
Male	42 (80.8%)
Female	10 (19.2%)
Race	
African-American	10 (19.2%)
Caucasian	42 (80.8%)
Race/Gender distribution	
African-American Male	9 (17.3%)
African-American Female	1 (1.9%)
Caucasian Male	33 (63.5%)
Caucasian Female	9 (17.3%)

Table 3
Baseline Clinical Characteristics

NYHA Class at Study Enrollment	
Class II	32 (61.5%)
Class III	20 (38.5%)
Left Ventricular Ejection Fraction (median 25th, 75th)	0.25 (0.19, 0.30)
History of atrial fibrillation	5 (9.8%)
Non-ischemic dilated cardiomyopathy	32 (61.5%)
Ischemic dilated cardiomyopathy	23 (44.2%)
Non-surgical regurgitant valvular disease	6 (11.8%)

Patient recruitment.

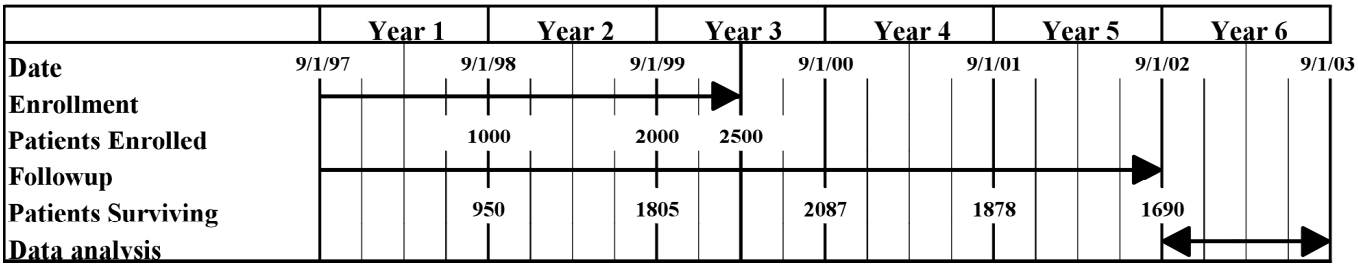
Patients for this study will come from two sources: the participating institution's heart failure clinic and community physicians. A minimum of 100 new patients with CHF that satisfy the entry criteria of this study are seen each year at each of the participating institutions. We conservatively anticipate an enrollment rate of 25% of the eligible candidates from each institution. We expect these numbers to be augmented by outside referral.

To satisfy our enrollment concerns, we have 95 centers committed to participating in SCD-HeFT. We anticipate 2 patients/month to be enrolled at each institution. In the unlikely event that enrollment should indeed fall below the required rate, additional centers will be added to the study.

Time Table.

The timetable for completion of the study is shown below. All 2500 patients will be enrolled in the first 2.5 years of this 5 year trial. The sixth year will be dedicated to data analysis.

SCD-HeFT Study Time Table



Minorities and women are specifically sought for inclusion in SCD-HeFT. Several of the participating sites (e.g., Los Angeles, Detroit, Chicago, Miami, New York, Philadelphia, Richmond) were chosen specifically for their large minority populations. Scant epidemiological data are available on the incidence and prevalence of CHF in minorities [Gillum 1991.] As a result, it will not be possible to have a known target percentage for minority enrollment in SCD-HeFT. Nevertheless, we will encourage minority enrollment to be at least 19% of the SCD-HeFT population, a figure consistent with the percentage of non-whites in the national population. Our pilot study results demonstrate that this is an achievable goal.

A diversity of epidemiological methods have been used to estimate the incidence and prevalence of CHF in men and women. It is difficult to discern the true incidence of CHF across all age groups. It is reasonable to state, though, that the incidence, and probably the prevalence, of CHF is greater in men than women, although at advanced age (> 75 years,) the prevalence of CHF is greater in women [Rodeheffer 1993; Schocken 1992; Ho 1993.] Even though the percentage of women with CHF is difficult to ascertain, we can use non-VA trials to guide us in our enrollment strategy. SOLVD, PROMISE, and the Vesnarinone in heart failure trial enrolled 20%, 22%, and 13% women, respectively [SOLVD 1991; Packer 1991; Feldman 1993.] Using these percentages as a guide, it is a goal of the SCD-

HeFT investigators to enroll a minimum of 25% women in the trial. In addition, in an effort to avoid age bias and to enhance the percentage of women in the study, no upper age limit has been set on recruitment.

The SCD-HeFT investigators will examine race and gender enrollment on a weekly basis. If enrollment of non-whites or women lags, every effort will be made in the web site newsletter, at meetings and over the phone to bring individual site recruitment policies in line with these goals of SCD-HeFT. Thus, we have an operational incentive to ensure enrollment of non-whites and women. It is a mission of this trial to represent non-whites and women in sufficient numbers for meaningful analyses of study outcome. (If you are unsure how to answer the question regarding the race of the patient, ask the patient directly, using language that you are comfortable with and that the patient will comprehend. What we are seeking is how the patient would describe himself or herself. The bottom line is, if you are unsure of what the patient's race is, the race is what the patient says it is.)

Enrollment.

Candidates for enrollment in SCD-HeFT will be evaluated by the investigators at the participating institution upon referral and must satisfy the inclusion and exclusion criteria shown below. Patients who satisfy the entry criteria and agree to be enrolled are then randomized to one of three arms: conventional CHF therapy and placebo, conventional CHF therapy and amiodarone, or conventional CHF therapy and an ICD. Placebo and amiodarone will be administered in a randomized, double-blind manner.

To ensure appropriate NYHA function class for congestive heart failure, definitions for Classes I-IV are provided below**:**

I. Patients with cardiac disease but without resulting limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitations, dyspnea, or anginal pain.

II. Patients with cardiac disease resulting in slight limitation of physical activity. They are comfortable at rest. Ordinary physical activity results in fatigue, palpitations, dyspnea, or anginal pain.

III. Patients with cardiac disease resulting in marked limitation of physical activity. They are comfortable at rest. Less than ordinary activity causes fatigue, palpitations, dyspnea, or anginal pain.

IV. Patients with cardiac disease resulting in inability to carry on any physical activity without discomfort. Symptoms of heart failure or the anginal syndrome may be present even at rest. If any physical activity is undertaken, discomfort is increased.

***Inclusion criteria*:**

1. Patients must be 18 years of age or older.

2. Heart failure must be present for at least 3 months.

3. Patients must have symptomatic CHF (NYHA Class II and III) due to ischemic or nonischemic dilated cardiomyopathy on the day of enrollment.

4. The left ventricular ejection fraction must be $\leq$ 35% as measured by nuclear imaging, echocardiography, or catheterization within 6 months of enrollment.

5. CHF must be present for at least 3 months prior to randomization and treated with a vasodilator. *Less than ideal doses of ACEI and beta blockers are approved as long as target doses are attained shortly after randomization (e.g., enalapril 5 mg bid and carvedilol for one week can be randomized then ramped up in the ensuing days-to-weeks to 10 mg bod or higher and carvedilol up to 25 mg bid).* Nitrates and hydralazine, and especially losartan, have not been proven to be of similar value, and should only be used if the patient is absolutely intolerant to ACE inhibitors.

6. *All patients are requested, **but not required**, to have had a coronary angiogram to document the nature of their disease*. The definition of ischemic cardiomyopathy (*for those patients who have had a coronary angiogram*) will be systolic LV dysfunction in the presence of $\geq$ 75% luminal coronary artery narrowing in one or more major coronary arteries or $\geq$ 50% in the left main coronary artery **or** insignificant coronary artery disease with definitive evidence of myocardial infarction (e.g., ruptured plaque, acute thrombosis on a modest plaque.) Patients with ischemic cardiomyopathy should have clinical findings consistent with stable coronary artery disease prior to inclusion into the study.

7. All patients with chronic atrial fibrillation must be anticoagulated with warfarin with documented INRs of at least 2.0 for $\geq$ 21 days prior to randomization.

8. Referring physicians to the participating study sites must be willing to allow joint patient management over the course of the study.

9. All patients must have performed a 6 minute walk at the time of randomization unless they are unable to walk due to amputation, stroke, or other disability.

10. All patients must have had a 24 hour Holter recording within 1 week prior to randomization. **The Holter recording must not be read, but forwarded to the *Central SCD-HeFT Holter Monitor Laboratory, Department of Veterans Affairs Medical Center, Washington, D.C.***

11. All patients must have a 12-lead ECG obtained at the time of randomization.

***Permanent exclusion criteria*:**

1. Patients with left ventricular ejection fractions > 35%.

2. Asymptomatic patients with LV dysfunction.

3. Patients unable to conduct activities of daily living, i.e., those with NYHA Class IV CHF.

4. Patients with a history of cardiac arrest or a spontaneous episode of sustained ventricular tachycardia (≥ 30 seconds at rates ≥ 100 bpm) not associated with an acute Q-wave MI. (Sustained VT or an aborted cardiac arrest within 48 hours of a myocardial infarction is not an exclusion criterion.)

5. Patients younger than 18 years of age.

6. Patients likely to die from any non-cardiac cause within 12 months.

7. Females who are pregnant or have child bearing potential and are not using reliable methods of contraception. (A pregnancy test should be done in the week prior to enrollment on all females with child bearing potential.)

8. Patients with restrictive, infiltrative or hypertrophic cardiomyopathy, constrictive pericarditis, acute myocarditis, congenital heart disease, surgically correctable valvular disease, and/or inoperable obstructive valvular disease.

9. Patients with mechanical prosthetic cardiac valves because of the risk in altering anticoagulation status for ICD surgery.

10. Patients with a history of a major psychiatric disorder, active alcohol/drug abuse, or non-compliance.

11. Patients in whom amiodarone is contraindicated for any reason.

12. Patients currently taking amiodarone.

13. Patients requiring antiarrhythmic drugs other than calcium blockers, beta blockers, or digoxin.

14. Patients concomitantly participating in any investigational clinical trial.

15. Patients with atrial fibrillation requiring catheter ablation of the atrioventricular conduction system or amiodarone for rate control.

16. Patients with unexplained syncope within the last 5 years.

17. Patients unable to accommodate ICD placement in the left infraclavicular region.

18. Patients expected to undergo cardiac transplantation within 12 months.

19. Patients with pacemakers.

20. Patients with liver function tests $\geq$ 2.5 times normal or a serum creatinine > 2.5 mg/dl.

21. Patients unable to provide informed consent.

***Temporary exclusion criteria*:**

1. Patients having had a myocardial infarction or CVA within 30 days.

2. Patients with unstable angina within 30 days.

3. Patients having had any cardiac surgery or catheter revascularization (angioplasty/stent or atherectomy) within 30 days.

4. Patients with atrial fibrillation/flutter and an uncontrolled ventricular rate defined as an average resting ventricular rate > 120 bpm.

5. Patients with congestive heart failure for less than 3 months and who have not been on an adequate dose of ACE inhibitor (e.g., enalapril 10 mg bid) for at least 1 month.

6. Patients currently receiving antibiotics.

7. New onset atrial fibrillation on ECG obtained on date of randomization.

If any patient satisfies a temporary exclusion criterion, that patient will be ineligible for immediate enrollment but may be re-approached when stable for entry into the study.

Consent Form

SUDDEN CARDIAC DEATH IN HEART FAILURE TRIAL
RANDOMIZED TRIAL FOR THE PREVENTION OF CARDIAC DEATH

INVESTIGATORS	POSITION	DEPARTMENT	PHONE
- - -	- - -	- - -	- - -

Insert your institution's communication numbers and study principals here.

24-Hour Emergency Telephone: ### - #### (Ask for any of the above physicians or nurses.)

INVESTIGATORS' STATEMENT

PURPOSE AND BENEFITS

The purpose of this research study is to compare three treatments for abnormal heart rhythms in weak hearts to see if the rate of sudden death is changed. This research study will last for up to five years.

There are two usual causes of death in people with decreased heart strength. The first cause is a progressive heart muscle weakness. This can eventually lead to complete heart failure. The second cause is a severe heart rhythm problem. This study will examine whether treatments can reduce deaths from the second cause.

There are two types of severe heart rhythms. The first type is a very slow heart rhythm called **bradycardia**. The second type is a very fast and disorganized heart rhythm called **ventricular fibrillation**. Both reduce the heart's ability to pump blood. The second type of heart rhythm is the central point of this study.

People with decreased heart strength can also die from progressive heart muscle weakness. In this study, your doctor will make every effort to improve the strength of the heart muscle to prevent death. Your doctor will use standard (well-accepted) treatments for this problem. The study will not change this treatment.

This study will compare three groups: 1) standard heart failure treatment, 2) standard heart failure treatment plus a drug to prevent bad heart rhythms, and 3) standard heart failure treatment plus a device placed in the heart to treat bad heart rhythms. The name of the drug is amiodarone. The use of this drug in this study is investigational. The device in this study is fully FDA approved but its use for this indication

is investigational. The Federal Drug Administration (FDA) regulates the use of this device. The FDA allows its use only in research. Amiodarone has been helpful in treating people with bad heart rhythms.

PROCEDURES

There will be 2500 patients for this study throughout the U.S. and Canada. If you agree to be in this study, you will receive one of three forms of treatment. Chance will decide which one. You have a one in three chance of any one treatment.

If you agree to be in this study, you must complete the 6-minute walk test at the beginning and every 6 months thereafter throughout the course of the study. This is a test to find out how far you can walk in 6 minutes. You will walk from one chair to another chair, at a set distance apart, continuously without pausing as many times as you can in the 6-minute period. If you need to, you can stop and rest, and then continue on when you are ready. The most important part about this test is that you cover as much distance as possible in the 6 minutes.

One of the choices is to provide only the **standard treatment** for heart weakness. This is the same treatment used for anyone with your kind of heart problem. There is no finding that this treatment can reduce death from bad heart rhythms. If you are assigned to this branch of the study, you will continue with your present treatment. Along with standard heart treatment, you will take a pill which contains no drug (placebo.) Neither you nor your doctor will know if this pill is a real drug or the placebo pill. Therefore, your doctor will provide care as though you are taking a drug for bad heart rhythms.

The second choice is to provide the standard treatment for heart weakness and add a medicine to prevent bad heart rhythms. The name of the medicine is **amiodarone**. If you enter this branch of the study, your care will not change unless it is necessary. Amiodarone comes in 200 mg pills. The dose of amiodarone will be a range of 400 milligrams (mg) a day (2 pills) to 800 milligrams (mg.) a day (4 pills) for one week. This will be followed by 400 mg. (2 pills) for three weeks. Thereafter, the daily dose will be dependent on your weight: 200 mg (1 pill) a day for patients weighing less than 150 lbs; 300 mg (1½ pills) a day for patients weighing between 150 and 200 lbs; and, 400 mg (2 pills) a day for patients weighing more than 200 lbs. Your doctor will not know if this pill is real drug or a placebo pill. Therefore, he or she will provide care as though you are taking a drug for bad heart rhythms.

The study doctors will manage these first two branches of the study in the same way. Since they will not know if there is an active drug, they will ask you to have some tests done from time to time. Sometimes, the drug (amiodarone) does have some side-effects. Your doctors will watch certain tests. These tests make sure that there is no change in your general health. These tests are part of this study.

The third of the choices is to continue standard treatment for heart weakness and to use an **automatic rhythm device**. In this branch of the study, your doctor will connect a device to your heart, an automatic implantable defibrillator (ICD), to treat bad heart rhythms. If you have a bad heart rhythm, the device will be able to correct the rhythm. People who had bad heart rhythms once and are likely to have them again use this device. In the past, this type of device has not been used to treat your type of heart problem. The device provides a known protection from bad rhythms. It has a “memory” to record any bad heart rhythms. Your study doctor will have you sign a separate consent form for this device. The procedure to place the ICD into your heart will take approximately 2 hours. The length of time you will need to be in the hospital for this procedure is approximately 23 hours. The ICD will need to be changed approximately every 6 to 8 years depending on whether or not you use it. Your doctor will discuss replacement with you

when the time comes. If you need your ICD replaced, there is minor surgery involved. The surgery involves making a small incision over the ICD pocket in the shoulder area, checking the ICD system, removing the old ICD, and replacing it with a new ICD.

The study doctors will see everyone, in every branch of the study, at one week, one month, and three months after entry into the study. The schedule thereafter will be every three months. The study group will schedule most visits during your regular clinic visits. At these visits, your study doctor or one of the study nurses will meet with you. On some visits, you will have some blood tests specifically for this study. Some of these tests may be part of your regular care. The blood tests require a needle stick and about 4 tablespoonsful of blood. The study can use these results, so there should be no duplication. If you are on blood thinner therapy (e.g. Coumadin, warfarin) and/or digoxin therapy a blood test two weeks after the start of the study therapy will be done to monitor blood thinner and digoxin levels.

If you are a woman of child bearing potential, a pregnancy test will be done. You must also use a reliable method of birth control before you enroll in the study. The reliable method of birth control must be ongoing throughout the study. The drug Amiodarone can cause harm to a fetus, therefore, if you are a woman and plan on becoming pregnant you should not enter the study.

The staff of (*enter your hospital name here*) and/or representatives of the SCD-HeFT Coordinating Center at Duke University may contact your doctor(s) and hospital(s) to obtain copies of your medical bills for up to 5 years (the length of the study.) When you are enrolled in the study and at 3 months, 1 year and 2.5 years after enrollment, they will ask you questions to see how you are doing and help provide information about your treatment. Some of the questions are of a sensitive nature. The questionnaires take about 20 minutes. You may refuse to answer any question. You may be asked to have your interview audiotaped in order to ensure standardization of interviews across study subjects. No identifying information will be included on the tape. The tape will be sent to the SCD-HeFT Coordinating Center at Duke University for analysis.

To be part of the study, the study doctor must have you sign a standard hospital defibrillator surgery consent form as well as this consent form before finding out which branch of the study you will enter. After you sign the consents, the study nurse will forward your name to the coordinating center at Duke University in North Carolina. By chance (one in three,) the Coordinating Center will place you in one of the branches of the study. You will then receive that treatment. You or the study doctor can not affect the choice of treatment. You will not know which treatment until after you enroll in the study.

POTENTIAL BENEFITS

Amiodarone and the automatic rhythm device (ICD) have been beneficial in treating bad heart rhythms. We do not know if you will benefit from taking part in this study. However, in addition to your regular health care providers, your study team will monitor your well-being very closely. The team will inform you of any results that the study may produce. This information may allow you to make better informed decisions about your health care management.

RISKS, STRESS OR DISCOMFORT

Some of the requirements of this study may cause some discomfort. There are some additional risks involved with being in this study. This part of this form will explain some of these extra concerns.

If you, by chance, enter the standard heart treatment branch of the study, your risk is the same as regular medical care. You will continue to receive all the standard care you would regularly receive. You will receive no additional care for the prevention of bad heart rhythms. The study doctor will monitor your health through certain lab tests and the questionnaire. Your study doctor or nurse will need to see you sometimes. These appointments may not be part of any other medical visits. These appointments take about 30 minutes. When possible, your study doctor will work with your heart doctor so you can have these visits and tests at the same time. This will keep any discomfort and inconvenience to as little as possible.

If you were to become ill and your heart doctor was concerned that the rhythm medicine used in the study could be the cause, the study managers would be able to find out what you were taking (placebo or amiodarone.) Then your doctor would know if a drug is used or not. This would be done for emergencies only.

If, by chance, you enter the drug (amiodarone) branch, there are certain risks. Doctors have used amiodarone for over 15 years. Previously, it was used only for life threatening heart rhythms. Presently, its use has grown. Physicians now use this drug for the treatment of less serious heart rhythms (atrial fibrillation). Some people using the drug have developed side effects. The side effects include skin rashes and changes in skin color (a slight bluish discoloration around the cheeks and mouth.) Abnormalities of liver and thyroid function, muscle weakness, bowel changes (constipation), and nerve problems, including fatigue, tremors, or poor coordination. Sensitivity to light and deposits on the surface of the eye that do not change vision are other side effects. There have been changes in the lungs causing a cough and a congestion like pneumonia. Unless the drug is stopped, these side effects could possibly lead to severe lung problems or even to death. This complication is rare in patients using the drug at this dosage. Since your doctor will not know if you are on amiodarone, your study doctor will watch you for these side effects. If there is any hint that you might be having any of these side effects, the study managers can find out what you were taking (placebo or amiodarone.) If you are on amiodarone and your doctor feels it is the cause of your symptoms, your doctor will stop the drug or decrease the dose. Most of the side effects go away after stopping the drug. The lung problems could continue even after the drug is stopped. Finally, there is some concern that in extremely rare circumstances, amiodarone may lead to marked visual impairment and blindness.

Whether you enter the “no drug” branch or the “amiodarone” branch, the doctors will need to watch your health. This will require some extra tests. Some of the tests are blood tests. There is some pain from the needle stick to collect the blood. This will help your doctors know if you are doing well or having any side effects from the drug. It also will be necessary to have x-rays of your chest from time to time. Your regular check-ups require most of these x-rays. The skin entrance radiation exposure from one chest x-ray is 30 millirems (a unit of radiation exposure.) You will have 2 x-rays for this study. By comparison, the natural background radiation in Seattle over one year is 300 millirems. Whenever possible, your study doctor will work with your heart doctor so tests can be done at the same time. This will keep any discomfort and inconvenience to as little as possible.

If you enter the device (defibrillator) branch, there are different risks. The insertion of the device requires a surgical operation. There are risks from this procedure that are not part of the other branches. There are risks associated with the use of an anesthetic. There are risks of infection from the operation. There are risks that the leads could cause damage to the heart or cause a bad heart rhythm during insertion. To test the device itself, the study doctor must cause you to have a bad rhythm (ventricular fibrillation.) To better explain all the risks, there is a separate, standard hospital consent form used by your doctor. Any of these

risks could cause serious injury or even death. An infection could cause the removal of the device. There is an extremely small chance of any complication, but the risk is not zero. You and your family should read all of the information about the device. You and your family should discuss this procedure with your study doctor before signing these consent forms.

OTHER INFORMATION

Your study records will be kept confidential. In addition to the investigators, the manufacturer of the device (Medtronic, Inc.,) the manufacturer of the drug (Wyeth-Ayerst,) the Food and Drug Administration, and the National Heart Lung and Blood Institute have the right to review study records. They may review information from your medical chart as it relates to this study. This information will be kept by the investigators for 7 years. The type of information needed are results of laboratory tests, chest x-rays and clinic visit notes. This information is used to outline the type of heart weakness your have. It also reflects how any treatment for your condition affects your general health.

You may refuse to participate and may withdraw from the study at any time. If you do, there will be no penalty or loss of benefits to which you are otherwise entitled. We will inform you if we learn any new information that might affect your decision to take part in this study. The alternatives to this study are not to take part in this study and receive standard care from your physician.

If you are injured or have questions about this study, your doctor or nurse will be able to answer any questions you might have throughout the duration of the study. You may call any of the doctors or nurses listed on Page 1 of this consent form for information.

There will be no payment to you for participating in this study. You or your insurance company must pay for tests that are part of your regular heart care and would otherwise be performed whether or not you participate in this study. If you are randomized to the ICD arm of this study, your insurer may be billed for the procedure to implant the ICD. However, the ICD itself, should you randomize to the ICD arm of the study, will be provided free of charge; you will not be responsible for this part of your care as part of this study. If you have a complication as a direct result of the ICD surgery, the investigators will treat you or refer you for treatment. The study will cover the costs of this treatment for ICD complications. However, any illness or injury related to your heart condition will not be covered by the study.

_____ _____

Signature of Investigator Date

SUBJECT'S STATEMENT

The study described above has been explained to me, and I voluntarily consent to participate. I have had an opportunity to ask questions and understand that future questions I may have about the study or about subjects' rights will be answered by one of the investigators previously listed.

_____ _____

Signature of Subject Date

Copies to: Subject and Investigator's file

Therapeutic arms.

1. Conventional therapy of CHF.

The control group, as well as both treatment groups, will require optimal CHF management with afterload reducing agents in accord with previously published studies (V-HeFT II, SOLVD, CHF-STAT.) ACE inhibitors will be used whenever possible, limited only by blood pressure, renal function, cough and allergic reactions. A target dosage of enalapril of 10 mg bid (or equivalent ACE inhibitor drug and dosage) is recommended for at least 1-3 months. It is recognized that the optimal dose of ACE inhibitor has not been established. However, this dose of ACE inhibitor has been established to reduce mortality in CHF patients. Target doses of commonly used ACE inhibitor drugs (as tolerated by blood pressure, renal function, symptoms) are as follows:

Enalapril:	10mg bid	Quinapril:	20mg bid
Captopril:	50mg tid	Benazepril:	40mg qd
Lisinopril:	20mg qd	Fosinopril:	20mg qd

Any candidate for SCD-HeFT who is not on adequate ACE inhibition at the time of screening for entry into the study can be randomized one month later following appropriate adjustments in ACE inhibitor therapy assuming they have been on some ACE inhibition therapy for at least 3 months.

If ACE inhibition is not tolerated by the patient, afterload reduction may be accomplished with either hydralazine and nitrates, or losartan. Target doses of hydralazine should be 75-100 mg every 6-8 hours if tolerated. Target doses of losartan should be 50-100 mg qd. Target doses of isosorbide dinitrate should be 30-40 mg t.i.d. is recommended, if tolerated. Dosing will be limited by blood pressure and medication side effects. Tachyphylaxis to isosorbide will be minimized by t.i.d. dosing rather than q8 hour dosing. Two weeks of appropriate dose hydralazine and nitrate therapy is required before randomization.

Conventional therapy may also include the use of digoxin. Diuretic therapy may be used as deemed appropriate to relieve pulmonary and systemic venous congestion. Beta-blocker therapy also can be used when considered reasonable by the managing physician.

As part of routine CHF management, serum potassium levels should be maintained above 4.0 mEq/L and serum magnesium levels should be maintained above 1.5 mEq/L. These levels should be monitored every three months.

Routine clinical laboratory tests should include an ECG, a chest X-ray, liver function studies (AST, ALT, bilirubin, alkaline phosphatase, LDH,) TSH levels, serum electrolytes, magnesium, BUN and creatinine, INR, PTT, platelets, a complete blood count, and a urinalysis.

These routine approaches to patients with CHF are subject to change if ongoing or future clinical trials provide data that affect SCD-HeFT. For example, the BEST study has the potential to alter our recommendations on routine clinical management or may affect enrollment. In this case, the DSMB would review the results of any related trials and increase the level of surveillance of our data. Recommendations for action would then be forwarded to the NHLBI and the Executive Committee of SCD-HeFT.

2. Amiodarone v. placebo.

Placebo and amiodarone therapy will be administered in a double-blind fashion packaged as "study drug" in scored 200 mg tablets. Study drug will be administered from the day of randomization on an outpatient basis to minimize study costs and to mimic present day clinical use of amiodarone. Amiodarone is often initiated as an outpatient for arrhythmias that are not life-threatening (Hohnloser 1994.) The low incidence of serious side effects with modest dose amiodarone makes outpatient administration feasible (Hohnloser 1994, Singh 1995.)

There will be an initial modest loading dose of 800 mg qd of study drug for one week followed by 400 mg qd for three weeks. These are smaller doses than those usually employed in patients with ongoing tachyarrhythmias requiring treatment. Thereafter, the maintenance dose will be weight dependent: 200 mg qd for patients weighing <150 lbs, 300 mg qd for patients weighing 150-200 lbs, 400 mg qd for patients weighing > 200 lbs. Placebo and amiodarone will be identical in appearance and provided by Wyeth Pharmaceuticals and maintained in the investigative institution's pharmacy. Patient compliance will monitored by performing pill counts during follow-up visits.

If *adverse drug reactions* develop in the course of the study that are thought to be related to study drug, specific guidelines for alteration in therapy are presented in Section 17. Any changes in study drug must be discussed with the Trial Director. Because a major weakness of other clinical trials of amiodarone is the failure to administer the drug in a majority of patients, we will vigorously endeavor to maintain at least 85% use of the drug until completion. Previous studies have discontinued the use of amiodarone too readily because of apprehension over side effects. Upon review of the side effects of the placebo arm in these studies, it is apparent that discontinuation of amiodarone has often been without merit. It is a goal of SCD-HeFT not to repeat this error.

Note that there will be no placebo administered in the ICD arm of the study. It will be impossible to avoid a placebo effect associated with the ICD surgery. Also, there is no scientific merit at this point in our knowledge to have a sub-population of ICD patients treated with amiodarone. This approach may be considered for future study pending the results of SCD-HeFT.

3. ICD therapy.

The ICD employed in this study will be limited to single lead, pectoral "active can" pacer-cardioverter-defibrillators. Active can defibrillators inserted in the left infraclavicular region have a proven high defibrillation efficacy rate, > 98% [Bardy 1993b, 1994a,b, 1995, 1996a; Kudenchuk 1994; Raitt 1995b.] The Medtronic model 7223Cx is currently the only small ICD with bradycardia hysteresis available. This ICD is used also because of the access provided by Medtronic to the SCD-HeFT investigators to data transmission codes that allow for us to develop a paperless data acquisition system for the trial.

ICD surgery will be done using a "23 hour" short stay admission as the procedure is similar to pacemaker surgery. This important aspect of this study will minimize study costs. Implantation may be done with general anesthesia or with local anesthesia and sedation, depending on physician and institutional preference. Single dose prophylactic antibiotic coverage with cefazolin 1.0 gm IV or vancomycin 1.0 gm IV will be administered one hour prior to making the left infraclavicular incision.

The Medtronic active can ICD employs a single 65 cm (or 75 cm) 8.5 Fr tripolar right ventricular (RV) electrode (Medtronic model 6932) for pacing, sensing and defibrillation. This lead allows for true bipolar sensing, an important safety concern. An alternative lead length of 75 cm is available for larger patients.

The RV lead should be inserted in the left cephalic vein to minimize lead fractures resulting from first rib-clavicular crush syndrome. If the cephalic vein is inaccessible, subclavian vein entry will be required for lead insertion. For subclavian entry, the puncture site should be laterally located to avoid first rib-clavicular crush. Once the lead is passed into the RV, it should be positioned into the RV apex as distally as possible.

Note that the lead selected for use in this study (Medtronic model 6932) has two additional features important for minimizing complications of ICD therapy. The first is a relative crush resistance by virtue of three stress relief lumens. This will likely minimize first rib-clavicular crush and anchoring suture ligature injury to the insulation. Second, the lead has a withdrawal support filament capable of withstanding at least 10 lbs of pull strength. This feature will enhance the ease of lead removal should infections, lead fractures, or the need for new hardware occur during the course of the study.

All ICDs should be inserted in the left infraclavicular region. Patients identified prior to enrollment as not being able to accommodate a left infraclavicular approach should not be included in this study. Right infraclavicular incisions should be considered only if, at the time of implant, the implanting physician finds that venous access is impossible from the left side.

The left infraclavicular ICD pocket should be subcutaneous in all cases. Subpectoral implantation is to be used only if adequate subcutaneous adipose tissue is absent. Subcutaneous implantation is preferred to minimize surgery, complications, and to facilitate subsequent battery replacement. If the patient is very small and will not comfortably accommodate subcutaneous implantation, the device can be inserted subpectorally as previously described [Bardy 1994b.] See Section 12 for further details.

ICD testing will follow a uniform protocol as outlined in the flow diagram in Section 12. The protocol is designed to confirm defibrillation efficacy, verify pacing and sensing capabilities, and assure ventricular fibrillation detection while simultaneously keeping the stress of implantation to a minimum. This protocol is a variation of an implant testing protocol that has proven effective in 98% of patients in a 74 center experience on an intention-to-treat basis in 473 cardiac arrest survivors and carries a modest 6.1% complication rate [Bardy 1996a.]

Programming the ICD is defined in detail in Section 12. A summary of the key features of the ICD detection and therapy algorithms follow**:**

1. VF/VT detection. Programming of the VF/VT detection algorithm will be kept uniform except where findings at the time of implantation argue for a change in the detection parameters. The nominal parameters for VF/VT detection will be to use a detection interval criterion of 320 ms (188 bpm) with an 18/24 initial interval duration (NID) criterion and a 12/16 redetect interval duration (NID.) Only 'VF' detection will be used. Fast VT (FVT) and VT detection activation are not permissible in this study unless the patient proves to have spontaneously occurring monomorphic VT following implantation. These initial detection parameters are intended to minimize inappropriate shocks for atrial fibrillation and nonsustained ventricular arrhythmias and to avoid proarrhythmia that can occur with anti-tachycardia pacing therapies or shocks into supraventricular arrhythmias, while maintaining sensitivity to rapid ventricular arrhythmias likely to lead to hemodynamic collapse.

2. VF/VT therapy. First shock energy strength for VF/VT will be based upon defibrillation efficacy testing during implantation. It will either be 20 J or 30 J depending on the outcome of

testing. The primary purpose for measuring the defibrillation threshold is to allow first shock energy strength to be low and therefore increase response time to avoid loss of consciousness in those with lower defibrillation thresholds. Also, use of the lowest effective shock strength will help minimize shock induced cardiac dysfunction observed when shock strength is unnecessarily high. Antitachycardia pacing (ATP) maneuvers are intentionally avoided in SCD-HeFT. This form of therapy is only useful in patients having monomorphic VT and there is no evidence these patients will have this relatively rare arrhythmia. Inappropriate activation of ATP may delay definitive therapy. If, however, the patient develops electrogram documented spontaneous monomorphic VT over the course of the trial that was initially treated by shock therapy (nonsustained, untreated monomorphic VT doesn't apply,) ATP can be activated subsequently at the discretion of the investigator. Note that a secondary goal of this study is to identify the frequency of monomorphic VT in patients with CHF that have no history of this arrhythmia. We suspect (but cannot yet prove) that this is rare. We also believe that ATP carries a risk of acceleration of SVT that is inappropriately high when activated before evidence of spontaneously occurring monomorphic VT exists.

3. Antibradycardia pacing. The ICD backup pacing rate will be 50 bpm but will only be triggered when the rate falls below 34 bpm, so called 'hysteresis' pacing. Each time the ICD is triggered to pace $\geq$ 3 consecutive beats in the hysteresis mode, the memory of the ICD will record the event and catalogue the duration of pacing that follows. This will allow the investigators to observe the incidence of marked bradycardia in the CHF patients randomized to the ICD arm yet treat patients with bradycardia appropriately.

General follow-up and test schedule.

For each arm of the study, follow-up visits will be identical in their frequency and intended to coincide with standard clinical practice for CHF patients as much as possible. All patients will be seen one week, four weeks and every three months after randomization. Data forms and quality of life questionnaires will be completed by the site PI or nurse coordinator. A time table for tests and follow-up visits is shown on the next page.

INR												

Additional tests to those shown above will be obtained whenever deemed clinically necessary by the investigator. Note that there are deviations from this schedule (as annotated on the schedule) that depend on patient circumstances and the arm to which the patient is randomized. These are explained below.

For patients on warfarin, INRs will be obtained at 1, 3, 7, 14 days and each month after randomization and will be monitored by the institutional nurse coordinator to ensure appropriate adjustment of medications. Section 7 below defines anticoagulation management depending upon clinical circumstances and arm of study.

Similarly, for those patients receiving digoxin, digoxin levels will be obtained on the day of randomization and 2 weeks and 1 month after randomization and in the course of routine clinical management every six months thereafter. Section 7 below defines the management of digoxin therapy in SCD-HeFT patients.

A TSH level will be obtained at 12 month intervals in all patients as routine clinical management. Additional TSH levels will be performed at the six month interval visits for study drug patients. TSH levels at six month intervals are not warranted in ICD patients for clinical or research reasons.

An additional chest X-ray will be required prior to hospital discharge following ICD surgery to ensure the absence of a pneumothorax prior to discharge and to document lead position for future reference.

Pulmonary function tests and gallium scans were specifically eliminated for the follow-up of patients on study drug. There are sufficient questions about the usefulness of these tests in determining the presence or absence of amiodarone pulmonary toxicity to make routine performance of such tests unwarranted.

As part of our testing protocol, the distance walked during 6 minutes of an 'uncoached' walk by the patient will be recorded at the time of enrollment and every 6 months thereafter. The 6 minute walk will be used to increase risk stratification at the completion of the trial and to monitor the effects of therapy of each of the arms on heart failure status. See Section 21 for a description of how to conduct the 6 minute walk.

Special Considerations.

This Section has been updated to contend with pilot study findings, site investigator suggestions for patient management, and NHLBI Review Committee comments for those patient issues that can lead to complications.

1. Special considerations for patients on digoxin randomized to study drug.

Management of patients on study drug receiving digoxin is guided by safety considerations. Digoxin toxicity may result from amiodarone therapy following initiation of the drug. Therefore, a digoxin level will be obtained on the day of randomization, at 2 weeks, 1 month, and every 6 months following randomization. The dose of digoxin will be adjusted during follow-up to achieve a digoxin level that is clinically acceptable. Digoxin dosing should not be routinely changed without justification from digoxin level measurements or from other strong clinical findings.

2. Special consideration for patients on anticoagulation randomized to study drug.

There is a potential interaction between warfarin and amiodarone in patients randomized to the drug arm. For patients randomized to the drug arm and receiving warfarin, we previously proposed to minimize the possibility of amiodarone induced bleeding diatheses by halving the dose of warfarin on the day of initiation of study therapy. We learned in the pilot, however, that this was not necessary and, in fact, potentially harmful. In our pilot experience, many patients had a significant decrease in their INR because of the halving of the warfarin dose, a decrease with its own risk. No patient had problems of over-anticoagulation. Thus, to maintain appropriate levels of anticoagulation, we will not change the warfarin dose in the drug arm for the main study but, rather, will obtain an additional INR measure at 2 weeks in order to identify those few patients who may actually develop a rise in INR. Our INR measurements will therefore be made on days 1, 3, 7, 14 and every month after randomization with dosage adjusted according to the INR.

3. Special considerations for patients with chronic atrial fibrillation randomized to the ICD arm.

Patients with chronic atrial fibrillation (AF) require special monitoring in the ICD arm of this trial. AF is a common problem in CHF and affects approximately 15% of patients [Carson 1993.] The NIH review committee asked us to re-address and eliminate the need for heparinization and hospitalization, our initial approach to this issue. Concerns were also raised about the extra cost of our earlier approach to these patients. In thoughtful review of the cost concerns in managing these patients while simultaneously recognizing the imperative of patient safety, we have settled upon the following approach.

All patients with chronic AF randomized to ICD therapy will be required to be anticoagulated with warfarin with an INR of 2.0-3.0 at least for 21 days prior to randomization. Patients with CHF and chronic AF randomized to ICD therapy will then have their warfarin discontinued 2-3 days prior to ICD surgery, an acceptable approach in routine medical practice for the typical AF patient. Heparin will not be initiated, as previously proposed. On the day of surgery, a stat INR will be obtained and if the INR is $\leq$ 1.6, ICD surgery can proceed as an outpatient. Warfarin anticoagulation will be reinitiated at the patient's preoperative dose on the evening of the day of surgery. This approach avoids a 2-3 day hospitalization, minimizes the potential of pocket hematomas, is recognized as reasonable medical practice, and limits costs in the majority of AF patients.

We will have one exception, however, to this revised approach to chronic AF patients randomized to the ICD arm: Patients with chronic AF who convert to sinus rhythm during ICD surgery (estimated to be 20% of patients) will require, for patient safety, a hospitalization for heparinization begun on the morning of the first postoperative day and continued into the evening of the second postoperative day. Heparin will then be discontinued and the patient will be discharged. Warfarin will be reinitiated at the preoperative dose on the evening of surgery. Cognizant of the fact that all such patients were anticoagulated for at least 3 weeks prior to surgery, this moderate course of action should minimize thromboembolism risk and reduce risk of ICD pocket hematomas. An alternative approach is also possible if ICD implantation converts AF to sinus rhythm. The physician can also elect to reinitiate AF prior to termination of the implant procedure. The decision to reinitiate AF will depend upon the physician's judgement as to the relative value of trying to maintain sinus rhythm for the particular patient under study. Note that if the AF patient is discharged in sinus rhythm, use of class I antiarrhythmic agents and sotalol are strongly discouraged because of the increasing concern over proarrhythmia. Use of amiodarone in this circumstance is also discouraged as it represents a crossover.

4. Special considerations for patients with previous emboli randomized to the ICD arm.

Approximately 8% of patients with CHF will have a history of previous systemic or pulmonary emboli [Dunkman 1993.] In these patients, as with AF patients, warfarin will be withheld 2-3 days prior to surgery. In addition, though, these patients will be hospitalized the day prior to surgery to receive heparin IV. The next morning, 3 hours before surgery, the heparin will be discontinued. In the evening after ICD surgery, the patient will receive warfarin at the preoperative dose. Heparin will be re-initiated on the morning of the day after surgery. In the evening of the second postoperative day, heparin will be discontinued and the patient will be discharged.

5. Special considerations for non-AF patients on anticoagulation randomized to the ICD arm.

Finally, for patients with no history of AF, who are on warfarin for general antithrombotic prophylaxis, estimated to be 30% of patients with CHF [Falk 1993], those patients randomized to the ICD arm will undergo warfarin withdrawal 4 days prior to ICD surgery. On the day of surgery, a stat INR will be obtained and if the INR is $\leq$ 1.6, the investigator can proceed with ICD surgery as an outpatient. Because of the low risk of adverse sequelae from discontinuing the warfarin in these patients who are in sinus rhythm, re-anticoagulation will be initiated at the preoperative warfarin dose on the day following surgery.

6. Unforeseen circumstances.

As in any clinical trial, circumstances will arise for which there is no immediate course of action defined in the protocol. If patient safety is in question, as regards any part of the general protocol, the specifics of the case should be discussed with Dr. Bardy, Dr. Fishbein, or Dr. Poole at the University of Washington Clinical Coordinating Center.

SECONDARY STUDY ENDPOINTS AND ICD DATA

A. To compare the relative incidence of cardiac mortality and arrhythmic mortality in the three arms of the study.

The Events Committee will be responsible for determining the cause of death in SCD-HeFT with the information provided by the Data Coordinating Center under the aegis of Dr. Lee. Because of the vagaries in defining cause of death (cardiac v. noncardiac, arrhythmic v. nonarrhythmic, sudden v. nonsudden,) the primary end point and specific aim of this trial will be total mortality. Nevertheless, every effort will be made to determine the likely cause of death to improve understanding of the relative incidence of different causes of death in patients with CHF.

The Events Committee will convene twice yearly at the National Heart meetings (AHA and ACC) and as needed for adjudicating the cause of death in SCD-HeFT patients. Prior to these meetings, each patient's event data will be sent by the DCC to two members of the Events Committee for review. Where there is perfect agreement in the classification, no further review will be required. However, where there is any disagreement, the event data will be reviewed by the full committee for classification. Determinations of cause of death by the Events Committee will be based upon the information collected by the investigator and study coordinator at the clinical site where the patient was enrolled and submitted to the DCC at Duke.

B. To determine the incidence of VT/VF and profound bradyarrhythmias (rates $\leq$ 34 bpm) in CHF patients in the ICD arm via the ICD memory log. (**ICD Memory Log Core Laboratory**.)

A unique feature of this study is use of the ICD memory log in patients randomized to the ICD arm to improve our understanding of the relative incidence of bradyarrhythmias as well as ventricular tachyarrhythmias in patients with CHF. The ICD data pertinent to this endpoint will be acquired during routine interrogations, following patient complaints of ICD therapy, and during post-mortem interrogations. Each site will be asked to store the ICD data on duplicate diskettes as it is directly downloaded from the ICD programmer (Medtronic model 9790) at the time of interrogation. One diskette and hard copy will remain in the patient's file at the site, and one diskette will be forwarded (electronically or via mail) to the ICD Memory Log Core Laboratory for analysis. Interpretations of the printouts will be the combined responsibility of the site electrophysiologist and Drs. Poole and Bardy at the University of Washington Clinical Coordinating Center. The details of the interrogation process and data transfer are described in Sections 12, 14 and 15. All events will be reviewed by the ICD Electrogram Review Committee for inclusion in the master DCC data file.

After ICD memory log review and categorization, an updated database of ICD tachyarrhythmic and bradyarrhythmic events will then be forwarded from the UW Clinical Coordinating Center on a weekly basis to Dr. Lee for inclusion in the overall database. The database for categorization of ICD events has been specially designed to facilitate storage and retrieval of ICD information. Each ICD therapy of VF/VT and the occurrence of bradycardia requiring pacing will be correlated with clinical events noted on the data forms.

In ICD patients who die, every effort will be made by the local PI/nurse to interrogate the ICD following death whether death occurs in-hospital or out-of-hospital. If the death occurs in-hospital, chest X-rays will be obtained prior to interment or cremation, to examine the integrity

of the ICD lead system. Performance of an autopsy will be encouraged as a matter of course regardless of arm to which the patient has been randomized. Autopsies conducted in patients with ICDs will also focus on the integrity of the ICD lead system and the integrity of the ICD itself. If an autopsy is performed, ICDs will be explanted for technical analysis. Pre-autopsy X-rays of the lead system will be a useful adjunct to any analysis of ICD lead integrity.

Several diagnostic criteria will be used to separate the diagnosis of VF from monomorphic VT, nonsustained VT, supraventricular tachyarrhythmias, and artifacts of detection. For any event stored in the ICD memory log, the diagnosis of ventricular fibrillation (VF) will require that all of the following criteria be met**:**

i. Tachyarrhythmia cycle length must be $\leq$ 320 ms for at least 18 intervals. These diagnostic criteria for VF correspond to the initial detection criteria programmed into the ICD. The cycle length criterion ensures that the arrhythmia is of sufficient rapidity to be consistent with VF [Bardy 1990; Olson 1992; Jones 1994.]

ii. Stored electrogram morphology must differ from the baseline sinus rhythm morphology, be polymorphic over its course, and have cycle length variation of $\geq$ 30 ms for at least half of the intervals [Bardy 1990; Hook 1993; Grimm 1993.] These criteria will exclude inappropriate categorization of supraventricular tachyarrhythmias and monomorphic VT as VF.

iii. The irregularity of electrogram morphology and cycle length must be of sufficient duration to not only satisfy the initial cycle length and interval detection criteria, but persist for a long enough time period for the ICD to charge its capacitors and reconfirm the presence of VF. This sequence requires 7-12 seconds of persistent tachyarrhythmia. The diagnosis of VF will **not** be made unless therapy is actually delivered, thereby ensuring a conservative categorization of events. Only those episodes likely to lead to a cardiac arrest therefore will be termed VF. Any tachyarrhythmia terminating prior to therapy delivery will be categorized as nonsustained VT.

iv. Signal artifacts must be absent to avoid inappropriate categorization of nonarrhythmic events as VF.

Patients in the ICD arm may also develop sustained monomorphic VT de novo. The diagnosis of sustained monomorphic VT will be made using the same cycle length, duration and therapy criteria used above for VF with the additional criteria that the stored electrogram morphology be uniform [Hook 1993; Grimm 1993] and the cycle length not vary by more than 30 ms on an interval-by-interval basis for the last 12 of the 18 intervals [Bardy 1990, 1993c.] The last criterion, regarding the requirement for interval stability for the last 12 intervals rather than for all 18 intervals, recognizes that many episodes of monomorphic VT have an initial polymorphic phase before stabilizing [Bardy 1990.]

The diagnosis of nonsustained VT, be it monomorphic or polymorphic, will be made for any arrhythmia that meets the initial detection criteria and persists for 5 intervals or more but stops spontaneously prior to therapy when the confirmation algorithm of the device observes that the

tachyarrhythmia is no longer present following capacitor charging [Medtronic 7223Cx ICD manual 1996.]

The ICD memory log can also provide a reliable means to document the incidence of marked bradyarrhythmias (≤ 34 bpm) in patients with CHF. Confirmation of the occurrence of marked bradyarrhythmia is possible by using bradycardia pacing *hysteresis* prior to initiation of backup VVI pacing. In the ICD used for SCD-HeFT, hysteresis will be programmed to the minimum rate of 34 bpm prior to initiation of VVI pacing at a rate of 50 ppm. A rate of 50 ppm with a hysteresis of 34 bpm is likely to prevent marked hypotension from bradycardia yet not be so high as to pace the patient too much and interfere with normal orthodromic depolarization which is likely to be more beneficial hemodynamically. The hysteresis rate of 34 bpm is the equivalent to requiring a 1.8 second pause to occur prior to pacing at 50 ppm.

In addition to the hysteresis function, the ICD used in SCD-HeFT will record and document the number of pacing events and their duration in the ICD memory log. Although we will not know the incidence of more severe bradyarrhythmias, such as asystole, this information still has clinical relevance. By quantifying the incidence of bradyarrhythmias where pacing therapy has been required, the SCD-HeFT investigators will be able to document, for the first time**,** the incidence of clinically significant bradyarrhythmias in CHF patients.

The ICD Memory Log Core Laboratory will be responsible for the careful evaluation of every ICD interrogation obtained, applying the above detailed arrhythmia diagnostic criteria prior to categorization. Information which will be distilled from the ICD interrogation include**:**

1. A definitive rhythm diagnosis for each event,
2. The frequency of each rhythm occurrence (VF, sustained monomorphic VT, nonsustained VT, and bradyarrhythmias,)
3. The length of time of each rhythm occurrence,
4. The time and date of each episode,
5. Sinus rhythm RR interval histograms prior to the onset of a bradycardia or tachycardia event.

The evaluation of each ICD interrogation will require substantial effort and expertise and forms the impetus for establishing a separate ICD Memory Log Core Laboratory. These data will be integrated into the master database at Duke for correlation with other clinical and quality of life measures.

C. To compare morbidity in the three arms of the study.

To compare the morbidity in the three arms of the study, we will focus on the following complications: frequency and duration of rehospitalization, prolongation of hospitalization for management of complications of CHF, deterioration of CHF status, incidence of atrial fibrillation, incidence of strokes, incidence of syncope, incidence of resuscitated cardiac arrest, and the occurrence of additional diagnostic or therapeutic procedures in the three arms. Our efforts will also include monitoring drug compliance with therapy, breaches of SCD-HeFT protocol, use of alternate therapies, and drop-out rates for cardiac transplantation. All the data pertinent to this secondary endpoint of the study will be available from the general clinical data forms and the EQOL data forms.

D. To compare health-related quality of life in the three arms of the study.

Comparing health-related quality of life for each treatment group is an important clinical goal that may complement or, conversely, counter the life-sustaining value, if any, of either amiodarone or ICD therapy. These data will have secondary importance to survival data but adverse quality of life outcomes may temper the enthusiasm to employ amiodarone or ICD therapy should they prove efficacious. Quality of Life specific aims are:

1. To compare health-related quality of life in patients randomized to pectoral ICD vs amiodarone vs conventional heart failure medical therapy according to intention-to-treat.

2. To identify factors in addition to treatment assignment that are associated with variations in quality of life outcomes.

E. To compare cost of care for each treatment group and calculate incremental cost-effectiveness ratios for the two intervention arms.

Comparing cost of care and calculation of incremental cost-effectiveness ratios for the two intervention arms are important goals for this project that have important health policy implications. Life-prolonging therapies are of limited value if fiscal constraints limit wide scale use. Although SCD-HeFT is designed to be broadly applicable, a lack of evidence of cost effectiveness may prove to be a significant barrier to acceptance of the study's clinical implications. Economic specific aims are:

1. To compare cumulative total medical costs and relevant non-medical costs for the three treatment arms in SCD-HeFT by intention-to-treat based on a minimum of 2.5 years of follow-up.

2. To estimate the incremental cost effectiveness of the experimental arms relative to the control arm and to each other, assessed as cost per life year added and cost per quality-adjusted life year added.

3. To identify factors in addition to treatment assignment that are associated with variations in medical costs and cost effectiveness.

Statistical Issues and Data Analysis:

A. Sample Size.

The sample size for this trial will be 2,500 patients enrolled over a 2.5 year period, with a subsequent minimum follow-up period of 2.5 years after the last patient enters the study. Detailed sample size and power calculations have been performed to guide the design and planning of the trial and to ultimately arrive at this proposed study size. A presentation of those computations is available from Dr. Lee at the Data Coordinating Center. To briefly summarize, however, a major guiding factor in arriving at the proposed study size is our estimate that the *total* death rate over 2.5 years in Class II and Class III CHF patients with ejection fractions $\leq$ 35% will be approximately 25%. This expected event rate is based on the data from SOLVD, V-HeFT II, and CHF-STAT that were presented in the background section. The *mean* EF in those studies was 25—29%. With the SCD-HeFT entry criterion of a left ventricular ejection fraction $\leq$ 35%, our study population may even prove to be at slightly higher risk. Notwithstanding this possibility, the sample size calculations were performed with the more conservative estimate of 25% mortality in 2.5 years. With 2,500 patients randomized in equal proportions across the three arms, the study will have > 90% power for detecting a 25% reduction in mortality if the event rate at 2.5 years in the control-arm is 25% or higher. Furthermore, if these assumptions should prove to be optimistic, 2,500 patients will still provide excellent power. For example, if the effect of either amiodarone or the ICD intervention is to reduce mortality by only 20% (instead of 25%,) the power for detecting this smaller benefit is still greater than 80%. Moreover, if the control-arm mortality rate at 2.5 years should only be 20% (rather than the expected 25%,) the power is still nearly 90% for detecting a treatment benefit amounting to a 25% reduction in mortality. Thus, the chosen sample size preserves excellent power even under relatively conservative assumptions regarding the control-arm event rate and the magnitude of the benefit from the intervention arms. One-third of the patients will be randomized to the arm receiving placebo, one-third will be allocated to the amiodarone-treated group, and one-third will be assigned to the arm receiving an ICD.

In the process of choosing the population to study, there was no attempt made to stratify patients according to Holter, EPS, SAECG, heart rate variability, VO_2 max, etc., given their debatable or only modest positive predictive value for SCD in the SCD-HeFT population. Moreover, the use of these various "risk stratification tools" removes the study from the near intuitive level that currently is operative. We prefer our study to have broad applicability, much like what is currently done with beta-blockers post MI and ACE inhibitors in CHF.

In estimating event rates for the trial, any consideration of amiodarone or ICD procedural mortality was excluded as we expect it to be very small in either case. Pulmonary toxicity, as well as Torsades de Pointes, is likely to be rare [Hohnloser 94; Singh 95.] Similarly, the ICD is easy enough to use and effective enough to not be associated with the usual surgical problems seen with older nonthoracotomy or epicardial ICD systems.

To enroll 2,500 patients over a period of 2.5 years will require randomizing an average of 83 patients/month. The number of sites planned is 95. All centers recruited to date see over 100 new patients with CHF/year. Achieving the desired enrollment will require each site randomizing an average of 1.5 patients per month. All sites agreeing to participate in this study have stated that they will be able to enroll at least 2 patients per month. We are confident, therefore, that by establishing a nucleus of proven, highly productive centers, the enrollment goals of this trial are achievable. Additional sites will be added if

needed in order to maintain the pace of recruitment that will be required to complete patient enrollment in 2.5 years.

B. Randomization.

Randomization and treatment assignment will be accomplished via a dedicated, toll-free telephone randomization line to the Data Coordinating Center at Duke University. Personnel will be available to respond to incoming calls and to enroll patients on a 24 hours per day, 7 days per week basis. This system has been used successfully in several large trials directed by the Duke Data Coordinating Center. Details are available from the DCC.

C. Statistical Data Analysis.

Statistical analysis will be performed at the Data Coordinating Center. Although the methodological approaches and operational details of the data analysis will be coordinated by the study biostatisticians, the major analyses of the study data will be highly collaborative among the Data Coordinating Center, the Clinical Coordinating Center, and the Economics and Quality of Life Coordinating Center, involving both statisticians and physicians to ensure appropriate interpretation of the data. Treatment comparisons between the randomized groups in this trial will be performed according to the principle of "intention-to-treat;" that is, subjects will be analyzed (and endpoints attributed) according to the treatment arm to which patients are randomized, regardless of subsequent crossover. Statistical comparisons will be performed using two-sided significance tests. Additional perspective regarding the interpretation of the data will be provided through extensive use of confidence intervals and graphical displays.

Treatment comparisons for the primary efficacy endpoint of all-cause mortality will consist of pairwise comparisons of each intervention arm versus the control arm. These comparisons will be performed using the Cox proportional hazard regression model which encompasses as a special case the log-rank test [Cox 1972, Breslow 1974.] The Cox model can accommodate varying lengths of follow-up, it uses information for each patient on the time from study entry until the occurrence of the endpoint, and it accommodates "censored" survival times which arise because many patients will be alive when the analyses are performed, and the length of time they will survive without an event is known only to be greater than the length of their current follow-up. The Cox model also allows adjustment for covariates. The analysis strategy will be to first perform treatment comparisons that are unadjusted for other prognostic factors. These standard group comparisons, separately contrasting each intervention arm versus the control arm, will constitute the primary analysis to assess treatment differences. Supplementary analysis involving a small number of predefined baseline characteristics (e.g., sex, ischemic or non-ischemic cardiomyopathy, CHF class, and ejection fraction) will also be performed to allow adjustment for relevant covariates. Kaplan-Meier (Kaplan 1958) survival curves will be calculated to graphically display the mortality patterns of each treatment arm. If the data provide evidence of an overall difference in outcome between treatment groups, analyses will examine whether the therapeutic effect is similar for all patients, or whether it varies according to specific patient characteristics. These analyses will be carefully executed by testing for interactions between the treatments and specific baseline characteristics.

Analysis of the secondary clinical endpoints of cardiac death, arrhythmic death and morbidity will proceed using the Cox proportional hazards, along with specialized techniques for the nonfatal morbidity outcomes as described by Dr. Lee.

Detailed plans for appropriate interim analyses of the key clinical endpoints, the specific group-sequential methodology that will be employed for those analyses, and the interim presentations of information to the Data and Safety Monitoring Board can be obtained in full from Dr. Lee. Details of the statistical analyses for the economic and quality of life data can be obtained from Dr. Mark.

D. Data and Safety Monitoring Board (DSMB.)

The DSMB is independent of the Clinical Trial Director and is responsible to the NHLBI and to the patients in the trial. In the pilot study, Dr. Ralph Lazzara served as the data and safety monitor. For the full trial, a committee selected by the NHLBI will be responsible for review of patient morbidity and mortality data every 6 months as the data are provided to them by Dr. Lee.

Study costs and reimbursements:

Every effort has been made in the SCD-HeFT study design to limit or, in fact, avoid hospitalizations or complicated interventions, and to administer test therapies at a reasonable cost. Complex and costly diagnostic evaluation strategies (e.g., electrophysiology studies) and those of uncertain value in this population, (e.g., electrophysiology studies, cardiopulmonary exercise tests, and serum norepinephrine levels) will be avoided. This approach will be key to keeping cost of therapy reasonable and enrollment hurdles low.

The protocol is designed to be performed as an outpatient with ICD insertion performed over a 23 hour short-stay hospitalization. We have demonstrated the feasibility of this in the pilot. Complications are few and usually minor with this approach helping to keep costs and risks low. Nevertheless, operating room/cath lab, and hospital fees can not be eliminated. As a consequence, a substantial part of the costs of SCD-HeFT are for the one day hospitalization and surgical costs of ICD therapy. Under current law, third party reimbursement is possible for this study (FDA category B.3) if the third party insurer is fully aware of the nature of the investigation and the fact that full FDA approved ICDs are being used in a new indication. This information aside, funding has been obtained to defray some of these expenses.

The NIH is supporting much of the direct research costs. Medtronic has agreed to provide the ICDs free of charge for the 833 patients that will be randomized to the ICD arm of the study, and the 84 ICD replacement discussed below. At a fully priced ICD cost of $26,900, this amounts to a potential contribution of $24,667,300 toward the completion of SCD-HeFT. In addition, Medtronic will provide $5,000 to defray hospital costs for ICD patients ($4,165,000) and research support in the form of a $2,000 payment to enrolling centers for each patient enrolled ($5,000,000) regardless of arm to which the patient has been randomized and $50 upon completion of each follow-up form ($1,692,000.) In addition, Medtronic will provide a complication fund of $250,000 to cover the costs of complications directly related to the ICD implant and provide up to $1,000,000 to fund investigator meetings.

Wyeth pharmaceuticals is providing amiodarone and placebo free of charge for the trial. The cost of amiodarone is $1.80/200mg tablet. If we conservatively assume chronic dosing to be 250mg/day in the 833 patients randomized to active drug and these patients have an average follow-up of 3.5 years over the 5 years of this trial, the cost of amiodarone will be more than $2,052,000.

Thus, industry will contribute as much as $2,394,300 for the amiodarone, $24,667,300 for the ICDs, $12,107,000 in hospital costs for ICD implants and for the effort directed toward enrolling patients and completion of data forms. This amounts to a total contribution toward SCD-HeFT of approximately $39M, excluding pilot study contributions and monies for investigator meetings.

Costs of replacement ICD therapy:

Upon completion of the study, the necessity of ICD replacement, and consequently the manner in which the costs will be covered, will be dictated by study outcome or by individual physician practice. If the patient should use his device for therapy of electrogram documented VT or VF, the cost for ICD replacement can be billed to third party payers. ICD replacement also can be billed to third party payers if SCD-HeFT proves that patients randomized to ICD therapy have lower mortality rates than those in the control arm following FDA approval of this new indication. If patients with ICDs do not use their device for VT/VF, and SCD-HeFT does not show any beneficial effect on mortality for those treated with ICDs,

then the ICD may either remain *in situ*, be replaced, or be removed per individual physician discretion depending on what is considered best for the patient.

If ICD battery depletion occurs prior to completion of the trial and the patient has not used his device, ICD replacement will be provided free of charge. This will occur only in patients enrolled in the first year of the study presuming a worse case scenario of 4—5 year battery life of the device. (In reality the ICD will likely last longer if antibradycardia pacing isn't frequent.) It is estimated that 40% of the ICD patients will be enrolled in the first year of the study and that half of these will deplete their battery before completion of the SCD-HeFT trial. Further, it is anticipated that half of these patients will have used their ICD for VT or VF sometime during follow-up and therefore will be covered by third party payers. Thus, the few remaining patients ineligible for third party reimbursement will need their ICD replacement costs covered by ICD manufacturer funds. This amounts to only 84 patients needing ICD replacement in the last year of the trial.

If billing is still thought to be necessary by a site because individual institutional expenses are higher than what can be covered by the above mentioned SCD-HeFT funds, the site should consider sending a full disclosure letter to the relevant third party payer explaining the study and its merits.

SCD-HeFT

Site Payments

***Standard Operating Procedure* (SOP)**

Before any payments are issued, a site is required to be "valid," which means they have all necessary legal documents and a payee code. The legal documents required for SCD-HeFT are as follows:

Document	**Status**
Site Agreement	Signed Executable
W–9 Form	Signed Executable

Benchmarks

All benchmarks are paid according to the site agreement.

Questions regarding the site payment process should be directed to Laura Kappert, CT Financial Programming Team Leader, **(919) 416-8029**, or Jay Johengen, **(919) 416-7830**.

The benchmarks for SCD-HeFT are as follows:

Amount	**Description**	**Requirements**
$2000	Capitation	'*RECEIVED*' status in tracking for 'BASELINE CRF' and 'EQOL BASE SUMMARY'
$5000	Patient care/ICD patient	'*RECEIVED*' status in tracking for 'ICD IMPLANT FORM'
$50	Scheduled Follow-up visit	'*RECEIVED*' status in tracking for 'FOLLOW-UP VISIT' and verification upon data entry that visit was scheduled
$50	Patient death	'*RECEIVED*' status in tracking for 'ENDPOINT FORM'

Data Collection & Processing of Site Payments

Tracking

As forms are received at the DCRI, they will be logged into a tracking application to track the date the form was received. This data is then transferred nightly to a financial tracking database and all benchmarks that rely on a status of '*RECEIVED*' are processed against this data.

Payment Schedule

Payments are generated monthly by the Financial Group on or around the 1st of each month.

Payments will reflect data logged into tracking as received through the 25th of the previous month.

An accompanying invoice will show the breakdown of what patient enrollment(s) and what follow-up contact(s) are included in each check.

Checks will be mailed by the 15th of each month.

Please direct questions regarding invoices and site payments to Keba Wynn – account manager for SCD-HeFT **(919) 286-8956**.

SCD-HeFT

Implant Complications

Obtaining Reimbursement from the SCD-HeFT Complications Fund

Standard Operating Procedure

When a site investigator believes that a patient has experienced a complication of a SCD-HeFT implantation and seeks reimbursement for the costs associated with that complication per the SCD-HeFT Site Agreement, the following procedures should be initiated:

The site investigator will:

1. Obtain an account of all costs to the institution incurred as a direct result of the suspected implant complication.

2. Dictate a summary of the events surrounding the suspected complication.

3. Write a formal request for reimbursement of clinical costs incurred. This request should specify the exact amount of reimbursement being sought.

4. Forward the account of costs, summary and reimbursement request, together with relevant source documentation and medical records to the Clinical Events Committee (CEC) at the Duke Data Coordinating Center (DCC) using the ICD Complications Reimbursement Cover Sheet and a pre-addressed SCD-HeFT envelope.

Prior to Committee Review: Clinical Events Committee personnel at the DCC will:

1. Copy the materials received from the site.

2. Blind one copy of the materials received. Blind the following identifiers: investigator name, site name, geographical information, patient name, and patient study number. Leave one copy of the materials received, not blinded. (Not blinded copy to be kept in CEC files.)

3. Copy the blinded materials and send them to two members of the SCD-HeFT Complications Committee (list of members attached.)

4. Track, aterials, progress, and responses from Committee members.

5. Via e-mail, communicate information about Committee decisions to the SCD-HeFT Project Leader, DCC PI, Study Director and Account Manager (who will see that the reimbursement is both made and documented in the next regular site payment cycle.)

6. Enter Committee decisions into the CEC database.

SCD-HeFT Complications Committee members will:

1. Review materials (e.g., medical records, source documentation, account of costs, summary and request for reimbursement) sent to them by the DCC in a timely manner.

2. Use the standard Complications Committee Review Form to communicate their impressions to the Clinical Events Committee of the DCC. Members will consider the following questions in reviewing each request:

    a) Was the adverse experience a direct result of the implantation of a SCD-HeFT ICD?
    b) Is the amount requested reasonable and appropriate?

3. Return all related materials and the standard form with a recommendation either for or against reimbursement or for an adjustment of the requested amount to the Clinical Events Committee of the DCC.

Following Committee Review: Clinical Events Committee personnel at DCC will:

1. Via e-mail, recommend payment in the event that a request for reimbursement is approved by the committee and the amount requested is deemed to be reasonable and well justified. This recommendation will be made to the Account Manager (who will enter the reimbursement information into the Site Payment system) and will be copied to the Project Leader, DCC PI, Study Director and Complications Committee.

2. Recommend full committee review if the request is denied by one reviewer and approved by the other reviewer. These cases will be prepared and distributed by the CEC for committee review in person or in the format of a conference call.

3. Generate a letter to the requesting SCD-HeFT Investigator in the event that the request is denied by both reviewers. This communication will be a form letter composed by the Study Director, DCC PI, and members of the Complications Committee. The letter will be signed by the Study Director.

4. Notify the Project Leader by e-mail if the amount requested is deemed to be inappropriate, but the complication is accepted by both reviewers. In these cases, the Project Leader will arrange a conference call among committee members, the Study Director, and the requesting SCD-HeFT Investigator in order to arrive at a mutually acceptable solution.

5. The status and resolution of each request will be entered into the CEC database.

Site Agreement

The site agreement document can be downloaded from the SCD-HeFT web site. See Section 22 for more information on accessing the web site.

Obtaining a Device System for a SCD-HeFT Patient Randomized to ICD Therapy

If your patient is randomized to an Implantable Cardioverter/Defibrillator (ICD) system, follow the steps outlined below to obtain an ICD system for your study patient:

1) Contact your Medtronic Representative

If you do not have a primary contact at Medtronic for ICD/pacemaker implant and follow-up support, the attached list provides the telephone numbers of all Medtronic representatives for all Districts/Territories in the U.S. and Canada.

Select the Medtronic representative for your location, and call the representative who will assist you in obtaining the ICD system for your study patient.

If you do not know the District/Territory in which you are located, call the main number for Medtronic and ask for assistance.

2) Provide the SCD-HeFT Patient Study Number to the Medtronic Representative.

When you request an ICD system for your study patient, provide the SCD-HeFT patient study number and the patient's initials to the Medtronic Representative. Procedure support and an ICD system cannot be provided without this identifying information.

3) ICD System Billing and Reimbursement*

Medtronic is providing all study ICD systems and support free of charge. After the study implant procedure, your hospital will receive a **no-charge invoice** for the Medtronic ICD, lead(s) and accessory(ies) used for the study implant procedure.

**** Note: It may be necessary to identify for your institution the patients enrolled in SCD-HeFT to ensure that the study patients or their third party payors are not billed directly for the ICD device, lead(s) and/or accessories.***

Medtronic Contact Numbers:

EASTERN REGION	ADDRESS	CITY, STATE	PHONE
Regional Office	One Meadowlands Plaza, Suite 710	East Rutherford, NJ 07073-2137	(201) 933-0078
Boston District	Three Burlington Woods Dr., Suite 310	Burlington, MA 01803	(617) 273-4720
New York Dist.	One Meadowlands Plaza, Suite 710	East Rutherford, NJ 07073-2137	(201) 933-0078
Pittsburgh Dist.	235 Alpha Dr., Suite 204	Pittsburgh, PA 15238	(412) 967-0549
Southern New England Dist.	741 Boston Post Rd., Suite 305	Gulliford, CT 06437	(203) 458-6674
Philadelphia Dist.	301 South State St., Suite S101	Newtown, PA 18940	(215) 968-1694
Buffalo Dist.	127 South Long St.	Buffalo, NY 14221	(716) 634-2820
New Jersey Dist.	One Meadowlands Plaza, Suite 710	East Rutherford, NJ 07073-2137	(800) 557-0938
Central Pennsylvania Dist.	134 Sipe Ave., Suite 102	Hummelstown, PA 17036	(717) 520-0147
SOUTHERN REGION			
Regional Office	2727 Paces Ferry Rd, N.W., Suite 1-1600	Atlanta, GA 30339-4053	(770) 434-7720
Washington D.C. Dist.	2191 Defense Highway, Suite 206	Crofton, MD 21114	(410) 451-2703
Louisville Dist.	9300 Shelbyville Rd., Suite 603	Louisville, KY 40222	(502) 432-7725
Richmond Dist.	4101 Cox Rd., Suite 315	Glen Allen, VA 23060	(804) 527-1550
Charlotte Dist.	2400 Yorkmont Rd., Suite 140	Charlotte, NC 28217	(704) 357-0600
Atlanta Dist.	2727 Paces Ferry Rd, N.W., Suite 1-1600	Atlanta, GA 30339-4053	(770) 434-7720
South Florida Dist.	100 West Cypress Creek Rd, Suite 920	Ft. Lauderdale, FL 33309	(954) 776-3723
Jacksonville Dist.	Quadrant II, Ste. 130, 4655 Salisbury Rd.	Jacksonville, FL 32256	(904) 296-8777
Clearwater Dist.	18167 U.S. Highway 19 N., Suite 130	Clearwater, FL 34624	(813) 530-4791
Charleston Dist.	200 Meeting Street, Suite 400	Charleston, SC 29401	(803) 853-0053
MIDWEST REGION			
Regional Office	8500 Normandale Lake Blvd., Suite 2150	Bloomington, MN 55437-3833	(612) 830-1858
Detroit Dist.	255 South Woodward, Suite 202	Birmingham, MI 48009	(810) 642-1482
Cleveland Dist.	5005 Rockside Rd., Suite 1160	Independence, OH 44131	(216) 642-1977
North Chicago Dist.	Four Westbrook Corporate Ctr., Ste. 100	Westchester, IL 60154	(800) 466-9738
South Chicago Dist.	Four Westbrook Corporate Ctr., Ste. 100	Westchester, IL 60154	(800) 466-9738
Indianapolis Dist.	305 East Washington Ctr.	Fort Wayne, IN 46825	(317) 842-1111
St. Louis Dist.	111 West Port Plaza, Suite 1015	St. Louis, MO 63146	(314) 878-5616
Milwaukee Dist.	411 E. Wisconsin Ave., Suite 1025	Milwaukee, WI 53202	(414) 223-1160
Minneapolis Dist.	8500 Normandale Lake Blvd., Suite 2150	Bloomington, MN 55437-3833	(612) 830-1840
SOUTHWEST REGION			
Regional Office	201 Main St., Texas Commerce Dr., Ste. 2000	Fort Worth, TX 76102	(817) 335-2090
Kansas City Dist.	6900 College Blvd., Suite 570	Overland Park, KS 66211	(913) 469-8555
Houston Dist.	16701 Greenspoint Dr., Suite 130	Houston, TX 77060	(281) 875-0375
Dallas Dist.	201 Main St., Texas Commerce Dr., Ste 2050	Fort Worth, TX 76102	(817) 335-4420
New Orleans Dist.	3900 North Causeway Blvd., Suite 1290	Metairie, LA 700002	(504) 837-7971
Memphis Dist.	6410 Poplar Ave., Suite 370	Memphis, TN 38119	(901) 763-0104
Tulsa Dist.	6100 South Yale Ave., One Warren Place, Ste. 308	Tulsa, OK 74136	(918) 493-3401
San Antonio Dist.	613 NW Loop 410, Suite 820	San Antonio, TX 78216	(210) 308-8434
Nashville Dist.	3319 West End Ave., Suite 920	Nashville, TN 37203	(615) 385-5758
WESTERN REGION			
Regional Office	21550 Oxnard St., Suite 400	Woodland Hills, CA 91367	(818) 716-1493
Irvine Dist.	2 Park Plaza, Suite 910	Irvine, CA 92614	(714) 975-1616
Los Angeles Dist.	21550 Oxnard St., Suite 400	Woodland Hills, CA 91367	(818) 716-5502
Los Angeles Metro Dist.	21550 Oxnard St., Suite 400	Woodland Hills, CA 91367	(818) 716-1744
San Francisco Dist.	2200 Powell St., Suite 675	Emeryville, CA 94608	(510) 655-0104
Denver Dist.	8101 E. Prentice Ave., Suite L-150	Englewood, CO 80111-2928	(303) 694-5130
Phoenix Dist.	426 North 44th St., Suite 310	Phoenix, AZ 85008	(602) 956-1960
Sacramento Dist.	2151 River Plaza Dr., Suite 190	Sacramento, CA 95833	(916) 924-8071
Seattle Dist.	3440 Carillon Point	Kirkland, WA 98033	(206) 803-0708

Medtronic Contact Numbers *(cont.)*:

TERRITORY		PHONE
Toronto, Ontario	Canada	(416) 948-8431
Ontario	Canada	(416) 524-7520
Ottawa, Ontario	Canada	(613) 725-6527
Ste-Foy, Quebec	Canada	(514) 984-9026
Quebec	Canada	(514) 895-1649
Montreal, Quebec	Canada	(514) 946-2557
London, Ontario	Canada	(519) 671-0072
Calgary, Alberta	Canada	(403) 660-4628
Alberta and B.C.	Canada	(604) 329-2631

ICD Implantation:

Implantation Materials.

- Medtronic 9790 programmer
- Patient programmer cable
- ICD (Medtronic model 7223Cx)
- 8.5 Fr RV tripolar pacing/sensing/passive fixation defibrillation lead (Medtronic model 6932)
- Peel away introducers: 9-11 Fr., depending upon practice of retaining a guidewire
- Sterile programming head sleeve
- Standard sterile supplies for ICD implants

Implantation Technique.

ICD surgery will be done using a 23 hour short stay admission similar to pacemaker surgery to minimize costs. Implantation may be done with local or general anesthesia depending on physician preference. Single dose prophylactic antibiotic coverage with Cefazolin 1.0 gm IV or, if allergic, Vancomycin 1.0 gm IV will be administered 1 hour prior to making the left infraclavicular incision.

The ICD used will be the Medtronic active can model 7223Cx which employs a single 65 cm 8.5 Fr. tripolar passive fixation right ventricular (RV) electrode (Medtronic model 6932) for pacing, sensing, and defibrillation. An alternative lead length of 75 cm is available for larger patients. Use active fixation (Medtronic model 6936) lead only if the passive fixation lead dislodges after insertion and is thought to be prone to repetitive dislodgment. Other leads that may be used include the Medtronic model 6942 (dual coil, integrated bipolar sensing, tined) and the model 6945 (dual coil, integrated bipolar sensing, screw-in.) As other leads become available, they may be used as well.

The RV lead will be inserted preferentially in the left cephalic vein to avoid lead fractures resulting from first rib-clavicular crush. If the cephalic vein is inaccessible, subclavian entry will be required for lead insertion. For subclavian entry, the puncture site should be as lateral as possible to minimize the possibility of first rib-clavicular crush. Once the lead is passed into the RV, it should be positioned into the RV apex as distally as possible.

After the lead tip is positioned into the RV and prior to defibrillation efficacy testing, the pacing threshold and sensing capabilities of the lead system will be evaluated. The bipolar R-wave signal amplitude should be at least 5 mV. The bipolar pacing threshold should be < 2.0 V using a pulse width of 0.4 ms. If these values are not present, the lead should be repositioned until suitable sensing and pacing values are obtained. A minimum of 3 repositioning attempts should be made before accepting less than ideal sensing and pacing numbers.

The left infraclavicular ICD pocket should be subcutaneous in all cases. Subpectoral implantation is to be used only if adequate subcutaneous adipose tissue is absent. Subcutaneous implantation is preferred to minimize surgery, complications, and to facilitate subsequent ICD replacement. If the patient is very small and will not comfortably accommodate subcutaneous location, the device can be inserted subpectorally as previously described [Bardy 1994b.]

Defibrillation testing.

Prior to beginning defibrillation testing, the RV lead will be used as the defibrillation anode for the initial phase (B>AX) of the biphasic waveform and connected to the Medtronic ICD (model 7223Cx) and positioned in the left infraclavicular pocket. The pocket should be closed, temporarily, by approximating the incision with two or three towel clamps. Care should be taken to avoid contact of the ICD with the towel clamps. Any air should be expressed from the pocket to improve tissue contact with the generator. Defibrillation testing can then proceed as follows.

The initial defibrillation test pulse, delivered via the Medtronic ICD (model 7223Cx) will be a 20 Joule (J) biphasic waveform. The RV lead should be connected to the ICD such that the device sits in the infrapectoral pocket with redundant lead placed around or under rather than over the unit. This lead location will limit tension on the overlying dermis and minimize interference with subsequent ICD replacement. The ICD should be anchored to the underlying pectoralis fascia with a single loose suture to prevent generator drift when the patient stands. However, do not anchor too tightly as tight sutures can lead to tenting of the ICD against the skin when the patient stands. It is recommended that the pocket not be completely closed with suture during the testing phase in the event changes in the lead or ICD position are required or insertion of an additional electrode prove necessary.

Prior to proceeding with the first induction of VF and a modified DFT determination, the ICD will be programmed to a bradycardia backup rate of 50 ppm with hysteresis activated at 34 bpm, a fibrillation detection interval (FDI) of 320 ms with 18/24 intervals required for initial detection (initial NID = 18) and 12/16 intervals for redetection (redetect NID = 12.) VF electrogram detection sensitivity will be set nominally to 0.3 mV, and first shock strength will be set initially to 20 J with all subsequent VF therapies programmed to 30 J. The SCD-HeFT nominal electrogram configuration is HVA to HVB (far field.) VT detection and therapy is NOT to be activated. VT detection and therapy can only be activated after consultation with the UW Clinical Coordinating Center following a spontaneously occurring episode of monomorphic VT in the course of follow-up.

VF will be induced with the "T–shock" mode using VVI pacing with 3 S1 stimuli (not 8) at a drive cycle length of 400 ms with a post pace refractory period of 240 ms and a 1.0 J monophasic T–shock at a coupling interval of 310 ms. If this T–shock is unsuccessful at inducing VF, coupling interval or shock strength can be adjusted as the physician deems appropriate. The physician can employ 50 Hz stimulation from the Medtronic ICD but only after at least 5 attempts of T–shock have failed. To facilitate T–shock effectiveness, a 10 ms 'scan' of the coupling interval from the initially used 310 ms value can help induce VF following each failed effort (e.g., 310 ms → 300 ms → 320 ms → 290 ms → 330 ms, etc.)

The initial 20 J test pulse should defibrillate > 90% of patients. If unsuccessful at terminating VF, a transthoracic rescue pulse of known efficacy (e.g., 200 J monophasic or 130 J biphasic) should be delivered promptly to minimize fibrillation duration to no more than 15 seconds rather than allowing the ICD VF therapy #2 to intervene. Care should be taken to avoid transthoracic pulsing too early in the event that VF termination follows a series of gradually slowing repetitive ventricular responses, sometimes referred to as a "Type II break." A maximum of 11 repetitive ventricular responses following a shock will be considered a "Type II break" given the relationship of this number of intervals to the ICD redetection algorithm where 12 post-shock intervals will lead to repeat shock therapy.

If defibrillation is successful at the 20 J level with the active can, the first shock energy should be reprogrammed to 10 J biphasic using the same polarity. Do not change VF therapies #2-6 from their 30 J

settings. After a 5 minute wait following the first VF induction, reinduce VF a second time using the "T–shock" VF induction mode described above. If the induced VF is terminated with the 10 J pulse, the DFT will be considered to be 10 J or less and the ICD will be programmed to a first VF therapy setting of 20 J before the patient leaves the operating room. All subsequent VF therapy settings will be 30 J. The last two VF therapies will have the polarity reversed.

If the 10 J pulse is unsuccessful, VF will be terminated with a transthoracic rescue pulse, and the DFT will be considered to be $\leq$ 20 J. The ICD will then be programmed to a first VF therapy setting of 30 J. All other VF therapies will also be 30 J and the last two VF therapy polarities will be reversed.

In the event that the initial VF induction is not successfully terminated with the 20 J pulse, the next option in ICD implantation will be at the investigator's discretion. See section below.

Note that we realize that the term 'DFT' is a very crude definition of the true DFT but this protocol is designed to maximize patient safety while ascertaining as much information about ICD function as possible. This method is also an effort to establish a simple, yet effective uniform implantation technique. Another purpose for testing the ICD in the manner described is to avoid shock induced cardiac dysfunction, a problem that may prove to be more troublesome in the SCD-HeFT population than in our usual VT/VF population where the LV EF has been reported to be 6-8 EF points higher than the group of patients we will be studying in SCD-HeFT.

Remember, that regardless of DFT, VF therapies 2-6 should be programmed to 30 J. The final two VF therapies, #5-6, should be programmed to have an opposite polarity to that used for VF therapies #1-4. This may aid in rescuing the patient should the patient's defibrillation characteristics change in the course of follow-up.

Upon determination of the DFT and assuming appropriate function of the VF detection algorithm, the procedure will be considered completed except for closure of the wound. The pulse generator should be anchored to the underlying fascia with a single 0 suture applied relatively loosely to an anchoring portal to prevent caudal drift of the ICD. A too tightly applied anchoring suture may actually leave the ICD little room to maneuver during activity and lead to untoward tension on the overlying dermis. An absorbable anchoring suture is recommended in anticipation of eventual ICD removal. PDS suture is a reasonable choice as an absorbable material because of its relatively slow absorption rate of approximately three months. This is an adequate time for a fibrotic pocket to form for long term support of the pulse generator to prevent caudal drift. Pulse generator migration has not been a problem in the use of this device [Bardy 1996a.] However, if you think the patient might prove to be a 'twiddler', a non-absorbable suture is recommended. The incision should be closed in three layers of an absorbable suture like Vicryl, 2—O and 3—O.

Defibrillation should the RV-Can system not defibrillate at 30 J.

All electrophysiologists participating in this trial are experienced implanters and may use whatever methodology they prefer. That said, we offer the following alternative methods for consideration.

First, it is reasonable to consider not adding any additional electrodes and program first shock energy to 30 J biphasic using the same polarity. After a 5 minute wait following the first VF induction, reinduce VF a second time using the "T–shock" VF induction mode as described above. If the induced VF is terminated with the 30 J pulse, the DFT will be considered to be 30 J or less and all ICD therapies will be

programmed to 30 J before the patient leaves the operating room. The last two VF therapies will have the polarity reversed.

If the investigator would like to endeavor to increase the defibrillation safety margin, the next recommended maneuver is to add a 35 cm superior vena cava (SVC) electrode (Medtronic model # 6933-5 cm coil or 6937-8 cm coil) and repeat testing at 20 J, then 10 J if successful, using the same polarity as before. Use of an SVC electrode is preferred rather than simply reversing polarity, a generally unacceptable maneuver unless the patient is too unstable to pursue alternatives. The SVC electrode should be inserted using Seldinger technique into the left subclavian vein and positioned high in the left innominate-left subclavian vein junction with the tip of the SVC electrode positioned in the mid-line fluoroscopically overlying the spinous processes. Insert the pin of the SVC lead and secure to the "HVX" portal. Maintain first VF therapy energy at 20 J with a biphasic shock.

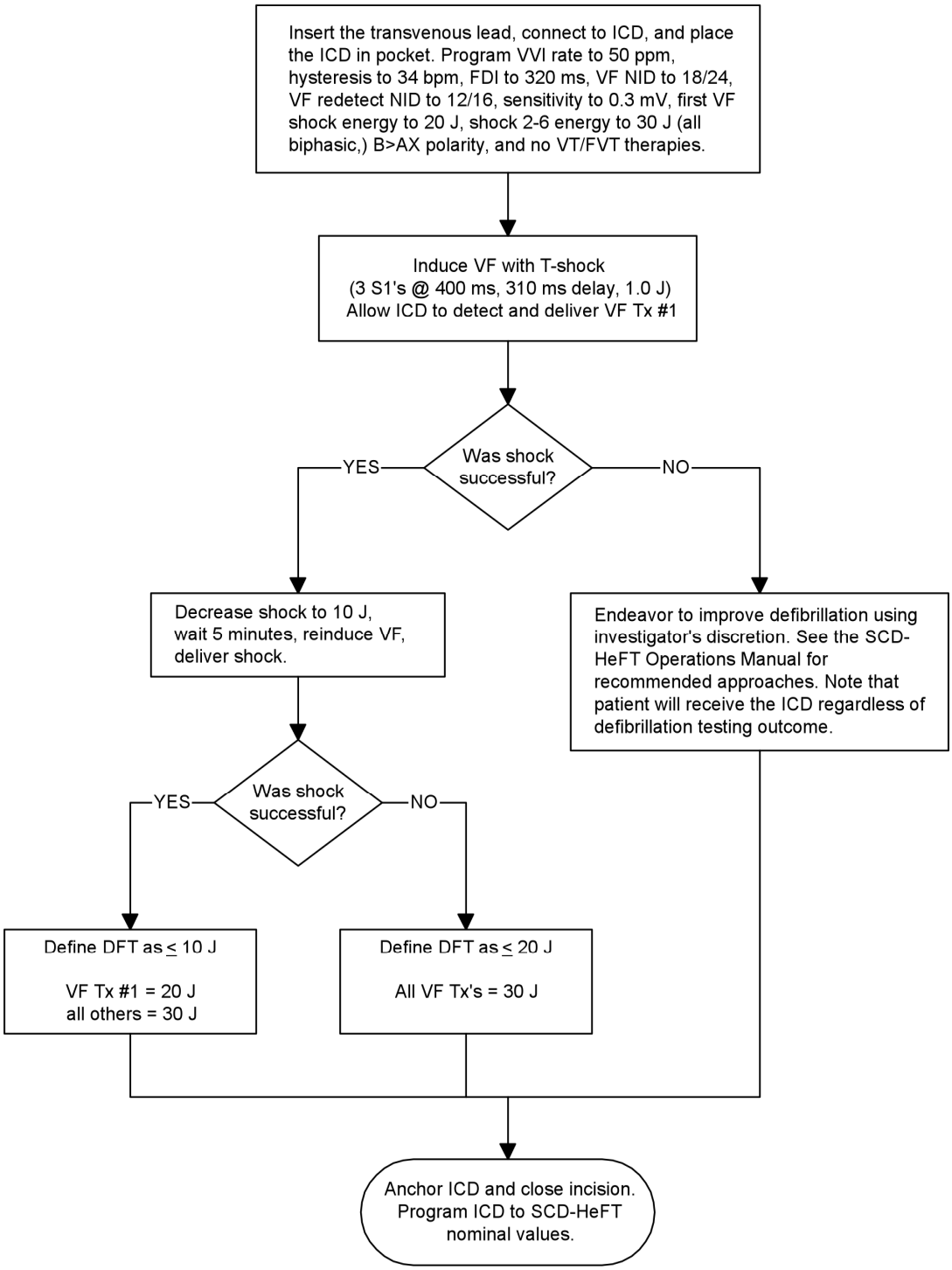
If use of the additional SVC electrode proves unsuccessful at 20 J, one could pursue alternative approaches (coronary sinus with 52 cm leads, low SVC, subcutaneous patch, etc.) or accept 30 J or higher DFTs. As mentioned in earlier communiqués, failure to defibrillate at 30 J does not in and of itself dictate failure to defibrillate out-of-hospital with spontaneously occurring episodes. Moreover, the ICD may provide a benefit via its antibradycardia pacing capabilities. As one final alternative, one might also consider allowing VF therapy #2 to be delivered by the ICD and observe and record outcome. In whatever course you choose, remember that there is risk with extensive testing and that accepting less than perfect results might be better for the patient. SCD-HeFT, after all, is a prophylactic study and may not merit the increased morbidity and mortality of prolonged defibrillation testing.

VF detection during defibrillation testing.

In the process of testing defibrillation, VF detection using a 320 ms fibrillation detection interval with an initial interval detection criterion of 18/24 intervals (initial NID = 18) and a sensitivity of 0.3 mV will be assessed. If 4 or more VF intervals remain undetected using the initial detection parameters, then either the NID, the sensitivity setting, or the fibrillation detection interval should be increased as clinically indicated. Most likely, the easiest maneuver will be to lower the initial NID to 12. For VF redetection, should the first shock fail, the number of intervals needed to redetect VF should be 12/16 (redetect NID = 12.) Using too low NID values can be harmful in that interventions may be increasingly likely to be inappropriate; all interventions carry risk.

Once defibrillation and VF detection is tested, the ICD will need to be interrogated and programmed as indicated below. Note that a critical feature of SCD-HeFT ICD patients will be the uniformity of study and the save-to-disk data.

ICD IMPLANT TESTING PROTOCOL



ICD Implant Checklist:

- ❑ Program ICD clock to current local time and date
- ❑ Interrogate ICD (initial interrogation)
- ❑ *Save-to-Disk* twice using two separate diskettes
- ❑ Program ICD to SCD HeFT nominal values
- ❑ Conduct ICD implant and testing procedure
- ❑ Interrogate ICD
- ❑ *Save-to-Disk* twice using two separate diskettes
- ❑ Print *Full Summary* report
- ❑ Measure *Pacing Lead Impedance*, print report
- ❑ Measure *Pacing Threshold* @ 4V, print report
- ❑ Record *P-/S to P+/S EGM*, print EGM strip (@ 1 mm/mV)
- ❑ Record *HVA to HVB EGM*, print EGM strip (@ 1mm/mV)
- ❑ Clear ICD memory
- ❑ Program ICD to SCD HeFT nominal values (if changed from above)
- ❑ Interrogate ICD (final interrogation)
- ❑ *Save-to-Disk* twice using two separate diskettes
- ❑ Store one diskette with the patient's records
- ❑ Send one diskette (electronically or via mail) to the ICD Memory Log Core Laboratory
- ❑ Complete ICD Implant Form

ICD PROGRAMMING AT INITIAL IMPLANT

Save-to-disk should be performed 3 times throughout the implant procedure: initially after the internal ICD clock has been set to current time and before any programming changes have been made; after all VF inductions have been performed; and a final time after clearing ICD memory.

The ICD should be programmed according to the following parameters:

1. **VF/VT detection:** Programming of the VF/VT detection algorithm will be guided by the results of testing during implantation. The nominal parameters for VF/VT detection will be to use a detection interval criterion of 320 ms (188 bpm) with a 18/24 intervals duration (NID) criterion. These initial detection parameters are intended to minimize inappropriate interventions into atrial fibrillation and non-sustained ventricular arrhythmias, yet maintain sensitivity to arrhythmias likely to lead to hemodynamic collapse.

   Parameters are as follows:

VF Enable:	ON
FVT/VT Enable:	OFF
VF Interval (FDI):	320 ms
VF Initial NID:	18/24
VF redetect NID:	12/16
Sensitivity (mV):	0.3
Stability:	OFF
Onset:	OFF

2. **EGM Source:** HVA to HVB (far field,) EGM Range (mV): +/- 15. Note that this electrogram source will help provide greater detail on electrogram morphology, P wave, QRS, ST and T wave data.

3 **VF/VT therapy:** First shock energy strength for VF/VT is selected based upon defibrillation efficacy testing during implantation as defined above. It will either be 20 J or 30 J. The primary purpose for measuring the defibrillation threshold is to allow first shock energy strength to be as low as possible for effective therapy of VF/VT and to correlate survival with defibrillation efficacy. Use of a 20 J shock strength, if appropriate because DFT $\leq$ 10 J, will help minimize shock induced cardiac dysfunction observed when shock strength is unnecessarily high. In addition, a 20 J initial shock will require shorter capacitor charge times and therefore be likely to intervene in an episode of VF/VT before the patient loses consciousness, a finding that will be monitored during the study. Antitachycardia pacing maneuvers are intentionally avoided in SCD-HeFT with initial ICD programming. This form of therapy is useful only in patients having monomorphic VT. If the patient develops monomorphic VT initially treated by shock therapy in the course of the trial, ATP can be activated after consultation with Dr. Poole or Dr. Bardy at the Clinical Coordinating Center.

Parameters are as follows:

VF Therapy status:	ON therapies 1-6
FVT/VT therapy status:	OFF
VF Therapy # 1 Energy (J):	20 J if DFT is ≤ 10 J, otherwise 30 J
VF Therapies # 2-6 Energy (J):	30 J
Waveform therapies # 1-6:	Biphasic
Pathway (Polarity) therapies # 1-4:	B>AX
Pathway (Polarity) therapies # 5-6:	AX>B

4. **Antibradycardia pacing:** The ICD backup pacing rate will be 50 ppm but will only be triggered when the rate falls below 34 bpm (hysteresis pacing.) Each time the ICD is triggered to pace ≥3 consecutive beats in the hysteresis mode, the memory of the ICD will record the event. This will allow the investigators to observe the incidence of marked bradycardia in the CHF patients randomized to the ICD arm.

   Parameters are as follows:

Mode: VVI, Rate:	50 ppm
Hysteresis:	34 bpm
Sensitivity:	0.3 mV
Amplitude:	4.0 V (5.0 V while charging, post shock)
Pulse Width:	0.4 ms (1.6 ms while charging)
Pace Blanking:	240 ms (240 ms while charging)

5. **Data Storage Option:** 10 Min EGM

   Episode Data:

Store EGM before Tachycardia Starts:	YES
Store EGM during charging:	YES

   Event Trend Data:

Recording Length:	90 days
Start Recording Event Trends On:	Date of follow-up
Premature Event Threshold (%):	69

   R-R Interval Data:

Storage Length:	SHORT

   (Note: "Long" storage length compromises the amount of R-R data if multiple episodes occur.)

   The ***Storage Option*** parameter of ***10 Min EGM*** allows acquisition of up to 10 minutes of EGM data, divided among the tachy episodes recorded. It also enables R-R Interval and Event Trend data storage. The ***Store EGM Before Tachycardia Starts*** parameter enables storage of about 20 seconds of EGM data prior to the detection of a tachyarrhythmia. The ***Store EGM During Charging*** parameter enables EGM data storage during a capacitor charging period. The R-R Interval ***Storage Length*** parameter will be set to ***SHORT***, enabling storage of up to 2048 R-R interval data points prior to each of the last two VF episodes and the last three VT episodes. Each (2048 point) R-R interval data set represents about one-half hours' worth of data.

6. **Holter Telemetry:** Duration (hours): OFF
7. **Auto Cap Formation** (months): 6

A table providing a quick reference to the differences between SCD-HeFT ICD nominals and Medtronic factory nominals is shown below.

ICD Programmable Parameters

Parameter		SCD-HeFT nominals		Factory nominals	
VF Detection Parameters					
Detection Enable		ON		OFF	
Interval (ms)		320		320	
Initial NID		18/24		18/24	
Redetect NID		12/16		18/24	
Sensitivity (mV)		0.3[(1)]		0.3	
FVT Detection Parameters					
Detection Enable		OFF		OFF	
VT Detection Parameters					
Detection Enable		OFF		OFF	
VF Therapy Parameters					
Therapy Status	(1-6)	ON		ON	
Energy (J)	(1)	30[(2)]		30	
	(2-6)	30		30	
Waveform	(1-6)	BIPH		BIPH	
Pathway	(1-4)	B>AX		AX>B	
	(5-6)	AX>B		AX>B	
Reconfirm VF		YES		YES	
Pacing Parameters					
Pacing Mode		VVI		VVI	
Pacing Rate (ppm)		50		40	
Hysteresis (bpm)		34		OFF	
Sensitivity (mV)		0.3[(1)]		0.3	
Pulse Amplitude (V)		4.0[(1)]	(5.0)	4.0	(5.0)
Pulse Width (ms)		0.4[(1)]	(1.6)	0.4	(1.6)
Pace Blanking (ms)		240[(1)]	(240)	240	(240)

( ) = While charging and post shock

Table continued on next page.

ICD Programmable Parameters - cont.

Parameter	SCD-HeFT nominals	Factory nominals
Data Storage		
Storage Option	10 Min EGM	10 Min EGM
Store EGM Before Tachycardia Starts	YES	NO
Store EGM During Charging	YES	NO
EGM Source	HVA to HVB	P-/S to P+/S
EGM Range (mV)	±15	±7.5
R-R Interval Data		
Storage Length	SHORT	SHORT
Event Trend Data		
Recording Length	90 days	90 days
Start Recording Event Trends On	[follow-up date](3)	—
Premature Event Threshold (%)	69	69
Holter Telemetry		
Duration (hours)	OFF	OFF
Auto Capacitor Formation		
Interval (months)	6	OFF

Notes:

(1) The programmed values for ***Sensitivity***, ***Pulse Amplitude***, ***Pulse Width***, and ***Pace Blanking*** will depend on what is appropriate at the time of implant. The nominal values should be adequate in the majority of cases.

(2) If the DFT at the time of implant is 10 J or less, then the first shock energy will be set to 20 J. Otherwise, it will be set to 30 J.

(3) The ***Start Recording Event Trends On*** parameter will be set to the date/time of programming at the follow-up visit.

PRE-OP IMPLANTABLE DEFIBRILLATOR SYSTEM ORDERS

1. **Admit to Short Stay Unit on_____at_____AM.**

2. **Notify EP/Cath Lab/OR personnel of patient arrival.**

3. **Verify NPO status. If patient has consumed food/fluids after midnight notify implanting physician ASAP.**

4. **Verify coagulation status (if on warfarin,) if INR is > 1.6 notify implanting physician ASAP.**

5. **Cefazolin 1.0 gm IV or, if allergic, Vancomycin 1.0 gm IV on call for administration 1 hour prior to making incision.**

POST-OP IMPLANTABLE DEFIBRILLATOR SYSTEM ORDERS

1. **Discharge to Short Stay Unit per EP/Cath Lab/OR routine.**

2. **Cap off IV line when able to take oral fluids, discontinue prior to discharge home.**

3. **Vital signs:**
   a. **q 30 minutes x 1**
   b. **q 1 hour x 3**
   c. **prn or per unit routine.**

4. **Notify _____M.D. if:**
   a. **Systolic BP < 90mm Hg.**
   b. **HR > 120 bpm.**
   c. **Temperature > 101.**
   d. **Deterioration of general condition.**
   e. **Incisional bleeding/hematoma.**

5. **Upright PA and lateral CXR prior to discharge home (patient may go to X-Ray unmonitored.)**

6. **12 lead ECG prior to discharge home.**

7. **Diet as tolerated.**

8. **May ambulate ad lib.**

9. Wound management: Instruct patient/caregiver to remove dressing 24 hours post-op and leave incision open to air. Call implanting MD if occurrence of persistent drainage, bleeding, erythema, hematoma, pain or fever.

POST-OP IMPLANTABLE DEFIBRILLATOR ORDERS — CONTINUED

10. Do not bind left arm/shoulder or use a sling and instruct patient to preserve reasonable use of left arm to minimize potential for frozen shoulder.

11. May take own medications as prescribed, instruct patient/caregiver to resume coumadin/ASA 24 hours post-op.

12. Discharge to home per unit routine with pain medication of choice prn incisional pain and anti-emetic of choice.

13. Give patient a SCD-HeFT study kit, instruct them to always bring the kit to every clinic visit, and to remind their physician/nurse to "Save to Disk" the initial and final ICD interrogation.

14. Return to outpatient clinic in 5 to 7 days for wound and ICD check.

IMPLANTABLE DEFIBRILLATOR
PATIENT DISCHARGE INFORMATION

Sudden Cardiac Death

SCD-HeFT

Heart Failure Trial

PATIENT: HOSPITAL NUMBER:
DIAGNOSIS: ATTENDING PHYSICIAN:
ADMIT DATE: DISCHARGE DATE:

FOLLOW-UP APPOINTMENTS:

1 Week Cardiology Clinic Appointment: **Date:** **Time:**
Located:
If there is a need to reschedule, please call:

1 Month Cardiology Clinic Appointment: **Date:** **Time:**
Located:
If there is a need to reschedule, please call:

3 Month Cardiology Clinic Appointment:
Located: **Date:** **Time:**
If there is a need to reschedule, please call:

ADDITIONAL INFORMATION

It is important that your defibrillator is checked every three months. Also, avoid holding cellular phones directly over your defibrillator (see page 2 for more information.)

IF ANY OF THE FOLLOWING OCCUR:

1. You receive a shock or shocks from your defibrillator and are conscious (awake):

a. Notify one of the following physicians (Attending on-call):

2. You receive a shock or shocks from your defibrillator and you are unconscious (unresponsive):

a. It is extremely important someone with you call 911 immediately and start CPR.

3. Redness and/or drainage occurs from your incision site, or you develop fever and/or chills:

a. Notify one of the following physicians:

4. Range of motion in your shoulders is very important after receiving an implantable defibrillator (i.e., raising arms above head, washing/combing hair.) However, heavy lifting, pulling, and pushing should be avoided to prevent damage to the implantable defibrillator lead system.

Cellular Phone Information:

Important information regarding your implantable defibrillator and cellular phones.

Recent studies have indicated there may be a potential interaction between cellular phones and implantable defibrillator operation. Either the radio-frequency signal or the magnet within the phone could inhibit delivery of therapy when the phone is within 6 inches (or 15 centimeters) to the implantable defibrillator.

It is important to note, based on testing to date, that any effect resulting from an interaction between the cellular phone and the implanted defibrillator is temporary. Simply moving the phone away from your defibrillator will return it to normal operation. Because of the great variety of cellular phones and the wide variance in patient physiology, an absolute recommendation to cover all patients cannot be made.

The following information provides a general guideline to patients having an implanted defibrillator who desire to operate a cellular phone:

- **Maintain a minimum separation of 6 inches (15 centimeters) between a hand-held personal cellular phone and the implanted device. Portable and mobile cellular phones generally transmit at higher power levels compared to hand-held models. For phones transmitting above three watts, a minimum separation of 12 inches (30 centimeters) between the antenna and the implanted device is advised.**

- **Patients should hold the phone to the ear opposite the side of the implanted device. Patients should not carry the phone in a breast pocket or on a belt over or within 6 inches (15 centimeters) of the implanted device as some phones emit signals when they are turned ON but not in use (i.e., in the listen or standby mode.) Storing the phone in a location opposite the side of implant is recommended.**

ICD Follow-up:

Neither pre- nor post-implant electrophysiologic studies via the ICD will be done in SCD-HeFT patients. Electrophysiologic studies are impractical, costly and potentially risky in this patient population where ease of ICD use and limitations of cost are critical to the clinical relevance of the ICD approach as a prophylactic therapeutic alternative. A post-implant, predischarge postero-anterior and lateral chest X-ray will be required as will one at 12 months post implant and every year thereafter.

It is expected that a very small number of patients (~1%) will develop a postoperative 'electrical storm' with repetitive episodes of VT or VF. This may be a result of transient decompensation of CHF. In this circumstance, some antiarrhythmic drug intervention might be required at least for a limited period. Magnesium is the recommended drug of first choice under this circumstance, followed by lidocaine, and procainamide until the patient recovers from surgery. Once the arrhythmia is suppressed and the patient is stable, the patient should be discharged from the hospital off of all antiarrhythmic drugs if clinically reasonable. Alternatively, antiarrhythmic medication can be continued for the first postoperative month and then discontinued. Any need to continue the medication upon hospital discharge must be discussed with the Clinical Coordinating Center. Similarly, a decision by the local PI to use amiodarone must be discussed first with the Clinical Coordinating Center.

Patients will be followed in clinic one week, four weeks, and every three months after ICD insertion for wound inspection, device interrogation, pacing threshold determination, electrogram amplitude and morphology observation during sinus rhythm, and lead impedance measurement. All of these evaluations will aid in ensuring the functional integrity of the lead system and the device.

Any treatment by the ICD will be categorized according to the data available in the event log. Any subject aware of a shock by the device will be requested to notify the local nurse coordinator and an event report form will need to be completed. The device should be interrogated and saved-to-disk within 48 hours after the event to ensure appropriate therapy has been delivered. Subsequently, the institutional investigator will categorize the event on the event forms and transmit the ICD interrogation to the Clinical Coordinating Center/ICD Memory Log Core Laboratory as described below.

ICD Follow-up post implant: 1wk, 1mo, 3mo, and every 3mo thereafter:

Set-up: Obtain Medtronic Model # 9790 Programmer. Attach surface ECG gray cable with electrodes from ICD programmer to patient. To activate programmer: locate plug on the backside of programmer and plug into a three pronged electrical outlet, turn on switch located on the left side of the programmer, place magnetic wand over ICD and position wand until the green light meter illuminates at least half way (this assures an adequate telemetry link is established.) The wand needs to stay over the ICD continuously during the follow-up check. Access the electronic pen attached to programmer located under the front lid (the electronic pen will allow you to drive the programmer,) select the *Automatic Model Select* icon located on the top middle part of the screen (this will load the appropriate ICD model 7223 software.)

ICD Follow-up procedure checklist:

- ❑ Interrogate ICD (initial interrogation)
- ❑ *Save-to-Disk* twice using two separate diskettes
- ❑ Print *Full Summary* report
- ❑ Measure *Pacing Lead Impedance*, print report
- ❑ Measure *Pacing Threshold* @ 4V, print report
- ❑ Record *P-/S to P+/S EGM*, print EGM strip (@ 1 mm/mV)
- ❑ Record *HVA to HVB EGM*, print EGM strip (@ 1mm/mV)
- ❑ Reprogram ICD if necessary
- ❑ Clear ICD memory
- ❑ Interrogate ICD (final interrogation)
- ❑ *Save-to-Disk* twice using two separate diskettes
- ❑ Store one diskette with the patient's records
- ❑ Send one diskette (electronically or via mail) to the ICD Memory Log Core Laboratory
- ❑ Complete Follow-up Form

Detailed ICD Follow-up procedure:

1. Initial interrogation with Save-to-Disk:
With the wand positioned over the ICD select *Interrogate* icon located on the bottom right side of screen. For each interrogation, it is important that all ICD data is interrogated, including Episode Data, EGM strips, Event Trend Data, and R-R Interval Data. Immediately following successful interrogation insert a 3½" diskette into the disk drive located on the right hand side of the programmer, select the *Special* icon located on the top right side of screen, then select *Save to Disk* from the menu. Replace the diskette that is currently in the drive with another diskette and select *Save to Disk* again. One diskette will be kept with the patient's records and the other will be sent to the ICD Memory Log Core Lab. To print a hard copy select the *Print* icon located on the top right hand side of the screen, then select *Full Summary* from the menu and this will printout the full summary interrogation.

2. Episode Retrieval:
If the ICD counters indicate an episode or episodes have occurred and you want to retrieve the stored intracardiac electrogram (EGM) data, after an initial interrogation and save-to-disk (including Episode Data, EGM strips, Event Trend Data, and R-R Interval Data,) select *Data* icon located on the top left side of screen, then select *Episode Data* from the menu. This will give you a log of episode(s) including date and time with the most recent episode listed first, if any episodes are stored. To view the stored EGM data, select an individual episode from the episode log. This will bring the stored EGM onto the programmer screen for viewing. To view the entire episode, scroll through using the cursors on the screen directly below the EGM strip. To print an episode, highlight the episode you want to print then select *Print Episode* icon located on the right hand side of the screen.

3. Pacing Lead Impedance:
Select *Tests* icon located on the top portion of the screen, then select *Pacing Lead Impedance*. To perform a pacing lead impedance press *Deliver* icon located on the bottom right hand portion of screen. A single paced beat will be synchronized on an R wave and a measured pacing lead impedance value will be recorded in the center of the screen.

4. Pacing Threshold at 4V:
To perform, select the *Tests* icon located on the top portion of the screen, then select *Pacing Threshold*. To perform a pacing threshold adjust the following parameters: pacing rate to a rate higher than the patients intrinsic rate by selecting the pacing rate icon which will give you a menu of rate parameters, leave the amplitude at 4.0V, turn auto decrement OFF, set the pulse width to 0.03 ms with the downward cursor. Using the *Deliver* icon in the right hand corner of the screen take the electronic pen and press the *Deliver* icon continuously, if capture occurs then the pacing threshold is ≤0.03 ms, if capture does not occur then increase pulse width to the next parameter (0.06 ms) with the upward cursor icon, repeat the same steps until capture is determined. The lowest pulse width where capture is determined is the threshold.

5. Real-Time Near-field EGM (P-/S to P+/S) and Far-field (HVA to HVB):
To check the near-field electrogram, select *Parameters* icon, go to *EGM source* icon in the menu and select. This will bring up a screen indicating which EGM source is programmed. The EGM source programmed should be *HVA to HVB (far-field.)* To obtain a real-time near-field EGM select the *white* window immediately next to *EGM Source* which will pull down a menu of four EGM sources, select *P-/S to P+/S (near-field,)* then press *Program* icon on the bottom right hand side of the screen. If the command is received by the ICD, the dashed box surrounding *P-/S to P+/S* will disappear. To obtain a recording, simply press the 25 mm/s small circular blue button to the left of the programmer handle. **Do not press the large square blue button with the yellow Z. This will deliver a manual 30J shock to the patient.** Pressing the 25 mm/s blue button again will stop the recording. The cursors below the EGM icon are for adjusting the EGM amplitude signal/calibration either larger or smaller (i.e., 0.2 mm/mV, 0.5 mm/mV, 1 mm/mV, 2 mm/mV, 5 mm/mV.) A 1 mm/mV real-time EGM recording measurement is requested. To obtain a real-time far-field EGM select the *white* window immediately next to *EGM Source* which will pull down a menu of four EGM sources, select *HVA to HVB (far-field,)* then press *Program* icon on the bottom right hand side of the screen. If the command is received by the ICD, the dashed box surrounding *HVA to HVB* will disappear. To obtain a recording, simply press the 25 mm/s small blue button to the left of the programmer handle. Once this recording is obtained leave the EGM source programmed to *HVA to HVB*.

6. Final interrogation with Save-to-Disk:
Prior to the final interrogation, ICD memory must be cleared. To do this, select the *Data* icon located on the upper left hand portion of the screen, then select *Clear Data* from the menu, then select *Clear Episode Data* icon, then *Continue* or *Program* icon to clear data. After the ICD memory has been cleared, select *Interrogate* icon located on the bottom right side of screen. Immediately following successful interrogation insert a diskette into the diskette drive located on the right hand side of the programmer, then select the *Special* icon located on the top right side of screen, then select *Save to Disk* from menu. Replace the diskette that is currently in the drive with another diskette and select *Save to Disk* again. Send one labeled diskette (including patient's SCD-HeFT ID #) to the SCD-HeFT ICD Memory Log Core Laboratory and keep one diskette with the patient's records. To print a hard copy, select the *Print* icon located on the top right hand side of the screen, then select *Full Summary* from the menu and this will printout the full summary interrogation.

ICD Data Transmission:
After all necessary interrogations have been performed and the data has been saved-to-disk, the data files must be sent to the ICD Memory Log Core Laboratory. See Section 15 for information on ICD data transmission.

ICD DATA FILE TRANSFER ADDRESSES

SCD-HeFT World Wide Web (WWW) home page:

http://scdheft.cardiology.washington.edu

If you receive DNS errors, use the equivalent numerical (IP) address of:

http://140.142.231.3

SCD-HeFT general e-mail address:

scdheft@u.washington.edu

ICD Memory Log Core Laboratory e-mail address:

icdlab@u.washington.edu

ICD Data Transmission Directions

After all necessary interrogations have been performed and the data has been saved-to-disk, the ICD data files must be sent to the ICD Memory Log Core Laboratory. Three methods may be used to send the data:

1. **WWW** (World-Wide-Web)

   ICD data files can be sent to the ICD Memory Log Core Laboratory by accessing the SCD-HeFT web site at **http://scdheft.cardiology.washington.edu** and going to the **ICD Data File Transmission** page. Complete instructions are provided there. Not all web browsers support this method of file transmission. A complete list of compatible web browsers is presented on the ICD Data File Transmission page.

2. **E-mail**

   ICD data files can be sent to the ICD Memory Log Core Laboratory by including or attaching the data files to an e-mail message addressed to the SCD-HeFT ICD Memory Log Core Laboratory. For complete instructions on how to set up this type of data transmission, send e-mail to: **icdlab@u.washington.edu**

3. **Public mail system** using diskette mailers

   The diskettes can be mailed to the ICD Memory Log Core Laboratory using a diskette mailer addressed to:

   SCD HeFT Clinical Coordinating Center
   7900 East Green Lake Drive North
   Suite 300
   Seattle, WA 98103

   The total cost of this method is over $1 per diskette, including the cost of the diskette, mailer, postage, and return of the diskette and mailer to the study center. All diskettes and pre-addressed diskette mailers will be provided to the study centers.

Accompanying each ICD data file should be a short memo which includes the patient's study ID and a description of each data file, e.g., "*18 month follow-up, initial interrogation*" or "*Between 21 and 24 month follow-up, ICD tachy therapy delivered, final interrogation*." For web site transmission, this information is entered on the **ICD Data File Transmission** page and is automatically sent along with the ICD data file. For e-mail messages, include this memo in the body of the e-mail message used to send the ICD data files. For diskettes mailers, this memo should be included in the diskette mailer or on the diskette label.

Study centers are strongly encouraged to use one of the electronic methods of data transmission because of the ease of use and low associated costs. Also, it is more efficient and convenient for the ICD Memory Log Core Laboratory if the data files are received electronically.

When the files are received by the ICD memory Log Core Laboratory, they are entered into a database and scanned for potential programming errors. If a potential error is detected, the study center will be

contacted to determine if it is fact an error. For severe programming errors, such as VF therapies being programmed off, the patient should be seen at the earliest possible opportunity for ICD reprogramming. For less severe errors, such as the automatic capacitor formation interval being programmed off, the reprogramming can occur at the next scheduled visit. The study center will be notified if an ICD requires immediate reprogramming.

Each data file received by the ICD Memory Log Core Laboratory will be examined to look for bradycardic and tachycardic events provoking ICD therapy. Dr. Poole will review all tachyarrhythmic episodes and discuss the diagnosis with the study center electrophysiologist. A mutually agreeable diagnosis will be arrived at which will be reviewed by Dr. Bardy and quarterly by the ICD Electrogram Review Committee.

SCD-HeFT PHARMACY INSERVICE MANUAL

STUDY MEDICATION

Introduction

Accurate study drug accountability is very important to the success of the SCD-HeFT trial. It is recommended that one individual be responsible for maintaining the study drug accountability records throughout the trial. All entries into the records should be made in a timely and chronological fashion, preferably at the time of dispensing. Please make all entries in a **black ink**; no pencil, colored inks, or correction fluids are acceptable. Errors should be crossed out with a single stroke, the correct entry made, and the correction initialed and dated.

Supply and Receipt of Study Medication

The day before the arrival of a shipment, sites will receive a fax indicating the number of study drug kits in the shipment and a tracking number for the shipment. Should delivery be delayed, the site personnel can use the shipment's tracking number to determine the status of the delivery simply by calling the toll free number provided. (sample fax attached)

All sites will receive 4 study drug kits in the initial shipment; each kit will contain 6 bottles of 70 tablets of Amiodarone 200mg or placebo for a total of 420 tablets, enough study drug supply for 1 patient for 6 months.

The accountability of study medication will be as follows:

With each shipment, the sites will receive a shipping document envelope containing:

- Two SCD-HeFT Packing Invoices for the enclosed study drug kits (sample invoice attached)
- One Study Drug Accountability Record for each study drug kit (sample record attached)
- One sample patient instruction card—initial shipment only. (sample card attached)

Upon receipt of study drug, the following checks should be performed against the Packing Invoice.

- Check for any obvious damage to the materials.
- Verify the correct number of drug kits were received and that the seals are intact.
- Verify that the Kit Numbers on the study drug kits match the Kit Numbers on the Packing Invoice.

Upon verification of information, sign and date both Packing Invoices. Keep one invoice for your records and return the other copy to the DCRI Pharmacy. If there are problems with the study drug shipment, notify the DCRI Pharmacy at 919-286-8880.

All study drug kits should be stored together in a secure location at room temperature (approximately 77° F.)

Study Medication, Dispensing and Return

Visit #1: Randomization Visit

Study medication dispensed:
Once the patient is randomized into the SCD-HeFT Drug Therapy arm and a five digit Study Kit Number is assigned to the patient by the Randomization personnel:

- Retrieve the assigned study drug kit and carefully check it against the assigned Study Kit Number to ensure you have chosen the correct kit.
- Dispense the bottle labeled *initial load bottle* – it is marked with a number 1 circle sticker on top of the bottle and ONE additional bottle. Complete patient initials, "dispensed by" and "date" (day of dispensing) areas on the label; calculate, based on the patient's weight, the number of tablets to be taken daily and fill in the instruction card and label of the second bottle. Give to the patient.
    - < 150 lbs 1 tablet (200mg) daily
    - 150-200 lbs 1.5 tablets (300mg) daily
    - >200 lbs 2 tablets (400mg) daily

- Give patient the SCD-HeFT wallet identity card and instruct the patient to keep it with him/her at all times.
- Review the dosing instructions with the patient for the initial bottle.
- Dispensing information needs to be recorded on the Study Drug Accountability Record. An example of a properly completed accountability record is provided at the end of this section.

Visit #2: Follow-up Visit, 1 week

- Collect the patient's medication bottle(s) from the previous visit.
- Record the number of tablets returned on page 18 of the Follow-up Form.
- After counting and recording the number of tablets, return the study drug to the patient to complete the initial study drug load for month 1.
- Do not dispense an additional bottle of study drug at this visit.

Visit #3: Follow-up Visit, 1 Month

Study medication returned:

- Collect the patient's medication bottle(s) from the previous visit.
- Record the number of tablets returned on page 18 of the Follow-up Form. This information also needs to be recorded on the Study Drug Accountability Log. An example of a properly completed accountability log is provided at the end of this section.
- Store returned medication in the patient's drug kit. Refer to the section on Disposal of Unused Study Drug below for destruction information.

Study Medication dispensed:

- Retrieve the assigned study drug kit and carefully check it against the assigned Study Kit Number to ensure you have chosen the correct kit.
- Calculate the number of tablets to be taken daily based on the patient's weight.
    - **< 150 lbs 1 tablet (200mg) daily**
    - **150-200 lbs 1.5 tablets (300mg) daily**
    - **>200lbs 2 tablets (400mg) daily**
- Dispense one bottle from the patient's kit. Complete the patient initials, bottle number, number of tablets to be taken, "dispensed by" and "date" (day of dispensing) areas on the label.
- Record the number of tablets dispensed and the patient kit number on page 18 of the Follow-up Form. This information also needs to be recorded on the Study Drug Accountability Record. An example of a properly completed accountability record is provided at the end of this section.

All Remaining Visits: Follow-up Visits, Scheduled Every Three Months and Unscheduled

Study medication returned:

- Collect the patient's medication bottle from the previous visit.
- Record the number of tablets returned on page 18 of the Follow-up Form. This information also needs to be recorded on the Study Drug Accountability Record. An example of a properly completed accountability record is provided at the end of this section.
- Store returned medication in the patient's drug kit. Refer to the section on Disposal of Unused Study Drug below for destruction information.

Study Medication dispensed:

- Retrieve the assigned study drug kit and carefully check it against the assigned Study Kit Number to ensure you have chosen the correct kit.
- Dispense three bottles from the patient's kit. Complete the patient initials, number of tablets to be taken, "dispensed by" and "date" (day of dispensing) areas on the label.
- Record the number of tablets dispensed and the patient kit number on page 18 of the Follow-up Form. This information also needs to be recorded on the Study Drug Accountability Record. An example of a properly completed accountability record is provided at the end of this section.

Disposal of Unused Study Drug

Once the quantity of returned, unused study medication and the date returned is documented on the Study Drug Accountability Record, the returned study medication may be destroyed at the site by the approved hospital procedure for study drug destruction. The destruction date and initials of the individual responsible for the destruction must also be recorded on the study drug accountability record. This policy will also apply at the end of the study to any remaining study drug kits that were not randomized or used during the study time period. You will be asked to inform the DCRI Pharmacy what method of destruction was used for study drug destruction at your site.

Do not return any study drug to the DCRI Pharmacy.

Study Drug Resupply

A. During enrollment period
After receiving the initial supply of four study drug kits, the frequency of resupply as well as the number of enrollment kits in subsequent shipments will vary depending on enrollment at the site. The pharmacy database automatically tracks site enrollment; when a site reaches a preset threshold level of kits available for randomization (usually two,) the database automatically triggers a need to ship report. The drug kits will be shipped by an overnight delivery service.

B. Patient resupply
Once a patient has been randomized into the SCD-HeFT study, the pharmacy database will monitor individual resupply needs. The patient resupply kits will be shipped to the site the month before the current kit is depleted. This resupply system is automatic and requires no input from the sites. **Please note that patient resupply kits will be labeled with the patient's enrollment number which remains the same throughout the study**. However, actual kit numbers will change with each resupply.

Lost Medication

In the event that a patient misplaces or loses study medication, site personnel should dispense an additional bottle from the patient's study drug kit. Each time a replacement bottle is dispensed, please notify the DCRI-P by completing the replacement fax (sample fax attached.) This will ensure that patient resupply will occur at the proper time.

If you have any questions concerning study drug supply and accountability, please contact Jenny Mabie at the DCRI Pharmacy (01-919-286-8880 or beeper 01-919-970-9671.)

Breaking study blinds and alternate therapies:

SCD-HeFT UNBLINDING PROCEDURE

- Contact SCD-HeFT site principal investigator (PI) to discuss reasons for unblinding
- If treatment is to be unblinded, call the DUKE HOTLINE at 1-800-545-3853.
- Personnel at the DUKE HOTLINE will conference into the conversation Dr. Gust Bardy or his designee to authorize unblinding of study patient.
- Site PI and SCD-HeFT clinical trial director determine whether to seek unblinding the treatment or not.
- Upon receipt of the authorization, HOTLINE personnel will provide the unblinded treatment to the site personnel.

A principal goal of this study is to avoid breaking study drug blinds or making therapeutic alterations that may affect study outcome. There are, however, several possible symptoms and events that might lead to breaches in protocol. These are discussed below.

As a general consideration to any alteration in study protocol, be it the use of ICD or pacemaker therapy or the use of a new antiarrhythmic drug or amiodarone, the decision to do so must first be discussed with the local site principal investigator. Subsequently, the site PI and the SCD-HeFT Clinical Trial Director must both agree that a breach in protocol or initiation of alternative therapy is clinically indicated for good patient care. In addition, the Study Biostatistician must be notified before study drug or ICD therapy is discontinued. All cases will be reviewed by the Data and Safety Monitoring Board (DSMB) for appropriateness of action at their semi-annual meetings. The following clinical problems can or may alter investigative therapy:

A. Terminations.

1. Deaths. Patient deaths constitute the primary study endpoint.

2. Withdrawal of consent. If after discussion with the patient by the site PI, consent is withdrawn, the reason for consent withdrawal will be discussed with Dr. Bardy and forwarded in writing to the Biostatistical Data Coordinating Center. The institutional Investigational Review Board will also be notified. The patient will then be censored at that point in time from continued monitoring within the trial.

3. Loss to follow up. Efforts to locate the patient through contact with family and employer will be made. By working with the sites and providing instruction and suggestions on maintaining contact with these patients, it will be a high priority in this trial to keep losses to follow-up to a minimum.

B. Permanent discontinuation of study drug.

1. Torsades de Pointes. Torsades de Pointes (TdP) unexplainable by other clinical circumstances is reason for drug discontinuation. TdP from amiodarone is rare [Hohnloser 1994.] If breaking the blind is an integral part of patient management, a discussion with the Trial Director is required. Note that the incidence of TdP in some placebo controlled amiodarone trials has been the same in both arms so the implication of amiodarone in TdP must be based on very strong evidence.

2. Aborted cardiac arrest. If the patient develops an aborted cardiac arrest while on study drug, then the drug blind may be broken. Therapy should proceed in a fashion consistent with the institution's routine practices. However, every effort should be made to maintain the patient on study drug if a precipitating and reversible cause for the cardiac arrest can be identified. Hypoxia, worsening CHF, ischemia, electrolyte imbalance, digoxin toxicity, etc., should be examined to rule out any treatable causes responsible for the patient's cardiac arrest. Patients resuscitated from a cardiac arrest will not be considered to have reached the primary trial endpoint and will continue to be followed on an intention-to-treat basis. Cardiac arrest is, however, a secondary endpoint of the study. A cardiac arrest survival form will need to be completed for patients who survive a cardiac arrest for 48 hours or more.

3. Symptomatic uncontrollable arrhythmias requiring treatment. Management of patients with symptomatic, documented nonsustained or sustained VT will be similar to those recovered from cardiac arrest. As with patients resuscitated from cardiac arrest, open label amiodarone or antiarrhythmic drug therapy or ICD therapy remain alternatives if the managing physician and Dr. Bardy believe this to be in the patient's best interest. Nonsustained or sustained VT not resulting in symptoms should not be treated and does not constitute a reason for study drug discontinuation.

4. Syncope or near syncope of uncertain etiology. Patients experiencing syncope or near syncope where no specific etiologic factor can be identified after a conventional evaluation, should not receive any new therapy or alteration of their pre-existing therapy merely on the basis of this complaint. In the event that an electrophysiology study is undertaken, and the results deem therapy is necessary, then the Trial Director will be notified and a decision will be made regarding the appropriateness of breaking the drug blind for purposes of patient care.

5. Pulmonary toxicity. The possibility of amiodarone related pulmonary toxicity will require exclusion of congestive heart failure and pneumonia as the cause for deterioration in pulmonary function. This can be difficult. Previous placebo controlled trials of amiodarone tend to over-diagnose pulmonary toxicity. Characteristic chest X-ray and pulmonary gallium scan patterns [Kudenchuk 1984, Fraire 1993], together with the exclusion of CHF and pneumonia, will be required prior to discontinuation of study drug. If the managing physician believes pulmonary toxicity is present, the patient should be managed first by a decrease in the study drug dose before discontinuing the study drug altogether, if clinically reasonable. Study drug can be held for 1-2 weeks and reinstituted at a lower dosage, preferably 100 mg qd below the initially employed dosage, in patients without life-threatening pulmonary disease.

6. Hepatic toxicity. Hepatic toxicity is a reason for study drug discontinuation or dose decrease if liver function tests (SGPT, SGOT, LDH and/or bilirubin) exceed 2.5 times normal and their rise is not attributable to other obvious secondary causes. As with other problems deemed secondary to amiodarone, we strongly encourage a temporary discontinuation of the drug for 1-2 weeks followed by a reinstitution of amiodarone at a lower dosage, preferably 100 mg qd below the initially employed dosage.

7. Other side effects. Intolerable side effects at the lowest possible dosage of study drug is reason for study drug discontinuation but only after such side effects from other drug causes have been excluded and lower doses have been tried for reasonable periods of time.

C. Permanent discontinuation of ICD therapy.

1. Sepsis. The only indication for permanent discontinuation of ICD therapy in patients randomized to the ICD arm is sepsis resulting from ICD infection. Pocket infections do not necessarily constitute reasons for permanent discontinuation of ICD therapy (see paragraph E below.)

D. Study drug temporary discontinuation or dosage decrease.

1. Surgery. The study drug can be continued up to the time of surgery (general or cardiac) for whatever reason. Study drug may be held post-operatively until the patient is able to accept medications by mouth, but oral intake should be resumed within 72 hours.

2. Bradycardia. Symptomatic sinus bradycardia or complete heart block occurring after randomization may require permanent pacing. A decision to implant a pacemaker does not constitute reason for withdrawal from the study. A temporary discontinuation of study drug may be necessary if, in the opinion of the investigator, the study drug has been implicated in the heart block and permanent pacing is not an option. Otherwise, we strongly encourage a lowering of the study drug dosage or continuation of the study drug with permanent pacemaker therapy. If the institutional PI is considering discontinuation of study drug, consultation with the Trial Director is indicated.

3. Side effects. In the event of persistent intolerable side effects attributable to the study drug, the dosage may be decreased or temporarily omitted for 1-2 weeks. The patient will be rechallenged with the same dose or with a lower dose. Should intolerable side effects continue, the study drug will be discontinued after consultation with the Trial Director. All attempts to continue treatment are strongly encouraged. No medication should be permanently discontinued without notification of the Trial Director and Study Biostatistician.

4. Thyroid dysfunction. Laboratory evidence of hyper- and hypothyroidism are not reasons for study drug discontinuation. However, symptomatic thyroid abnormalities may be cause for lowering of study drug dosage or temporary drug discontinuation after consultation with the Trial Director.

E. Temporary discontinuation of ICD therapy.

1. Superficial dermal infections. Superficial dermal infections over the ICD do not constitute reasons for discontinuation of ICD therapy and should be treated with antibiotics.

2. ICD pocket infections without sepsis. ICD pocket infections without sepsis do not necessarily constitute reasons for permanent discontinuation of ICD therapy. In the event an ICD infection necessitates explantation, the patient should receive appropriate antibiotic coverage until reimplantation can be considered in the right infraclavicular area or elsewhere in the left infraclavicular area. This should be done within 1—2 months following explantation of the original ICD. Because of the intention-to-treat principle, these patients will remain in the ICD arm of the study whether or not re-implantation occurs. Consequently, every effort to re-implant should be made.

F. Symptomatic bradycardia in the ICD arm.

1. Patients with symptomatic bradycardia not relieved by the VVI pacing capabilities of the ICD in the group randomized to ICD therapy will need to be considered for atrial or dual chamber pacing if no reversible cause of the bradycardia is found. If a reversible cause can be identified, every attempt should be made to avoid the addition of a second device. If an atrial or dual chamber pacemaker must be inserted, care should be taken to avoid interference with the normal function of the ICD. If possible, an atrial pacemaker should be used if the dominant problem is sinus node dysfunction and AV abnormalities are infrequent. If a dual chamber system must be used, the RV pacing lead should probably be screwed high into the RV septum to avoid contact with the RV defibrillation lead.

G. VT/VF in the ICD arm.

1. Aborted cardiac arrest. Aborted cardiac arrest occurring in patients with an ICD does not necessarily merit antiarrhythmic drug therapy. Prior to initiation of antiarrhythmic drug therapy, the device should be interrogated and the detection and/or therapy algorithms adjusted to better treat the patients arrhythmia if clinically reasonable. At least two episodes of VT or VF should occur prior to considering long term use of antiarrhythmic drugs. Initiation of antiarrhythmic drugs will require prior discussion with the Trial Director. Hypoxia, worsening CHF, ischemia, electrolyte imbalance, digoxin toxicity, etc., should be examined to rule out any treatable causes responsible for the patients cardiac arrest. If there is evidence of monomorphic VT on the ICD memory log, then the managing electrophysiologist should consider activation of antitachycardia pacing. Otherwise, the ICD should remain programmed to its original parameters unless clinical and ICD memory findings suggest that ICD diagnostic and therapeutic algorithms can be improved with reprogramming. Any patient with an ICD resuscitated from a cardiac arrest will require a chest X-ray to ensure that there is no lead fracture or lead dislodgment responsible for the arrest. Patients resuscitated from a cardiac arrest in the ICD arm will not have reached the primary trial endpoint and will continue to be monitored.

2. Syncopal VT. Syncope resulting from nonsustained or sustained VT in patients with an ICD do not necessarily merit antiarrhythmic drug therapy and generally should be managed in a manner similar to patients resuscitated from a cardiac arrest.

The following EQOL instructions and data forms can be downloaded from the SCD-HeFT web site. See Section 22 for more information on accessing the web site.

EQOL Baseline Data Collection Protocol
EQOL Follow-up Data Collection Protocol
Economic Data Collection Protocol
EQOL Baseline Questionnaire Summary
EQOL Baseline Questionnaire
EQOL Follow-up Questionnaire Summary
EQOL Follow-up Questionnaire
EQOL Follow-up Proxy Questionnaire

The following clinical data forms and instructions can be downloaded from the SCD-HeFT web site. See Section 22 for more information on accessing the web site.

Randomization Form
Baseline Case Report Form
Supplemental Medication Form - Beta Blocker Therapy
ICD Implant Form
Follow-up Form
Cardiac Arrest Survival Form
Patient Discontinuation Form
Death Report Form
Notification of Patient Death Form
Missed Visit Notification Form
Comments Form
ICD Complication Reimbursement Cover Sheet
T–Wave Alternans Sub-Study Cover Sheet
French-Canadian version of Living with Heart Failure Questionnaire (for Baseline Case Report Form)
French-Canadian version of Living with Heart Failure Questionnaire (for Follow-up Form)

Clinical Data Form Instructions

The following substudies have been approved as part of the SCD-HeFT study:

VO_2max: A VO_2max is not a mandatory part of the study but is highly recommended as a baseline measure and at 1 and 2.5 years follow-up. Given the expense and difficulty of coordinating a uniform protocol at all 95 centers, the data are not mandatory.

Troponin I: Troponin I levels will be obtained at the outset at the following institutions (Ochsner Clinic, University of Washington, ? other sites can enroll too.) If a center is interested in participating, please contact Dwight Stapleton, MD at the Ochsner Clinic at 1-504-842-3439.

T–wave alternans: T–wave alternans measurements are not yet formalized substudies in SCD-HeFT. Centers interested in conducting these measurements may come on line as funding is secured and the methodology defined. Please direct inquiries to Dr. Michael Gold at 1-410-328-6056.

Six-minute walk test:

The Six-Minute Walk Test will be administered at baseline immediately prior to randomization and at every 6 months following randomization.

The test will be conducted in an enclosed corridor that is free of traffic, obstacles and distractions. A pre-measured 60 foot length of corridor should be used for the test. Chairs will be placed at either end of the 60 feet as distance markers. In addition, the corridor should be discretely divided into 5 foot sections for ease of distance calculation. Patients may eat a light meal 3 to 4 hours before the test. Patients should refrain from smoking for at least 2 hours prior to the test. Routine cardiovascular medications may be given 2 hours or more prior to the test.

Patients will be asked to walk at their own pace from chair to chair attempting to cover as much ground as possible during 6 minutes. They may rest whenever necessary. The walk test will be terminated prior to the 6 minutes only if the patient has developed severe shortness of breath, lightheadedness, angina, or musculoskeletal pain. Prior to the walk test, patients will be asked to sit quietly for 10 minutes in one of the two chairs. Patients will be instructed to walk from end to end of the 60 foot course in the following manner:

> *"The purpose of this test is to find out how far you can walk in 6 minutes. You will walk from this chair to the chair at the end of the hallway, then turn and, without pausing, walk back. You will continue to walk back and forth from chair to chair as many times as you can in the 6 minute period. If you need to, you can stop and rest, and then continue on when you are ready. The most important part about this test is that you cover as much distance as possible in the 6 minutes."*
>
> *"I will let you know the time intermittently. I will let you know when the 6 minutes are up by saying 'STOP'. At that time, you should stop walking and stand right where you are."*
>
> *"Do you have any questions about the test?"*

The person administering the walk test should answer any questions that the patient may have. The patient should then be asked to repeat what he or she has been asked to do in the following manner:

> *"Please explain to me what you are going to do."*

Repeat the following:

> *"The most important part about this test is that you cover as much distance as possible in 6 minutes."*

Begin the test by stating:

"Start when I say 'Begin'."

The patient should be encouraged every 30 seconds in a standardized fashion using one of the two following phrases:

"You're doing well." or "Keep up the good work."

If the patient is not concentrating on the walk test, the person administering the test should use the following phrase:

"Remember, concentrate and walk as far as you can go."

If the patient slows down and expresses that he or she wants to rest, the following information should be delivered:

"If you need to, you can stop and rest, just remain in your spot until you are ready to start again."

The walk test administrator should call out the time at 2 minute intervals using the following phrases:

"You have walked 2 minutes," "You have walked 4 minutes."

The test administrator should not respond to questions about the time and distance elapsed.

When the 6 minutes have elapsed, the person administering the walk test should say:

"Stop, remain where you are for just a minute."

The test administrator will need to count the lengths (distance one way) walked during the test time and the length of the partial lap completed. Data to be collected will include: patient identifiers, date and time of test, total distance walked, whether or not patient is symptomatic.

When the distance walked has been recorded the patient will be instructed to sit down and will be observed for 10 minutes.

A World-Wide-Web (WWW) internet site has been established for the SCD-HeFT trial for the following reasons:

1. **To facilitate the dissemination of up-to-the-minute, SCD-HeFT related information to all of the study centers participating in the trial.** This information includes news, data forms and other study materials, and a directory of addresses, phone numbers, and e-mail addresses. Data forms and other documents will be available for downloading in a form that is computer-platform independent, so that all study centers will have access regardless of the computers they use. This method of information exchange may help reduce personnel workload and expenses relating to mailings, phone calls, and faxes if these resources are fully used by the study centers.

2. **To provide access to software aids such as the follow-up scheduling utility.** See Section 23 for more information on generating patient-specific follow-up schedules.

3. **To provide a convenient and reliable method of transmitting ICD data files to the ICD Memory Log Core Laboratory.** It is our goal to have as many study centers as possible use this method of ICD data file transmission due to its low cost, high reliability, and convenience for both the study centers and the ICD Memory Log Core Laboratory. This is discussed further in Section 15.

4. **To provide a means of communication via on-line conferencing**. A conference center has been set up at the web site which enables study participants to ask questions on-line. Questions that others have asked can be reviewed or participants can provide help to others. Each conference section will be overseen by Data Coordinating Center and Clinical Coordinating Center personnel who will answer questions and serve as conference moderators. The conference center is divided into sections relating to various aspects of the trial, including *Announcements*, *Data Collection Issues*, *EQOL Issues*, *Follow-up Visit Procedures*, *Heart Failure Management*, *ICD Data Issues* and *ICD Surgery & Programming Issues*. In addition, a private conference center has been established for the members of the various SCD-HeFT Committees to discuss committee business.

The address of the SCD-HeFT WWW site is: **http://scdheft.cardiology.washington.edu**

The WWW site will not be open to the general public. Each study participant will be allowed to select a log-on name and password in order to gain access. The Clinical Coordinating Center can be contacted to request a log-on name and password and they can be registered or changed via a utility on at the web site. The Clinical Coordinating Center can be contacted at (206) 616-6060 or by e-mail at: **scdheft@u.washington.edu**

We strongly encourage study centers to fully use the resources available at the WWW site.

In order to aid the study centers with follow-up visits, a utility is available on the SCD-HeFT WWW site (**http://scdheft.cardiology.washington.edu**) for generating a patient-specific follow-up schedule. This utility creates a list of the procedures and tests to be performed at each follow-up visit. The approximate date of each scheduled follow-up visit will also be shown, with all dates falling on a Monday (except for the initial and 1 week visits.) The allowable range of dates for each scheduled follow-up visit is shown as well. The schedule can be printed and kept with the patient's records for future reference. Each test shown can be checked off as it is performed and the patient's next visit can be scheduled based on the approximate date indicated on the schedule.

This utility can be accessed on the **Follow-up Scheduling** page at the SCD-HeFT WWW site. Complete instructions for generating and printing a follow-up schedule are presented there. If the web site is inaccessible, the Clinical Coordinating Center can be contacted and a patient's follow-up schedule will be generated and faxed or mailed to the study center.

An example follow-up schedule is shown on the next page.

Example Follow-up Schedule:

Initials: ABC

Study ID: 001-001

Week of (Allowable Range)	Visit	Scheduled Procedures											
09/01/97 ( )	Initial	1	2	3	4	5	6	7	8	9	10	11	12
09/08/97 (09/06 - 09/15)	1 week	1							8			11	
09/29/97 (09/16 - 10/31)	1 month	1							8			11	12
12/01/97 (11/01 - 01/12)	3 month	1		3					8		10	11	
03/02/98 (01/13 - 04/12)	6 month	1		3			6		8			11	12
06/01/98 (04/13 - 07/13)	9 month	1							8			11	
08/31/98 (07/14 - 10/13)	12 month	1	2	3	4	5	6	7	8	9	10	11	12
11/30/98 (10/14 - 01/12)	15 month	1							8			11	
03/01/99 (01/13 - 04/12)	18 month	1		3			6		8			11	12
05/31/99 (04/13 - 07/13)	21 month	1							8			11	
08/30/99 (07/14 - 10/13)	24 month	1	2	3	4		6	7	8	9		11	12
11/29/99 (10/14 - 01/12)	27 month	1							8			11	
02/28/00 (01/13 - 04/12)	30 month	1		3		5	6		8		10	11	12
05/29/00 (04/13 - 07/13)	33 month	1							8			11	
08/28/00 (07/14 - 10/13)	36 month	1	2	3	4		6	7	8	9		11	12
11/27/00 (10/14 - 01/12)	39 month	1							8			11	
02/26/01 (01/13 - 04/12)	42 month	1		3			6		8			11	12
05/28/01 (04/13 - 07/13)	45 month	1							8			11	
08/27/01 (07/14 - 10/13)	48 month	1	2	3	4		6	7	8	9		11	12
11/26/01 (10/14 - 01/12)	51 month	1							8			11	
02/25/02 (01/13 - 04/12)	54 month	1		3			6		8			11	12
05/27/02 (04/13 - 07/13)	57 month	1							8			11	

Procedure codes

1 = History and Physical	7 = TSH
2 = CBC	8 = 12-lead ECG
3 = Chemistry Panel	9 = Chest X-ray
4 = INR	10 = QOL Questionnaire
5 = LV Ejection Fraction	11 = ICD Interrogation
6 = 6 Minute Walk	12 = Digoxin Level

SCD-HeFT - CEC Review Process

This section provides a brief outline of the Clinical Events Group at the Duke Clinical Research Center. The Clinical Events Committee (CEC) classifies and validates suspected clinical events that relate to primary or secondary endpoints. This process involves the identification of suspected events, procurement of supporting documentation and classification of events through independent reviews using pre-defined criteria based on supporting documents. It includes a description of the events to be reviewed, how patients are identified, the records that will be procured and used for review, a system for tracking the status of the review process, and a system for documentation of adjudicated events.

The SCD-HeFT Trial
The primary endpoint for SCD-HeFT is to compare all cause mortality based on a minimum of 2.5 years of follow-up in the three arms of the study. All patients suspected of having a death event will be reviewed by the CEC.

- 2500 patients to be enrolled
- 25% estimated Death rate

The secondary endpoints for SCD-HeFT are:

- To compare arrhythmic cardiac mortality in the three arms of the study.
- To compare non-arrhythmic cardiac mortality in the three arms of the study.
- To compare morbidity in the three arms of the study, defined as all cause mortality and re-hospitalization for congestive heart failure.
- To compare health-related quality of life in the three arms of the study.
- To compare cost of care for each treatment group and calculate incremental cost-effectiveness ratios for the two intervention arms.

Additionally, all patients suspected of having ICD complications will be reviewed.

The Clinical Events group will classify and validate ICD complications and/or Death events for the SCD-HeFT Trial. All other endpoints will be classified through data collection and statistical analysis.

Identifying Cases for Review
Events will be identified from the CRF and Follow-up data. The CEC will be alerted of all cases in which suspected ICD complications and/or Death have occurred. The identification process will be assisted by a computer program which will identify cases for review from key data fields in the CRF and from the Follow-up data. Source documentation will be requested and reviewed in cases where circumstances indicate that an ICD complication and/or Death event definitely, probably or possibly may have occurred.

Medical Records for Review
Patient medical records will be necessary for the CEC to complete the review process. The site coordinators are aware that these documents will be needed for endpoint review and requests for medical records are processed through the site coordinators to the extent possible. Records may be requested directly from the treating institution following receipt of patient consent in selected circumstances where a site coordinator cannot perform this task. All records will be blinded prior to release to the CEC. The CEC Clinical Coordinator will be responsible for requesting and tracking all medical records.

Please refer to the attached document to identify the source documentation that will be requested and used in the clinical review process.

Events to be reviewed:

Death
The CEC will validate the date and time of death. Classification of the cause of death will be determined by physician review. Deaths will be described in terms of primary organ cause, the relationship to operations, and documentation. A classification of **unknown** will be used for patients for whom confirming descriptive documentation of death cannot be obtained.

ICD Complications
Classification of a complication as it relates to the ICD implant will be determined by physician review. This review will include the approval of any site reimbursement for valid ICD complications.

Data regarding criteria used for adjudication and the validating source documentation will be collected and entered into the CEC database.

The CEC Process
The CEC will identify all patients with ICD complications and/or Death and will coordinate the procurement and processing of all relevant documentation and the review of suspected events by expert medical reviewers.

Deaths will be reviewed independently by two physician members of the Clinical Events Committee. If the two reviewers agree, the suspected event will be considered resolved. If the two reviewers disagree, the case will be adjudicated after discussion by one full committee.

ICD complications will be reviewed independently by two physician members of the ICD Complication Committee. If the two reviewers agree, the suspected complication will be considered resolved. If the two reviewers disagree, the case will be adjudicated after discussion by one full committee.

Data Management
Every patient enrolled in SCD-HeFT will be entered into the SCD-HeFT trial database. Patients identified with a suspected ICD Complication and/or Death will be entered into the SCD-HeFT CEC database. The CEC database will track the disposition of identified patients, the status and details regarding medical records, the status and resolution of the clinical review process and the criteria and documentation used to adjudicate endpoint events. Data regarding ICD Complications and/or Death will be recorded in the SCD-HeFT event database.

Personnel Associated with the CEC Process

Support Team Personnel
The CEC Support Team is involved with the daily processing of medical records. Responsibilities include logging in received documents in a computerized tracking database, copying and distributing files to the Clinical Trials assistants when needed.

Clinical Trails Assistants
Clinical Trials Assistants identify and verigfy suspected clinical endpoints, review the source documents, and assemble the cases for review by the Clinical Coordinators and/or the Physician Reviewers.

Clinical Support
The Clinical support persons (designated nurse and/or physician) are responsible for answering any clinical questions that the Trial Assistant may have regarding the CRF, source documentation, events triggered or criteria used for adjudication.

Records Needed for SCDHeFT
Death and/or ICD Complications

Death

Form Needed

- Death Report Form

Records Needed

- MD and RN notes relating to event
- Discharge or Death Summary
- EMT Notes
- ER Notes
- History and Physical
- Consult Report
- Procedure Reports
- Autopsy Report
- All ECGs
- Lab Reports
- Pertinent Diagnostic Reports
- Death Certificate

ICD Complications

Form Needed

- ICD Complications Reimbursement Cover Sheet

Records Needed

-
- RECORDS NEEDED ARE TO BE DETERMINED PER COMPLICATIONS COMMITTEE
- WILL BE IDENTIFIED LATER
-
-
-
-
-
-
-
-
-
-

*All information needs to be typed or printed

1.	University of Washington Medical Center	Peter Kudenchuk, M.D. Wayne Levy, M.D.	Seattle, WA
2.	Mayo Clinic—St. Mary's Hospital Complex	Douglas Packer, M.D. Robert Franz, M.D.	Rochester, MN
3.	University of Maryland	Michael Gold, M.D. Stephen Gottlieb, M.D.	Baltimore, MD
4.	Midwest Heart Research Foundation	Michael O'Toole, M.D. Matthew Nora, M.D.	Lombard, IL
5.	Oregon Health Sciences University	Blair Halperin, M.D. Ray Hershberger, M.D.	Portland, OR
6.	Sentara Norfolk General Hospital	John Herre, M.D. John Parker, M.D.	Norfolk, VA
7.	Cardiology of Tulsa	Wayne Adkission, M.D. R. Douglas Ensley, M.D.	Tulsa, OK
8.	Loyola University Medical Center	Brian Olshansky, M.D. Marc Silver, M.D.	Maywood, IL
9.	Brigham and Women's Hospital	Michael Sweeney, M.D. Lynn Warner-Stevenson, M.D.	Boston, MA
10.			
11.	LDS Hospital	Sanjeev Trehan, M.D. David Rawling, M.D.	Salt Lake City, UT
12.	Michigan Heart & Vascular Institute.	Lorenzo DiCarlo, M.D. J. Peter Longabaugh, M.D.	Ypsilanti, MI
13.	Columbia Presbyterian Medical Center	James Coromilas, M.D. Deborah Aschein, M.D.	New York, NY
14.	Allegheny University Hospitals	Frances Marchlinski, M.D. Mariell Jessup, M.D.	Philadelphia, PA
15.	Pepin Heart Center	Stephen Mester, M.D. Juan Garcia, M.D.	Southfield, MI
16.	Montefiore Medical Center	Soo Kim, M.D. Rachel Bijou, M.D.	Bronx, NY
17.	University of Calgary, Foothills Hospital	Brent Mitchell, M.D. J. Wayne Warnica, M.D.	Calgary, Alberta
18.	University of Louisville	Igor Singer, M.D. Stephen Wagner, M.D.	Louisville, KY
19.			
20.	London Health Sciences Centre	Raymond Yee, M.D. Peter Pflugfelder, M.D.	London, Ontario
21.	Veterans Affairs Medical Center	Pamela Karasik, M.D. Peter Carson, M.D.	Washington, DC
22.	Institute de Cardiologie de Montreal	Mario Talajic, M.D. Guy Pelletier, M.D.	Montreal, Quebec
23.	University of Connecticut Health Center	Ellison Berns, M.D. W. David Hager, M.D.	Farmington, CT
24.	Maine Medical Center	Joel Cutler, M.D. Joseph Wight, M.D.	Portland, ME
25.	Mission Hospital	Stephen Ehrlich, M.D. Greg Thomas, M.D.	Mission Viejo, CA
26.	Medical College of Virginia	David Gilligan, M.D. Pramod Mohanty, M.D.	Richmond, VA
27.	Washington University Medical Center	Marye Gleva, M.D.	St. Louis, MO

		Joseph Rogers, M.D.	
28.	University of Kentucky	Andrea Natale, M.D.	Lexington, KY
		Andrew Cross, Jr., M.D.	
29.	Marshfield Clinic	John Hayes, M.D.	Marshfield, WI
		Shereif Rezkalla, M.D.	
30.	Optima Health - CMC	Bruce G. Hook, M.D.	Manchester, NH
		Robert C. Dewey, M.D.	
31.	Temple University Hospital	Henry Hsia, M.D.	Philadelphia, PA
		Ileana Pina, MD	
32.	Midical City - Dallas	Jodie Hurwitz, M.D.	Dallas, TX
		David Musselman, M.D.	
33.	Beth Israel Deaconess Medical Center	Mark Josephson, M.D.	Boston, MA
		Beverly Lorell, M.D.	
34.	New York University Medical Center	Larry Chinitz, M.D.	New York, NY
		Barry Rosenzweig, M.D.	
35.			
36.	Rhode Island Hospital	Dan Foreman, M.D.	Providence, RI
		Robert Lemery, M.D.	
37.	Duke University Medical Center	Ruth Ann Greenfield, M.D.	Durham, NC
		Christopher O'Connor, M.D.	
38.	Indiana University Medical Center	William Groh, M.D.	Indianapolis, IN
		Lincoln Ford, M.D.	
39.	Lankenau Hospital	Roger Marinchak, M.D.	Wynnewood, PA
		James Burke, M.D.	
40.	University of Massachusetts Medical Center	Robert Mittleman, M.D.	Worcester, MA
		Theo Meyer, MD	
41.	The Albany Medical College	Jaggarao Nattama, M.D.	Albany, NY
		Robert Cappone, MD	
42.	Houston Cardiac Electrophysiology Associates	Antonio Pacifico, M.D.	Houston, TX
		Neil Strickman, M.D.	
43.	Southwestern Medical Center, Dallas	Richard Page, M.D.	Dallas, TX
		Clyde Yancy, M.D.	
44.	Tulane University School of Medicine	Michael Prior, M.D.	New Orleans, LA
		Dwight Stapelton, M.D.	
45.	Northside Cardiology, PC	Eric Prystowsky, M.D.	Indianapolis, IN
		Mary Walsh, M.D.	
46.			
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48.	Regional Cardiology Associates	Arjun Sharma, M.D.	Sacramento, CA
		John Chin, M.D.	
49.	Cardiology Associates, PC	Nicholas Stamato, M.D.	Johnston City, NY
		Richard Ryder, M.D.	
50.	University of Ottowa Heart Institute	Anthony Tang, M.D.	Ottowa, Ontario
		Stuart Smith, M.D.	
51.	The University of Chicago	David Wilber, M.D.	Chicago, IL
		Alan Anderson, M.D.	
52.	Lancaster Heart Foundation	Seth Worley, M.D.	Lancaster, PA
		Neil Clark, M.D.	
53.	Hackensack University Medical Center	John Zimmerman, M.D.	Hackensack, NJ
		Joel Landzberg, M.D.	

54.	The Johns Hopkins Hospital	Hugh Calkins, M.D. Edward Kasper, M.D.	Baltimore, MD
55.	Sunrise Medical Tower III	Thomas Ahern, M.D. John Bedotto, M.D.	Las Vegas, NV
56.	Iowa Heart Center	Steven Bailin, M.D. William Wickemeyer, M.D.	Des Moines, IA
57.	University of California-Irvine Medical Center	Michael Brodsky, M.D. Byron Allen, M.D.	Orange, CA
58.	University Hospitals of Cleveland	Mark Carlson, M.D. Ottorino Costantini, M.D.	Cleveland, OH
59.	The Heart Institute of Spokane	Don Chilson, M.D. David Stagaman, M.D.	Spokane, WA
60.	Cardiac Disease Specialists, PC	Thomas Deering, M.D. Walter Mashman, M.D.	Atlanta, GA
61.	St. Elizabeth's Medical Center of Boston	Charles Haffajee, M.D. Bernard Kosowsky, M.D.	Boston, MA
62.	University of Florida.	Anne Curtis, M.D. Juan Aranda, M.D.	Gainesville, FL
63.	Fairfax Hospital	Ted Friehling, M.D. Jake O'Brien, M.D.	Fairfax, VA
64.	Stucky Research Center	Raymond Dusman, M.D. Mark O'Shaughnessy, M.D.	Ft. Wayne, IN
65.	University of Minnesota Medical School	David Benditt, M.D. Spencer Kubo, M.D.	Minneapolis, MN
66.	Carolinas Medical Center	John Fedor, M.D. Alan Thomley, M.D.	Charlotte, NC
67.	Northern Indiana Heart Rhythm Specialists	Scott Kaufman, M.D. Jack Zeigler, M.D.	Holbert, IN
68.	Medical University of South Carolina	Robert Leman, M.D. Kirk Walker, M.D.	Charleston, SC
69.	Westchester Medical Center	Carmine Sorbera, M.D. Rob Belkin, M.D.	Valhalla, NY
70.	Northwestern University Medical School	George Horvath, M.D. Rebecca Quigg, M.D.	Chicago, IL
71.	The Stern Cardiovascular Center	Eric Johnson, M.D. Frank McGrew, M.D.	Memphis, TN
72.	Ochsner Heart and Vascular Institute	Mandeep Hehra, M.D. Freddy Abi-Samra	New Orleans, LA
73.	University of Utah Medical Center	Richard Klein, M.D. E. Michael Gilbert, M.D.	Salt Lake City, UT
74.	Mid Carolina Cardiology	Mark Kremers, M.D. Daniel Wise, M.D.	Charlotte, NC
75.	Consultants in Cardiology	John Haas, M.D.	Omaha, NE
76.	St. Paul Heart Clinic	Stuart Adler, M.D. Thomas Johnson, M.D.	St. Paul, MN
77.	Berkeley Cardiovascular Medical Group	Randy Lieberman, M.D. Ernie Hauslein, M.D.	Berkeley, CA
78.	Florida Arrhythmia Consultants	Richard Luceri, M.D. Charles Russo, M.D.	Fort Lauderdale, FL
79.	Idaho Cardiology Associates	Melinda Marks, M.D.	Boise, ID

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82.	University of Virginia Health Sciences Center	John Dimarco, M.D. James Bergin, M.D.	Charlottesville, VA
83.			
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86.	Kaiser Los Angeles Medical Center	Navneet Dullet, M.D. Prakash Mansukhani, M.D.	Los Angeles, CA
87.	University of California, San Francisco	Leslie Saxon, M.D. Kanu Chatterjee, M.D.	San Francisco, CA
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90.	Cedars-Sinai Medical Center	C. Thomas Peter, M.D. Ann Hickey, M.D.	Los Angeles, CA
91.	Heart Place - Dallas	Jerold Shinbane, M.D. Shelley Hall, M.D.	Dallas, TX
92.	Penn State College of Medicine	Deborah Wolbrette, M.D. John Boehmer, M.D.	Hershey, PA
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94.			
95.	Memorial Hospital	Kenneth Curry, M.D. Ted Eastburn, M.D.	Colorado Springs, CO
96.			
97.	Washington Adventist Hospital	James Cockrell, M.D. Robert DiBianco, M.D.	Takoma Park, M.D.
98.			
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104.	St. Michael's Hospital	Paul Dorian, M.D. Gordon Moe, M.D.	Toronto, ON
105.	Montreal General Hospital	Tom Hadjis, M.D. M. Smilovich, M.D.	Montreal, Canada
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122. Hahnemann University Hospital	Frances Marchlinski, M.D. Mariell Jessup, M.D.	Philadelphia, PA
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124. University of California Los Angeles	Zenaida Feliciano, M.D. Gregg Fonarow, M.D.	Los Angeles, CA
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128. Rush Presbyterian, St Luke's Medical Center	Sergio Pinski, M.D. Maria Rosa Costanzo, M.D.	Chicago, IL
129. Providence Hospital	Christian Machado, M.D. Wolf Duvernoy, M.D.	Southfield, MI
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133. New York Hospital - Cornell Medical Center	Bruce Lerman, M.D.	New York, NY
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	James Dougherty, M.D.	
137. Valley Hospital	Jonathan Steinberg, M.D.	Ridgewood, NJ
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139. New York Heart Center	Ali Al-Mudamgha, M.D.	Syracuse, NY
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