ADDENDUM FOR THE AVID PROTOCOL

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The following are the only changes instituted in the AVID protocol to transition from the pilot phase to the main phase.

Addition to C *Implementation of the Study* - Phase 2: (page 4).

Recruitment of patients will continue without delay at the centers involved in the pilot phase, and additional clinical centers will be added as soon as possible.

Section 3 B *Exclusion Criteria* (pages 7 & 8) are replaced by the following:

Patients who meet inclusion criteria may not be enrolled if one or more of the following conditions exist:

- the event occurred in-hospital within 5 days after myocardial infarction
- the event occurred within 5 days after cardiac surgery or PTCA
- prior ICD implant or attempted implant
- intra-aortic balloon pump or other device or inotropic drug (not digitalis) necessary for hemodynamic support
- New York Heart Association Class IV heart failure
- currently on a heart transplant waiting list
- life expectancy less than one year
- chronic serious bacterial infection
- inability to give verbal consent due to severe neurologic impairment
- CABG or PTCA planned or performed and ejection fraction greater than 0.40
- arrhythmia surgery or ablative procedure planned or successfully completed
- index event occurred on amiodarone
- exposure to amiodarone in the last six months unless total dose is less than 10 grams, exposure is less than 2 weeks, or serum level is less than 0.2 mcg/ml
- contraindication to amiodarone
- long QT syndrome
- atrial fibrillation or other supraventricular arrhythmia requiring class I or III antiarrhythmics
- symptomatic sinus bradycardia
- 2nd degree or 3rd degree AV block in the absence of a pacemaker
- arrhythmia treatment already determined by private physician
- condition likely to limit cooperation
- geographically inaccessible
- current conflicting study
- prisoner or ward of the state

Addition to Section 5 *Randomization* (page 8):

If a decision to do CABG surgery has been made for an eligible patient who is willing to participate, the CABG surgery may either be done before or after randomization. CABG surgery done before randomization might prevent morbidity or mortality related to the surgery from being ascribed to either AVID treatment arm. If the CABG surgery is done before randomization, sufficient time must elapse between surgery and randomization that the time between surgery and implantation (should the patient be randomized to the ICD) will provide adequate patient safety consistent with good clinical practice .

Section 6 A 4 *Revascularization* (page 11) is replaced by the following:

If the patient is randomized to ICD prior to CABG, then the patient should have an epicardial device implanted during the operation with minimal intraoperative DFT testing to minimize operative mortality and morbidity (the only exception would be if the device implantation were thought to make the risk unacceptable to the patient, in which case an NTL device could be implanted later at a separate procedure). Patients randomized to drug therapy and going to CABG surgery should not have ICD leads placed.

Section 6 B 4 *Dosing of Drugs* paragraph on amiodarone (pages 12 & 13) is replaced by the following:

Amiodarone - In general, the amiodarone regimen should follow the package insert. A minimum loading dose of 800 mg/day should be given for one week. At least this total dose (5.6 grams) should be given with in-hospital monitoring, although the duration of in-hospital monitoring should be determined by the physician and modified based on the severity of the arrhythmia and clinical response. A dose of 400-800 mg/day should be given for four weeks and then a maintenance dose of 400 mg/day. Some patients may require a higher maintenance dose; on the contrary lower doses may be required if adverse symptoms occur. However, the minimum acceptable maintenance dose, will be 200 mg/day for 5 of 7 days. EP testing or Holter monitoring are not required, and are in fact discouraged.

A CONTROLLED TRIAL OF
IMPLANTABLE CARDIAC DEFIBRILLATORS
VERSUS MEDICAL ANTIARRHYTHMIC DRUG THERAPY

Version date August 5, 1993

1. INTRODUCTION

The implantable cardiac defibrillator (ICD) has been introduced into clinical practice as a means of treating sustained ventricular tachycardia and ventricular fibrillation. Much of the enthusiasm for this device is based upon its demonstrated capability to abort catastrophic ventricular dysrhythmias (1-4). If the capacity to reverse these arrhythmias is, indeed, translatable into a reduction in total mortality with the use of the device, then the ICD is likely to be the centerpiece in secondary prevention of sudden arrhythmic cardiac death (SCD). It must be recognized, however, that eliminating arrhythmias that cause sudden death may not significantly extend longevity. In some patients, for instance, the underlying disease may progress and cause relatively near-term, nonarrhythmic death. Also, there is some risk to the implant and use of devices (although the risk of ICD implant has been substantially reduced with the use of newer lead systems that do not require thoracotomy for placement). Furthermore, antiarrhythmic drug therapy may prove equally effective in reducing mortality.

There is some evidence to suggest that ICD may be more cost-effective when compared to either amiodarone or conventional drug therapy. A prospective economic evaluation of ICD versus drug therapy as a part of a randomized clinical trial would help address this issue.

The main objective of this study is to determine whether ICD placement reduces total mortality when compared to antiarrhythmic drug therapy. Secondary objectives include an economic assessment of the relative cost-effectiveness of the alternative treatment options and a quality-of-life evaluation.

There are ample data, albeit not from any large, randomized, controlled trial, that suggest the usefulness of the ICD. Winkle et al (5) reported an 8% one year total mortality and a 1% sudden death rate in 270 patients with malignant arrhythmias treated with an ICD. This is substantially mortality below published data for amiodarone (6) or for untreated patients. However, an important problem in the interpretation of these and other data (discussed below) is the possibility that different populations were involved in the different studies.

Fogoros (7) reported a study of 50 patients in which 21 received amiodarone and an ICD, while 29 received only amiodarone. The group receiving the ICD had a mortality of 0%, while the 24 month actuarial risk of death in the group treated with amiodarone only was 31%. However, the treatment group was not selected by randomization.

Crandall (8) also reported a lower risk of sudden death in patients treated with an ICD compared to those treated with drug alone. In this study there was similar total mortality in the two groups; this may have been due (1) to a sicker group of patients getting the ICD in this nonrandomized trial and/or (2) to the perioperative mortality of 3% (which likely would have been near zero had non-thoracotomy leads been available).

A case control study by Newman (9) studied 60 ICD patients and 120 control patients who were carefully matched (age, ventricular function, arrhythmia, underlying heart disease and drug therapy) in an attempt to reduce bias in another nonrandomized comparison. This study showed a significant reduction in sudden death (10% versus 5%) and in 3 year actuarial mortality (51% versus 35%) in the ICD treated patients.

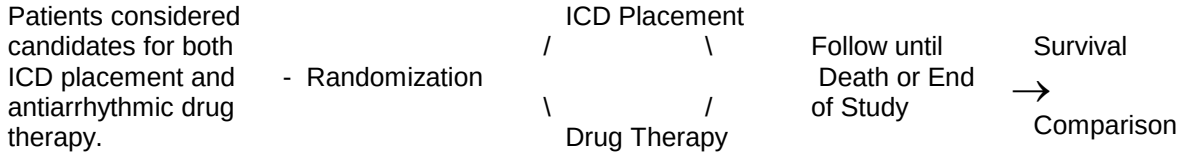
The only currently available data from a randomized, controlled trial come from a study still in progress with initial results reported only in abstract form (10). In this report, 139 patients had been randomized, and hence in its preliminary form lacked the power to exclude a 30% mortality difference. Nonetheless, despite a significant decrease in SCD in ICD patients compared to patients treated with drugs (0% versus 9%), there was no difference in overall mortality.

These data, in aggregate, suggest, but do not demonstrate conclusively, a central role for the ICD in the treatment of potentially lethal ventricular arrhythmias. Because of the large number of patients at risk for SCD and the attendant high cost of placement of ICDs, a clear answer about the usefulness of the ICD is needed to guide practice. The NHLBI recognized this need in supporting this randomized trial of ICD placement versus antiarrhythmic drug therapy in the treatment of patients with catastrophic ventricular dysrhythmias.

2. DESCRIPTION OF THE STUDY

A. Primary Objective

This study will determine whether a treatment strategy based on initial placement of an ICD or one based on antiarrhythmic drug therapy results in longer survival. Accordingly, the study design will follow the simple classical pattern:



B. Secondary Objectives

1. Quality of Life

While death is the primary endpoint, quality of life is also very important. Quality of life will be assessed for clinical and psychosocial factors adjusting for baseline differences. Measures of treatment effect on psychosocial factors relating to both the patient and the patient's spouse or companion will be obtained.

2. Cost

This trial will have major implications for clinical practice from the perspective of the public health financial burden of medical care by providing an opportunity to assess the relative cost-effectiveness of alternative treatment options. Using Medicare utilization, cost data, and literature estimates of effectiveness, Kupperman et al.(11) constructed a decision-analysis model and determined that the ICD was cost-effective when compared to a control group not receiving ICD. They estimated a cost-effectiveness of between $15,000 and $25,000 per year of life saved for patients undergoing ICD implantation. O'Donoghue et al. (12) reported that early implantation of the ICD is more cost-effective compared to therapy guided by serial electrophysiologic testing. Larsen and colleagues (13) determined cost-effectiveness ratios for ICD, amiodarone and conventional drug therapy using a Markov modeling technique (14) similar to Kupperman et al. Assuming that the ICD was replaced every 24 months, the marginal cost-effectiveness ratio for ICD versus amiodarone therapy was $29,200 per year of life saved, reduced to $21,800 per year of life saved if the average battery life could be improved to 36 months. These three reports suggest that ICD may be cost-effective when compared to alternative pharmacologic therapy. However, all three studies were retrospective and relied on sets of assumptions that may affect model results. In addition, Kupperman and Larsen used expert opinion to generate estimates of clinical probabilities and did not use actual clinical data. A prospective cost-effectiveness analysis comparing ICD placement to conventional drug therapy will be conducted and the results subjected to sensitivity analyses.

3. Mode of death

Statistical comparisons between treatment arms for specific modes of deaths are not planned. However, description of the modes of death in each arm may be useful in explaining the mechanism by which the ICD arm was beneficial or why it was not. Death will be classified as noncardiac or cardiac, and cardiac deaths will be subclassified as arrhythmic or nonarrhythmic. Arrhythmic deaths will be further subclassified according to initiating mechanism as primarily arrhythmic, or due to ischemia or congestive heart failure. Nonarrhythmic deaths (more precisely, non-

tachyarrhythmic deaths) will be further classified according to initiating cause as primarily due to heart block or bradycardia, and, by mechanism, of ischemia or congestive heart failure.

4. Surgical Morbidity

All instances of surgical morbidity will be reviewed by an experienced surgeon. Rates of surgical morbidity by site will be prepared for and reviewed by the Data and Safety Monitoring Board.

5. ICD and Lead Performance

ICD and lead performance will be tabulated for each device class used. Statistical comparisons between devices will not be performed unless randomization between devices is incorporated in the trial. Such randomization is not thought to be practical for the pilot. Device and lead failures will be reported to the FDA. In addition, performance of specific devices and leads will be reviewed by the Data and Safety Monitoring Board.

C. Implementation of the Study

The study is designed to occur in five phases:

Phase 1: 10/1/92-5/31/93	Protocol Development, Recruitment of Clinical Investigators and Manual of Operations Preparation (8 months). A planning committee will develop the protocol in collaboration with the Clinical Trial Center (CTC) and Clinical Trials Branch of the National Heart, Lung, and Blood Institute (NHLBI). Implementation of the protocol (Manual of Operations) will be developed by the CTC in collaboration with clinical investigator subcommittees.
Phase 2: 6/1/93-11/30/94	Pilot Study (18 months). The primary purpose of the pilot study is to collect data on study feasibility that will also be useful in refinement of the protocol.
Phase 3: 12/1/94-2/28/95	Prepare report on Pilot Study, refine protocol and train investigators for the full study (3 months).
Phase 4: 3/1/95-8/30/98	Recruitment (24 months) and follow-up (18 months) for the full study.

Phase 5: 9/1/98-2/28/2000 Complete data aggregation and analysis and report the study (18 months).

D. Pilot Objectives

1. Feasibility

The primary objective of the pilot will be to determine feasibility of a full-scale trial. The primary components of feasibility will be the recruitment rates, crossover rates and completeness of follow-up.

2. Protocol Refinement

A major secondary goal of the pilot will be to refine the protocol for the trial. In particular, the pilot will be critical for determining the final instruments for measuring quality of life and cost. The subrandomization between sotalol and amiodarone will permit assessment of whether the subrandomization should continue in the main trial. The principal purpose of refinement would be to use the information gained during the pilot to eliminate unfeasible or uninformative aspects of the protocol.

3. Count in final comparison

A goal of the study is to conduct the pilot in such a fashion that there is a high probability that the observations obtained on patients enrolled during the pilot can be counted in the final comparison of the primary endpoint. Attainment of this goal should be possible provided the full trial is not altered significantly with regard to the primary goal from the design used in the pilot because of analysis of the pilot data.

E. Study design

The design of the study is shown in Figure 1. Patients resuscitated from primary ventricular fibrillation (VF) and certain patients experiencing sustained ventricular tachycardia (VT) without correctable cause and who are considered to be candidates for ICD placement will be considered for random assignment to either immediate ICD placement or to drug therapy. Patients assigned to drug therapy and without contraindications to sotalol and amiodarone will be randomly allocated to empiric amiodarone therapy or to sotalol therapy guided by electrophysiologic (EP) testing and/or Holter monitoring as determined to be appropriate by the enrolling center. Patients assigned to, but unable to have EP/Holter guided therapy (<30 PVCs/hour and

noninducible VT/VF or one of these if only one method of testing is chosen or indicated), and patients with contraindications to sotalol will receive empiric amiodarone therapy. If, even after dosage adjustment, it is considered necessary to

Figure 1 - study design

discontinue either drug, the other drug may be used. Patients with a contraindication to amiodarone cannot be entered into the study.

Frequency of follow-up will be identical for the ICD and drug arms. Comparisons will be based on intention-to-treat. A pilot study will be conducted to assess feasibility of the trial.

3. PATIENT SELECTION

A. Inclusion Criteria

Patients can be considered for inclusion if, within the preceding 6 months, they:

- were defibrillated for primary cardiac arrest due to ventricular fibrillation (no ejection fraction limitations), not associated with definite acute myocardial infarction (defined by electrocardiographic changes, or enzyme changes, or both) nor with transient reversible causes
- experienced syncope in conjunction with documented sustained ventricular tachycardia (no ejection fraction limitations), or
- experienced hemodynamically compromising sustained ventricular tachycardia (systolic blood pressure less than 80 mm Hg or symptoms of chest pain or near syncope — but not simple palpitations or anxiety) and have left ventricular ejection fraction ≤ 0.40

B. Exclusion Criteria (see Addendum page i)

Patients who meet inclusion criteria may not be enrolled if one or more of the following conditions exist:

- The cause of the index arrhythmic event is transient or correctable.
- Index arrhythmic event occurring while patient is taking amiodarone.
- CABG performed since index arrhythmic event
- A decision has been made to perform revascularization (CABG or PTCA) and the left ventricular ejection fraction is >0.40
- Inability to undergo thoracotomy or have a device implanted.
- Have contraindications to amiodarone.
- More than 6 weeks exposure to amiodarone in the last 6 months or maximum plasma level of amiodarone of 0.2 mcg/ml.
- Atrial fibrillation or other supraventricular arrhythmia requiring Class I or III antiarrhythmic drugs.
- Less than age of consent.

- Long QT syndrome.
- Index event occurred within 7 days after revascularization (either CABG or PTCA).
- Intra-aortic balloon pump (or other mechanical device) or inotropic drug (excluding digitalis) necessary for hemodynamic support.
- NYHA Class IV heart failure.
- On a heart transplant waiting list.
- Life expectancy <1 year.
- Chronic serious bacterial infection.
- Sensorium depressed to the extent that informed consent cannot be obtained.
- Psychiatric condition likely to limit cooperation.
- Geographically inaccessible for follow-up.
- Concurrent study with an investigational antiarrhythmic drug or an antiarrhythmic device.
- Concurrent study with any investigational drug or device unless approved by the executive committee.

4. INFORMED CONSENT

No patient may be randomized without signed informed consent. If the ICD device to be used is investigational, such fact must be included in the informed consent. Signed informed consent is not required for entry into the registry unless the local IRB requires it.

5. RANDOMIZATION

Clinically indicated baseline tests (angiography, RNVG, ETT, etc.) to define underlying disease processes and to determine if revascularization (CABG or PTCA) is necessary must be completed before randomization. Decisions about use of beta-blockers, ACE inhibitors and aspirin therapy should be made prior to randomization. In general, an electrophysiologic (EP) study should not be performed before randomization unless the arrhythmia diagnosis is in question. However, previous electrophysiologic study will not preclude patient enrollment and randomization. Randomization will be accomplished by telephone call to the Clinical Trial Center. Confirmation of eligibility and informed consent and information critical for stratification will be collected at the time of the call. Randomization will be stratified by the primary rhythm disorder (VF versus sustained VT) and site. Randomization will be based on equal probabilities.

6. INTERVENTION

A. Implantable Defibrillator

1. Device availability

This protocol will use state-of-the-art device technology, which means that devices will be inserted transvenously whenever possible, and tiered therapy will be necessary. Because it is unlikely that any such device will be approved for clinical use by the beginning of randomization on June 1, 1993, the National Heart, Lung, and Blood Institute (NHLBI), through the Clinical Trial Center, will obtain an Investigational Device Exemption (IDE) for each device used. This IDE will be dependent upon cooperation from each device manufacturer, but allocation of devices from the Food and Drug Administration (FDA) will be separate from the manufacturers' allocations for their own studies. Device manufacturers will work closely with investigators, providing guidance and training in their use, as necessary.

2. Device requirements:

In general, device selection should have general clinical applicability to all patients randomized to the device study arm, utilize clinical techniques that are likely to be clinically relevant, and maximize patient safety. Choice of the device will be the responsibility of the clinical investigator provided it meets the requirements outlined below:

a. The generator will preferably have the capability of nonthoracotomy application and of tiered algorithms for programmable tachycardia detection and therapy, including the capability of antibradycardia and antitachycardia pacing (ATP), and storage of event therapy data. Capability of biphasic shock is highly desirable.

b. Each device and lead system must be approved by the Investigators' ICD Device Selection Committee. At a minimum, device experience must include at least 100 implantations with at least 6 months follow-up (some of which could be European implants) and the device and lead system must have a USA-approved IDE. Mixing of devices and lead systems will not be allowed. Each device can only be used with a lead approved for use by the Device Selection Committee, and covered by either the approved labeling or an IDE approved by the FDA.

3. Implant Protocol

Non-thoracotomy (NTL) lead placement must be tried first (unless patients are otherwise undergoing thoracotomy for revascularization or valvular surgery). It is strongly encouraged that at least a 10 Joule safety margin for defibrillation be achieved with the nonthoracotomy system, and that an epicardial system be used if such a safety margin cannot be achieved. However, the final decision regarding the safety margin and the configuration of the system will be left to the investigator. Testing of a biphasic device approved by the Device Selection Committee which delivers high energy shocks only (non-tiered therapy) is a possible option in the patients with a high defibrillation threshold (DFT), particularly for patients whose index arrhythmia was VF where an NTL biphasic device is considered superior to a thoracotomy device with ATP. The investigator is strongly encouraged to use a device with antitachycardia pacing capability in patients whose presenting rhythm was VT. Exceptions to this guideline will be allowed only as dictated by good medical practice.

Only test shocks (not "rescue" shocks) should be counted in the measurement of DFT, and shocks should be delivered 10 seconds after initiation of VF (range between 7 and 15 seconds). Thresholds for conversion of ventricular tachycardia cannot be substituted for thresholds for conversion of ventricular fibrillation. The onset of VF will be defined as the positive identification of VF on the electrocardiogram and loss of blood pressure, not simply either the beginning or end of rapid ventricular stimulation. It is recommended, but not required, that at least 3 minutes elapse between induced VF episodes. There should be at least 3 successful DFT measurements and no more than 20 high energy shocks at any evaluation.

If nonthoracotomy implantation is not possible, it is strongly recommended that the procedure be terminated and thoracotomy (or other approach) implantation shall be performed on a different day. However, the ultimate decision to implant a thoracotomy device on the same or different day shall be left to the investigator.

Even if a >10 Joule safety margin cannot be demonstrated with either endocardial or epicardial leads, device implantation will still be encouraged, as long as ventricular defibrillation can be accomplished with maximum output of the unit. In other respects, implantation will be carried out according to general practice at the site.

Post-operatively, the device should be turned "on" at least for VF/VT detection and therapy at $\geq$200 bpm unless otherwise clinically contraindicated. It is recommended that a single test for termination of induced VF be conducted at a separate electrophysiologic study prior to hospital discharge with the device at maximum output minus 10 Joules. If defibrillation is unsuccessful, the investigator must evaluate the reason for the loss of defibrillation efficacy and alter the system and/or programming as clinically appropriate. A PA and lateral chest x-ray should be obtained

prior to hospital discharge and retained for future comparisons. At discharge, VT/VF sensing should have at least a two-fold safety margin. The device should be programmed to deliver at least 2 discharges at maximum output, and anti-bradycardia pacing should be turned "on." Antitachycardia pacing should be "on" only if VT is inducible and pace terminable. Use of "shock only" programming for VT is discouraged. Details of antitachycardia pacing therapy will be left to the clinical judgment of the investigator.

In patients randomized to ICD therapy, electrophysiologic or Holter evaluation for drug responsiveness should not be undertaken. Arrhythmias occurring after device implantation should be managed, within the bounds of good clinical practice, by device reprogramming only. Addition of drug therapy to the device randomization arm is discouraged. Late follow-up testing of the device after hospital discharge is not required.

4. Revascularization (see Addendum page ii)

Patients randomized to an ICD and going to CABG surgery will have an epicardial device implanted during the operation with minimal intraoperative DFT testing to minimize operative mortality and morbidity. Patients randomized to drug therapy and going to CABG surgery should not have ICD leads placed.

5. Concurrent Drugs

Antiarrhythmic drugs should not be administered. Other drugs, such as ACE inhibitors, aspirin, and beta-blockers will be administered when medically indicated.

B. Drug Therapy

1. Institution of Drugs

All patients randomized to the sotalol drug therapy arm will have therapy guided by Holter and/or EP, chosen by the clinical investigator. In patients in whom Holter guidance is to be done, a baseline 24-hour or greater (minimum of 18 analyzable hours) drug-free Holter recording will be obtained off antiarrhythmic therapy between 7 days prior to and 1 day after randomization. In patients in whom EP guidance is to be used, baseline EP study shall be performed within 7 days prior to and 3 days after randomization. Empiric sotalol therapy (without Holter or EP guidance) will not be allowed. Patients randomized to the EP/Holter guided sotalol therapy arm will be evaluated by Holter and/or EP study that meets the requirements below. Patients randomized to empiric therapy with amiodarone will have drug therapy instituted empirically without Holter or EP evaluation.

If, after dosage adjustment as appropriate, during the course of the trial it becomes necessary to withdraw either drug in an individual patient, the other drug should be instituted. Crossover to the other study drug or addition of or crossover to other antiarrhythmics will be managed according to accepted practices at the local center. Implantation of an ICD should be avoided.

2. Holter Protocol

Baseline Holter monitoring should be performed in the drug-free state for a minimum of 24 hours (minimum 18 analyzable hours). A minimum average frequency of ≥30 VPDs/hour for the entire duration of the analyzable recording is necessary for efficacy assessment. Drug testing requires repetition of the entire recording period at steady state drug levels. Drug response is defined as ≥75% suppression of single VPDs and >90% suppression of all couplets and VT events. That is, if a patient has 10 or less couplets or 10 or less runs of VT on baseline 24 hour, Holter drug-free recording, all of the couplets and VT runs must be suppressed for the drug to be considered efficacious, in addition to the requirement of ≥75% suppression of single ventricular premature beats.

3. Electrophysiology Protocol

Standard electrophysiologic techniques will be employed. At least two sites of stimulation and two rates (one of which must be 400 msec) should be used. At least triple extrastimulation must be used, both for the drug-free study and for the drug testing, to call the patient non-inducible. To be eligible for electrophysiologic-guided therapy, the patient with a history of VF must demonstrate either inducible sustained monomorphic VT, sustained polymorphic VT, sustained ventricular flutter, or sustained ventricular fibrillation with a maximum of triple extrastimuli. "Sustained" is defined as lasting 30 seconds or requiring earlier termination because of hemodynamic compromise. Burst pacing is neither required nor encouraged. To be eligible for electrophysiologic-guided therapy, the patient with a history of sustained VT must demonstrate inducible sustained monomorphic VT with a maximum of triple extrastimuli. Use of isoproterenol is neither required nor encouraged. Induced arrhythmias must be reproducible. However, reproducibility is not required if CPR is needed to restore a stable hemodynamic state. Suppression is defined as the inability to induce >15 beats of nonsustained VT.

4. Dosing of Drugs — Initiation and stabilization of drug dosing should be performed in-hospital.

(see Addendum page ii)

Amiodarone — In general, the amiodarone regimen should follow the package insert. Loading doses of 800-1600 mg/day are usually required for 1-3 weeks (occasionally longer). The dose should then be reduced to 400-800mg/day for 4 weeks (however, a lower dose can be used if side effects occur) and then to the maintenance dose, usually 400 mg/day. A cumulative loading dose of 10 grams should be achieved in-hospital before discharge. Some patients may require larger maintenance doses. The minimum acceptable maintenance dose will be 200 mg/day for 5 of 7 days. EP testing is not required.

Sotalol — In general, the sotalol regimen should follow the package insert. The recommended initial dose is 80mg twice daily.
Dosage of sotalol should be adjusted gradually, allowing 2-3 days between dosing increments in order to attain steady-state plasma concentrations, and to allow monitoring of QT intervals. The lowest effective dose should be used. Graded dose adjustment will help prevent the usage of doses which are higher than necessary to control the arrhythmia. The dose may be increased, if necessary, after appropriate evaluation to 240 or 320 mg/day. In most patients, a therapeutic response is obtained at a total daily dose of 160 to 320 mg/day, given in two or three divided doses. Some patients with life-threatening refractory ventricular arrhythmias may require doses as high as 480-640 mg/day; however, these doses should only be prescribed when the potential benefit outweighs the increased risk of adverse events, in particular proarrhythmia. Because of the long terminal elimination half-life of sotalol, dosing on more than a BID regimen is usually not necessary. Because sotalol is excreted predominantly in urine and its terminal elimination half-life is prolonged in conditions of renal impairment, the dosing interval of sotalol should be modified when creatinine clearance is lower than 60 mL/min. Testing on sotalol should be performed only after a minimum of 5 doses of a stable dosing regime. Patients must not be given sotalol empirically; sotalol use must be directed by either Holter recording or electrophysiologic studies.

All drug dosing should be modified only as dictated by prudent clinical practice. Care must be taken to avoid drug-drug interactions.

If a patient fails a drug because of intolerable side effects, consideration should be given to reduction of the drug dosage first, then treatment with the alternative drug. When it is necessary to discontinue amiodarone and start sotalol, the investigator should use his own clinical judgment about: (1) the length of time the patient should remain off amiodarone before doing the "baseline" Holter recording and/or

electrophysiologic study; (2) the need, or lack of need, for hospitalization for these drug changes; and (3) appropriate initial dosages of sotalol. These judgments should be based upon: (1) the seriousness of the index arrhythmia; (2) the dose and length of time the patient had been taking amiodarone; and (3) the interim arrhythmias and side effects. In general, if amiodarone is stopped because of side effects or non-serious arrhythmia recurrences, a minimum of 2 weeks should elapse before starting sotalol, unless new life-threatening arrhythmias develop in the interim, and at least 4 weeks should elapse before assessing the efficacy of sotalol. If neither drug is efficacious, or if side effects preclude the use of both drugs (after appropriate dosage adjustments), then the investigator may choose another antiarrhythmic drug (or drug combinations) consistent with good clinical practice. Investigators are encouraged to keep patients in their assigned randomization groups, within the limits of good clinical practice.

5. Concurrent Drugs

ACE inhibitors, aspirin and beta-blockers will be administered when medically indicated.

7. PATIENT FOLLOW-UP

A. General

To the extent possible, follow-up procedures should be identical among patients randomized to device and to drug therapy. In particular, patients will be followed with equal frequency and equal intensity. However, it is understood that certain particular procedures at follow-up will be necessitated by the randomization arm. Follow-ups should be obtained within ± two weeks of the follow-up schedule date. Any events, including hospitalization, which occur during follow-up must be reported promptly. In particular, the Clinical Trial Center should be notified of any death within 24 hours.

Decision about whether these patients would be allowed to drive would be left to local practice but whatever policy is followed, it should be the same for patients randomized to either therapy.

Table 7.1
Follow-up Procedures

	ICD Arm								Drug Arm							
Time from randomization	B	1M	3M	6M	9M	12M	15M	18M	B	1M	3M	6M	9M	12M	15M	18M
History/Physical	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
ECG	X			X		X		X	X			X		X		X
Chest X-ray	X[1]			X				X	X					X		
Ejection Fraction	X								X							
Other Lab Tests [2]									X			X		X		X
Holter/EP									X[3]							
ICD Test	X	X	X	X	X	X	X	X								
Hosp [4]	X								X							
Events [5]																
Quality of Life Form	X		X	X	X	X		X	X		X	X	X	X		X
Cost	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X
Follow-up Form	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

B = baseline M = months EP = electrophysiologic test ECG = electrocardiogram
1 To include chest x-ray both before ICD implantation and after ICD implantation, annually for patients on amiodarone
2 For patients on amiodarone: thyroid function, liver function, diffusion capacity per local clinical practice
3 Sotalol patients only, both baseline, drug-free and evaluation after drug administration
4 And for each subsequent hospitalization

5 At any event: death, MI, CHF (new or worsened), sustained VT, cardiac arrest with resuscitation pacing therapy or shock from ICD, syncope, hospitalization

B. The Follow-up Schedule

Follow-ups will be scheduled at one month, three months and every three months thereafter for the duration of follow-up. The procedures to be completed are shown in Table 7.1. In addition, a vital status determination will be made for all patients just prior to each Data and Safety Monitoring Board (DSMB) meeting.

C. Events During Follow-up

The following events and subsequent therapy are to be reported if they occur during follow-up. The Investigator is encouraged to maintain the patient in the assigned arm of therapy, within the bounds of acceptable medical practice.

Cardiac arrest with resuscitation - Consideration should be given to changing the drug or increasing drug dosage in the patients randomized to the drug arm of the trial. Patients initially assigned sotalol could be given amiodarone. Patients initially given amiodarone could be given sotalol with EP and/or Holter guidance (see pages 13-14). Patients assigned to amiodarone could be given an increased dose of amiodarone if side effects are not limiting. In addition, other antiarrhythmic drugs could be used in place of, or in addition to amiodarone and sotalol, with EP and/or Holter guidance. Patients randomized to the device arm of the study could have reprogramming of the device.

Sustained VT - As noted above for patients who experience cardiac arrest with resuscitation, many alternatives are available for treatment which would allow the patient to be maintained in the assigned arm of the study. Precise alterations in drug or device therapy will not be specified, but will be left to the clinical judgment of the investigator, with the admonition to maintain the original randomization assignment if at all possible.

Syncope - Patients will be investigated as clinically appropriate for the cause of syncope, to include postural hypotension related to other drugs, bradycardias, or tachycardias. Appropriate adjustment of concurrent drugs will be made, and alteration of drug therapy or device programming will be performed as noted above.

Recurrent device intervention - Reprogramming of the device to emphasize antitachycardia pacing is encouraged if patients are receiving recurrent device shocks. Recurrent device intervention with successful pacing therapy will not require further programming of the device or addition of drugs.

Myocardial infarction — All episodes of myocardial infarction must be reported.

Hospitalization — All hospitalizations must be reported, regardless of the medical/surgical reason for the hospitalization.

Withdrawal — Only if the patient categorically refuses all further contact with the study will he/she be withdrawn from assessment of non-fatal events and routine follow-up. Vital status will continue to be assessed. Patients who discontinue their assigned study therapy, crossover to alternate therapy, or add the alternate therapy must continue to be followed. Withdrawal requires a letter explaining the circumstances of the withdrawal and documenting efforts to keep the patient in the study. This letter must be signed by the clinical investigator.

Discontinuation of allocated study therapy — In the absence of a compelling reason for crossover, every effort must be made to keep patients on the therapy allocated by the random assignment. Any alteration in allocated study therapy must be reported promptly.

Deaths — The Clinical Trial Center should receive notification of any death within 24 hours of the time that the site becomes aware of the death. Thereafter, as rapidly as possible, as much obtainable detail concerning the death should be forwarded to the Clinical Trial Center. These data must include the death certificate, hospital and emergency room notes, paramedic notes, interview information, rhythm strips, electrocardiogram, blood tests, and autopsy report. It will also include a death form reviewed by the Principal Investigator and a summary letter prepared by the Principal Investigator.

Atrial Fibrillation — Atrial fibrillation requiring antiarrhythmic drug therapy is an exclusion criterion for this study. Atrial fibrillation which occurs after randomization and which, in the judgment of the investigator, requires antiarrhythmic drug therapy should initially be treated in the drug therapy arm by increasing the dose of the assigned drug or utilizing the alternative drug. Furthermore, addition of other antiarrhythmic agents for control of atrial fibrillation will be allowed after appropriate attempts at controlling the atrial fibrillation with either sotalol or amiodarone. Investigators will be encouraged to consider whether anticoagulation and rate control alone would be appropriate for an individual patient. Patients assigned to the device therapy will be treated as clinically appropriate, with due consideration for the possibility of anticoagulation (or aspirin therapy) and

rate control alone, rather than the addition of antiarrhythmic drugs. However, if, in the opinion of the investigator, antiarrhythmic drugs are needed, prudent clinical practice must prevail.

8. ENDPOINTS

A. Primary Endpoint

The primary endpoint of this study is death from any cause. It will not include aborted or resuscitated death.

B. Secondary Endpoints

1. Quality of life — This will be multifactorial, looking at clinical factors including heart failure, adverse effects of therapy, and psychosocial factors. Psychosocial factors will be examined both for the patient and for the patient's spouse or companion.

2. Cost-effectiveness — A marginal cost-effectiveness analysis will be conducted comparing ICD placement to conventional drug therapy. Cost effectiveness comparisons will be made utilizing survival time and also quality adjusted survival time. Sensitivity analyses will be performed where appropriate.

C. Descriptive

1. Mode of Death — The determination will be made utilizing the CAST instrument (with slight modification). Death will be classified as noncardiac or cardiac, and cardiac deaths will be subclassified as arrhythmic or nonarrhythmic. Arrhythmic deaths will be further subclassified according to initiating mechanism as primarily arrhythmic, or due to ischemia or congestive heart failure. Nonarrhythmic deaths (more precisely, non-tachyarrhythmic deaths) will be further classified according to initiating cause as primarily due to heart block or bradycardia, and, by mechanism, of ischemia or congestive heart failure.

2. Surgical morbidity and mortality — These will be summarized by type of implant, type of index arrhythmia and site.

3. Device and Lead Performance — Device-specific events including device and lead failure and device interventions will be described.

9. QUALITY OF LIFE PROTOCOL

The Quality of Life protocol for the main trial will be developed during the pilot trial. During the pilot phase the Quality of Life instrument will be administered frequently to assess timing of data collection points to optimize usefulness of the measures ultimately chosen for measuring effects of drug and ICD therapy. In particular, the question of the usefulness of baseline measures needs investigation.

The Quality of Life questionnaire will be administered as a self-assessment instrument: during the study follow-up visit for the patient and at the time of the study follow-up by mail for the patient's spouse or companion.

The assessment will be multidimensional, for example, physical roles, social functioning (such as measured by the SF36) and psychological measures, especially of cognitive impairment. In addition, affect (depressive symptoms) as well as life satisfaction and disease-specific symptoms will be measured.

10. ECONOMIC EVALUATION PROTOCOL

A. Objective

Recent retrospective studies have documented the potential cost-effectiveness of ICD compared to drug therapy (11, 13). No studies to date have compared the economic benefit of these two alternatives in a prospective fashion. The primary objective of the economic evaluation component is to assess prospectively the cost-effectiveness of ICD versus drug therapy in the prevention of death and to subject these results to sensitivity analysis. To achieve this objective, several clinical and economic endpoints are necessary, including a determination of the effectiveness of the alternative treatments (e.g., years of life saved) and an assessment of total medical and nonmedical costs and other relevant medical outcomes across the two groups.

B. Research Perspective

Analysis of differences in resource consumption will be performed from the perspective of society, which mandates the accounting for productivity and functional losses due to the alternative treatment options.

Health care and non-health care resources will be valued using currently accepted economic methods for assigning costs to resources. We will use an approximation of medical costs to value the health care utilization endpoints and will use the "human capital" approach to assign economic values to non-medical productivity and functional losses (14).

C. Analytic Approach

Cost-effectiveness analysis will be performed using an intention-to-treat assumption. Health care utilization data will be collected and valued in economic terms using standard evaluation methods and appropriate discounting for differences in timing of costs. A marginal cost-effectiveness ratio (MCE) is defined by $\Delta TMC/\Delta E$ where TMC is total medical care costs and E is survival (in years). Sensitivity analyses will be performed where appropriate.

D. Pilot Phase

The primary purpose of the pilot study is to assess the feasibility of the recruitment, randomization, and data collection procedures of the study protocol. Specifically, the economic assessment requires data collected directly from individual patients. The feasibility of the data collection process and accuracy and validity of the data are of particular interest during the pilot phase. Health care utilization data will be collected from each patient in the pilot study over the entire period of the pilot study or until death or termination. A few simple economic baseline questions will be completed for all patients. The collection of utilization data will be based on a patient completed Utilization Diary. The patient will bring the diary to the follow-up to assist in completion of the Medical Care Utilization Form. Half of the patients will be randomly assigned to receive monthly phone calls reminding them to complete the diary to test whether this will improve diary compliance. The diary will also be used to obtain a weekly quality of life score based on a visual analog scale to enable quality adjusted life years analysis.

Productivity losses will be assessed by a self-administered instrument completed at the 6-month follow-up.

Utilization data will be valued in economic terms by obtaining charge and reimbursement data for two patients (one from each arm) at each site. The patients will be selected as follows: the second patient randomized and the first subsequent patient randomized to the other arm with similar index arrhythmia and type of hospital or after 5 months of enrollment (patients at VA or HMO hospitals are excluded). The study coordinator at each of the study sites will be required to assist in acquiring billing and reimbursement data for procedures and services incurred by these two patients. Health care utilization and bills incurred by these two patients out-of-hospital will be collected (shoeboxed) by patients and will be valued by the study health economist using secondary data sources when bills are not available.

Medical care costs incurred by patients during the course of a randomized trial may be different than those incurred during ordinary care. We will attempt to identify and account for these protocol-induced costs.

The economic assessment component is designed to minimize interference with the medical care of the patient. Contact with the study participants will be kept to a minimum. The three month health care utilization diary review with the patient by the study coordinator should not last longer than 10-15 minutes each follow-up.

E. Main Trial

Utilization and cost data from the pilot will provide estimates of the variability of these measures in the two treatment arms . These estimates will allow estimation of the sample size needed in the Main Trial to obtain desired precision of the point estimates of cost. It is anticipated that cost data will only be needed for 20 to 40% of each randomization arm, stratified by site and year of study.

11. ANALYSES

A. Primary

The primary endpoint, death, will be compared between groups based on intention-to-treat and will be performed by a randomization test based on the log rank (or Generalized Wilcoxon) statistic.

This pilot study is not designed, nor is there sufficient power, to compare amiodarone and sotalol. Nor will devices be compared to one another.

B. Secondary

1. Quality of life — Analyses of quality of life measures will be performed by intention-to-treat. Methods of assessment of the quality of life measures need to be defined because of the multifactorial nature of the quality of life data. Furthermore, censoring due to death or other comorbidity so severe as to prohibit obtaining certain quality of life measures creates a problem for quality of life data. A semiparametric approach such as that described by Hallstrom, et al. (15), as well as other nonparametric semiparametric, and parametric methods should be explored.

2. Cost-effectiveness — Cost-effectiveness analysis will be performed using an intention-to-treat assumption. Health care utilization data will be collected and valued in economic terms using standard evaluation

methods and appropriate discounting for differences in timing of costs (14). A cost-effectiveness ratio will be constructed as specified in Section 8 above. If necessary quality of life data are available, a cost-utility assessment will be performed that will provide for a quality of life adjustment to the survival endpoint. In such an analysis, the endpoint is cost per quality-adjusted year. The sensitivity of the cost-effectiveness ratio to various cost components will be evaluated.

C. Descriptive

1. Mode of Death — Time to Event (Kaplan-Meier estimates) for specific modes of death.

2. Surgical morbidity and mortality — descriptive summary

3. ICD and Lead Failure — descriptive summary

D. Subgroup Analyses

The number of *a priori* subgroup hypotheses permitted will be limited and must be formulated before or during the pilot study. Selection of *a priori* hypotheses will be made by the Steering Committee based on subcommittee recommendation.

Specific subgroups to be analyzed will include: 1) primary VF patients and 2) primary VT patients. Specific secondary analyses will include a comparison, if randomization is continued in the main trial, of the sotalol and amiodarone arms and, if randomization between devices occurs, comparisons between device arms. Because the study is not powered for these subanalyses, only large differences will be significant and the purpose of randomization is to make plausible the assumption that large differences represent a real effect.

E. Pilot Analyses

In general, the pilot data should be explored exhaustively for any clues that might aid the main trial. However, the limited number of patients dictates extreme caution; acceptance of a finding for implementation in the main trial should depend upon whether implementation could only benefit the trial or could cause harm. If the potential for harm exists, then acceptance should depend upon plausibility based on corroborative findings from other studies and physiologic or mechanistic models supporting the finding.

12. REGISTRY

A registry of patients being evaluated for antiarrhythmia (ICD and/or drug) therapy will be maintained. Adequate background data will be obtained on registry patients so that the trial patients and results can be put in proper perspective. In addition, name, social security number, date of birth and gender will be obtained for each registrant. This latter confidential information will be kept at the site and will be only used to conduct efficient and inexpensive vital status determination through the National Death Index. Depending upon local requirements, informed consent may be required.

13. STUDY PARAMETERS

A. Study Design

The primary endpoint will be evaluated in a symmetric two-tailed design with the α level set at 0.05.

B. Sample Size

At least 200 patients (at least 100 with primary VF) will be recruited for the pilot and a total of at least 1,000 (at least 500 with primary VF) patients recruited for the full-scale trial. The power of the trial then becomes primarily a function of the control event rate, the crossover rate, and the assumed effect of the ICD treatment. Figure 2 shows the power as a function of control event rate for a 0%, 10%, 20% and 30% crossover from drug arm to ICD arm and with assumed 30% treatment effect.

14. SEQUENTIAL MONITORING

A Data and Safety Monitoring Board, (DSMB) independent of the clinical investigators, will review the study data at least twice yearly. Formal monitoring boundaries will be formulated by the DSMB in conjunction with the Clinical Trial Center and Project Office.(16) It is anticipated that the boundary will be based on a Lan-Demets spending function in which half of the α is expended linearly over the duration of the trial. The first sequential monitoring would not occur until one year (i.e., at the time of evaluation of the pilot data).

Figure 2 - power curve

15. STUDY ORGANIZATION

A. Participating units and Primary Function

1. **Clinical Trial Center.** The Clinical Trial Center (CTC), located at the University of Washington in Seattle, Washington, has the responsibility of selecting Clinical Investigators and directing and administering the subcontracts of the Clinical Investigators. This will be done in close collaboration with the NHLBI Project Office. The CTC has the primary responsibility for statistical design of the study, data collection and management and analysis of results of the study. CTC staff will develop the operations manual and pretest all data forms, conduct sample size calculations and design and implement the randomization procedure. Moreover, the CTC is responsible for preparing and distributing regular progress reports and minutes, reports for the Data and Safety Monitoring Board, monitoring endpoint results, preparing data bank study analyses, and ensuring the accuracy and quality of data collection. CTC staff will also assist in training of Clinical Investigators' staff.

2. **Clinical Investigators.** The Clinical Investigators will be subcontractors of the CTC and will be selected by the CTC. Clinical Investigators are responsible for screening and recruitment of eligible patients, patient treatment and follow-up and collection of all clinical information and test data required by the study protocol.

3. **NHLBI Project Office.** The NHLBI Project Office in the Clinical Trials Branch is responsible for the overall direction and management of the study. The Project Office monitors the progress of the study and provides organizational and scientific guidance for the study.

4. **Data and Safety Monitoring Board.** The Data and Safety Monitoring Board (DSMB) is composed of an independent group of experts. The Study Chair, the Principal Investigator of the Clinical Trial Center and representatives of the NHLBI Project Office also participate in meetings as nonvoting members. The primary role of the DSMB is to advise the NHLBI on scientific, safety, ethical and other policy issues relating to the study. The DSMB meets at least twice a year. Specific functions include:

    a. Review of the study protocol.
    b. Review of any changes in the design or operation of the protocol that are recommended by the Steering Committee.

c. Review of study performance, including its progress and findings, at regular intervals.
d. Formation of recommendations for the continuation or termination of the study based on evidence of beneficial or adverse effects of the therapy or enrollment of a sufficient number of patients.
e. Assurance of safety and ethical treatment of study participants.

Recommendations made by the DSMB must be approved by the NHLBI prior to implementation.

5. **Endpoint Classification Committee.** The Endpoint Classification Committee is responsible for classification of each primary endpoint by cause and mechanism. The membership of this committee is responsible to the Steering Committee and must be independent of the participating Clinical Investigators in the study. The committee will be convened by the Steering Committee as needed (probably annually or semi-annually) to review and classify all endpoints.

6. **Steering Committee.** Membership on the Steering Committee will consist of the Principal Investigator from each Clinical Center, representatives from the CTC and Project Office and others (appointed by the Project Office) because of special expertise.

The Study Chair is appointed to serve for the duration of the study unless other arrangements are decided upon by the Director of the NHLBI. If, for any reason, the Study Chair is unable to serve, the Director of the NHLBI will appoint a new Study Chair.

Responsibilities of the Study Chair include:
a. Convening the Steering Committee.
b. Serve as an ex-officio member of the DSMB.
c. Representing the Steering Committee as required by the Program Office.

B. Functional Organization — Steering Committee

1. Structure. Day-to-day study management will be primarily the responsibility of the Clinical Trial Center with guidance from the Project Office and the Executive Subcommittee (see below). The Steering Committee will act on recommendations of appointed subcommittees. Subcommittees could include persons not on the Steering Committee because of particular expertise. Recommendations made by the Steering Committee are subject to the approval of the NHLBI.

C. Subcommittees

1. **Executive Subcommittee.** The Executive Subcommittee will consist of the NHLBI Project Officer, Director of the Clinical Trial Center and Study Chair. Ex officio members will include appointees from the NHLBI Project Office, the Clinical Trial Center Deputy Director, and CTC Cardiologist. The Executive Committee will hold monthly conference calls and will function to advise the Clinical Trial Center on matters that arise and must be resolved between Steering Committee meetings.

2. **Recruitment Subcommittee.** This subcommittee will be charged with developing recruitment goals and strategies and materials to aid in recruitment. Plans for dealing with poor recruitment including specific protocols for dropping a clinical center will be defined . The work of this committee must be completed during the planning phase. The committee may be reconstituted after the pilot when additional centers are to be enrolled.

3. **ICD Device Selection Subcommittee.** This committee will be charged with determining which devices would be suitable for the study.

4. **Drug/EP/Holter Protocol Subcommittee.** This committee will be charged with establishing and reviewing guides and bounds for the electrophysiology and Holter guided procedures and reviewing cumulating information about antiarrhythmic drugs.

5. **Quality Control Subcommittee.** This committee will be charged with reviewing all events that occur during implantation. It will be chaired by a surgeon/implant doctor.

6. **Data/Substudy/Ancillary Study Subcommittee.** This committee will be charged with developing procedures for substudy proposals and database analyses.

7. **Authorship/Publication/Presentation Subcommittee**. This committee will be charged with developing procedures for publications and presentations. It will review all proposed publications and presentations.

8. **Cost Subcommittee**

9. **Quality of Life Subcommittee**

16. CLOSEOUT OF THE STUDY

A. Informing the Patients and Primary Care Physicians

In a real way, the individuals contributing the most to the study are the patients who give informed consent to participating in the study. At the end of the study, all appropriate medical and background information will be communicated to the patient and the patient's primary care physician to aid in the patient care. When the study is over, the results and any general recommendations will be presented to the patients and participating physicians so that continuing care for these important participants can be based on the individual patient's response to therapy, the physician's judgment, and the most objective information available.

B. Delivery of Material to the National Heart, Lung, and Blood Institute

Since the study is financed by public funds through the National Heart,Lung, and Blood Institute, it is appropriate that the Institute document the study and at the conclusion, make information available to the widest possible audience. For this purpose, the investigators, especially the Clinical Trial Center, will supply the Clinical Trials Branch of NHLBI with a study archive of important study documents, computer tapes of the main computer file,and simplified "rectangular" or "flat" files that may be used more easily for analysis. A description of the format and use of the material will also be supplied.

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APPENDICES

A. Sample Informed Consent for Randomized Trial
B. Sample Informed Consent for Registry
C. Sample Informed Consent for Spouse/Partner Quality of Life Questionnaire