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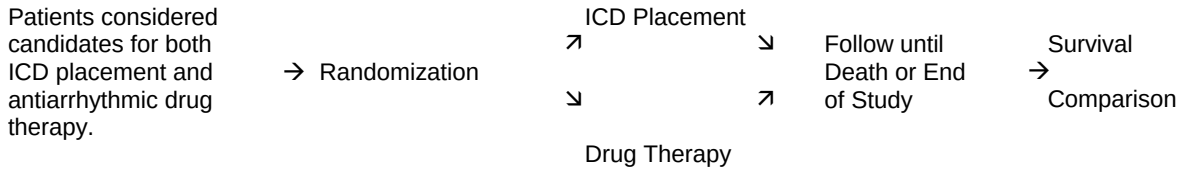
13. AVID UPDATE

OVERVIEW

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 by measuring clinical and psychosocial factors. Measures of treatment effect on psychosocial factors relating to both the patient and the patient's significant other 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. A prospective cost-effectiveness analysis comparing ICD placement to conventional drug therapy will be conducted.

3) Mode of death

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.

4) Surgical Morbidity/Mortality

5) ICD and Lead Performance

ICD and lead performance will be tabulated for each device used. Comparisons between devices will not be performed unless randomization between devices is incorporated in the trial. Such randomization will not be done in the pilot phase.

PHASES

The study will have two phases; a pilot phase (1 year to recruit ≥200 patients) followed immediately by a final (or main) phase (2 years to recruit ≥1,000 patients, followed by 18 months of follow-up), for a total of 1,200 patients.

Timeline:	
6/1/93	Begin recruitment of patients for pilot
6/21/94	Complete recruitment of 200 patients for pilot
Summer 94	Plan for full-scale trial Solicit additional investigators Begin recruitment for main phase
2/28/97	Complete recruitment of additional 1,000 patients
8/31/98	Complete follow-up

C. Pilot Objectives

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. A major secondary goal of the pilot will be to refine the protocol for the trial, in particular, the final instruments for measuring quality of life and cost utilization. Finally, a goal of the study is to conduct the pilot in such a fashion that there is a high probability that the follow-up information on patients enrolled during the pilot can be counted in the final comparison of the primary endpoint.

D. Study design

The design of the study is shown in Figure 1. Patients experiencing primary ventricular fibrillation (VF) and/or hemodynamically compromising 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 investigators. Patients assigned to, but unable to have EP/Holter guided therapy (<30 PVCs/hour and noninducible VT/VF), and patients with contraindications to sotalol will receive empiric amiodarone therapy. If, even after dosage adjustment, it is considered necessary to discontinue either drug, the other drug may be used. Patients with a contraindication to amiodarone cannot be entered into the study.

Comparisons will be based on intention-to-treat. The comparison will be 2-sided with an overall alpha level of 0.05. Power is estimated to be between 0.8 and 0.9.

No patient may be randomized without signed informed consent.

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. Randomization will be stratified by the primary rhythm disorder (VF versus sustained VT) and site.

This protocol will use state-of-the-art device technology, which means that devices will, whenever possible, be inserted transvenously and have tiered therapy capability. Choice of the device (from among those approved for the study) will be the responsibility of the clinical investigator.

Non-thoracotomy (NTL) lead placement must be tried first (unless patients are otherwise undergoing thoracotomy for revascularization or valvular surgery). In patients randomized to ICD therapy, electrophysiologic or Holter evaluation for drug responsiveness should not be undertaken. Addition of drug therapy to the device randomization arm is discouraged. Patients randomized to an ICD and going to CABG surgery should have an epicardial device implanted during the operation with minimal intraoperative defibrillation threshold (DFT) testing to minimize operative mortality and morbidity. However, if the patient's condition mandates, a later NTL attempt is permitted. Patients randomized to drug therapy and going to CABG surgery should not have ICD leads placed.

All patients randomized to the sotalol drug therapy arm will have therapy guided by either Holter or EP, chosen by the clinical investigator. Patients randomized to empiric therapy with amiodarone will have drug therapy instituted empirically without Holter or EP evaluation. No baseline testing is required. Initiation and stabilization of drug dosing should be performed in-hospital.

If, after appropriate dosage adjustment, during the course of the trial it becomes necessary to withdraw either drug in an individual patient, the other drug should be instituted. If it is considered necessary to discontinue both drugs, other antiarrhythmics may be used.

Frequency of follow-up will be identical for the ICD and drug arms. Follow-ups will be scheduled at one month, three months and every three months thereafter for the duration of follow-up.

A Data and Safety Monitoring Board, (DSMB) independent of the clinical investigators, will review the study data at least twice yearly.

SCREENING

A. Recruitment

Patients will be recruited from a number of sources, primarily the hospital Coronary Care Unit (CCU), post CCU and referrals from other hospitals. Referrals can be increased by a careful plan of publicizing the study among physicians in your hospital and the community. It is important to educate those who will be potential sources of patient referrals about the criteria which make a patient eligible for the Trial. AVID physician brochures are available to circulate to your referring physicians for this purpose. A slide set for lectures and conferences is also provided.

Personal contact with community cardiologists made by the AVID physician is the most valuable tool for recruitment. Whether or not arrhythmia patients are routinely referred to your center, the cooperation of these physicians is essential.

All patients who have had a serious ventricular arrhythmia (VF or VT), regardless of cause should be screened. In addition, patients who have experienced unexplained out-of-hospital syncope and are found to have structural heart disease and inducible VT with symptoms, should be screened. Those thought to be candidates for ICD placement (or equivalently antiarrhythmic drug therapy) should be entered into the Registry. Some of these patients (arrhythmias (A) - (C)) may be randomized. Others (arrhythmias (D) - (F); unexplained syncope (G)) will be entered into the Registry for the purpose of assessing risk in this population.

The AVID Registry brochure is available to inform the patient and family about the details of the Registry. Informed consent, if locally required for the Registry, should be obtained before collecting Registry information. Patients who have had ventricular arrhythmias eligible for the Trial will then be approached for participation in the Trial. The AVID patient information booklet is available for people medically eligible for the AVID Trial.

B. Screening and Eligibility

The Screen form comprises a worksheet for screening patients for the Registry and Trial. Patients should be screened for the Registry if, within the preceding 6 months, they experienced any of conditions (A) through (G) and are being evaluated for potential treatment.

Arrhythmias (A)-(E) can occur either in-hospital or out-of-hospital, provided they are considered primary (see below). Arrhythmia (F) includes non-primary (i.e. transient or correctable) arrhythmias occurring out-of hospital and condition (G) includes unexplained syncope occurring out-of-hospital.

Primary arrhythmia refers to an index arrhythmia occurring either in-hospital or out-of-hospital and NOT associated with a transient or reversible cause. An arrhythmia occurring in-hospital within 5 days after an MI (defined by ECG changes, enzyme elevations, or both) is not considered primary. An index arrhythmia occurring post-MI and out-of-hospital (even within 5 days of the MI) is considered primary. Arrhythmias

occurring more than 5 days after an MI while the patient is still hospitalized can be considered primary, if all transient or correctable causes are carefully ruled out. Patients with in-hospital index arrhythmias must be carefully screened to exclude patients whose arrhythmia was potentially caused by in-hospital treatment, appropriate or inappropriate.

(A) **Primary cardiac arrest due to VF requiring defibrillation** — There is no ejection fraction limitation for eligibility, unless the patient requires revascularization (CABG or PTCA), in this case, LVEF must be ≤0.40.

(B) **Documented sustained primary VT with syncope** — Sustained VT is defined as ≥30 seconds of either monomorphic or polymorphic VT at a rate ≥100 bpm or, if <30 seconds, requiring medical intervention to terminate the arrhythmia. Syncope need not be witnessed. Documentation includes medic ECG rhythm strips, 12-lead ECG, "quick-look" paddles, or reliable observations from medical personnel present at the time of the arrhythmia. There is no ejection fraction limitation for eligibility, unless the patient requires revascularization (CABG or PTCA), in this case, LVEF must be ≤0.40.

(C) **Documented hemodynamically compromising sustained primary VT (e.g., systolic BP <80 mmHg or significant cardiac symptoms such as chest pain or near syncope, but not simple palpitations or anxiety) with EF ≤0.40.** Sustained VT is defined as ≥30 seconds of monomorphic VT at a rate ≥100 bpm or, if <30 seconds, requiring medical intervention to terminate the arrhythmia. Hypotension or significant cardiac symptoms must accompany the VT AND the EF must be ≤0.40.

If the patient experienced arrhythmia (A), (B), or (C), you should further screen the patient for exclusion criteria for the Trial. Other patients with an index event eligible for the Registry will include those with:

(D) **Documented hemodynamically compromising sustained primary VT (systolic blood pressure <80 mmHg or significant cardiac symptoms such as chest pain or near syncope)** BUT EF >0.40. These are patients with arrhythmias as defined under (C) above, but with EF >0.40.

(E) **Documented sustained primary VT, hemodynamically stable** — These include patients with monomorphic or polymorphic VT lasting ≥30 seconds at a rate ≥100 bpm with no EF limitations. The patient was clinically stable, i.e., had no significant cardiac symptoms requiring emergent care.

(F) **Out-of-hospital documented sustained VT or cardiac arrest due to VF associated with a transient or correctable cause** — These include patients with out-of-hospital VT, monomorphic or polymorphic lasting ≥30 seconds and at a rate ≥100 bpm, or patients with VF. The arrhythmia may be attributable to, but not limited to, one of the following:

New MI — Arrhythmia occurs in the setting of an MI, either Q wave or non-Q wave, but before hospital admission for treatment of the MI.

Antiarrhythmic drug reaction — Arrhythmia occurs after initiation of antiarrhythmic drug or drugs which, in the investigator's opinion, was likely responsible for the arrhythmia.

Electrolyte imbalance — Arrhythmia occurs with hypokalemia or hypomagnesemia significant enough, in the investigator's opinion, to be primarily responsible for the arrhythmia.

Cocaine or other illicit drug — Arrhythmia occurs with ingestion of an illicit substance which, in the investigator's opinion and in the absence of other clinical cause, was likely responsible for the arrhythmia.

(G) **Out-of-hospital unexplained syncope in a patient determined to have structural heart disease and to have inducible symptomatic VT during EP Study with symptoms** — EP symptoms may include syncope, near syncope, dizziness or other significant cardiac symptoms, but does not include general discomfort, anxiety or simple palpitations.

These patients may be followed in the Unexplained Syncope Substudy. See Section 10.

In patients with VT as described by (C) and (D) above, you should obtain an EF determination a minimum of 24 hours after the index arrhythmia event, but otherwise as soon as feasible. Patients entering the randomized trial (arrhythmias A-C) will require documentation of EF (see Registry form).

If a patient has more than one qualifying index arrhythmia, choose the most serious event as the index arrhythmia (e.g., VF over syncopal VT). If a patient has 2 similar arrhythmias (e.g., symptomatic sustained VT), choose the episode that brought the patient to your attention.

C. Exclusion Criteria for the Registry

Some patients with conditions (A) - (G) will obviously not be considered for long term treatment with either an ICD or antiarrhythmic drugs. These patients should not be included in the Registry.

Screen all patients with a condition described by (A) - (G) for Registry exclusion criteria (criteria 1 through 10). If any exclusion (1-10) is checked, screening is completed and this patient is not eligible for the Registry. If no Registry exclusion is checked, you should begin to complete the Registry form.

FAX the Screen form to the CTC. If any Registry exclusion is checked, the Screen form is all that is required.

Specific exclusion criteria are discussed in the description of the Screen form.

D. AVID Registry

A Registry will be maintained of all sustained VT or VF patients, regardless of EF, meeting any of the inclusion criteria (A) through (G) and not meeting any of the Registry exclusion conditions 1-10 on the Screen form. The intent of the Registry is to collect baseline data about the index event and treatment on all survivors of life-threatening arrhythmias who would be candidates for antiarrhythmic drugs or ICD therapy.

The Registry will not include:

(1) Patients who die out-of-hospital,
(2) Patients who die en-route to hospital or in the Emergency Room,
(3) Patients who are admitted comatose and who never regain neurologic function,
(4) Patients who have VF or VT in-hospital within 5 days of MI.

Medical and demographic information will be collected on all Registry patients. In addition, social security number, name, and birthdate will be recorded. This information will be kept at the site and not sent to the CTC. This confidential information will be used to conduct vital status determinations through the National Death Index, a service of the Federal Government. Patients enrolled only in the AVID Registry need only to have the Registry form completed. No further follow-up is required. Remember that Trial patients are also Registry patients.

Revascularization:

Note that the exclusion criteria concerning a decision to revascularize are not static. Clinically indicated baseline tests (angiography, radionuclide ventriculogram, treadmill test, echocardiogram, etc) to determine if revascularization (CABG or PTCA) is necessary and the subsequent decision of whether or not to revascularize must be completed before randomization. If the decision is made to revascularize the patient, and the left ventricular ejection fraction is >0.40, the patient is excluded as a candidate for the Trial. However, if the decision has been made to perform revascularization and

the EF is ≤0.40, the patient is randomizable. Quantitated EF is desirable on all patients (Registry and Trial) but, in any case, is required on Trial patients.

All tests and procedures will be paid for by the patient/insurance . As you review the patient's eligibility, you should make use of tests which have already been scheduled or performed or are otherwise medically indicated.

EP Studies:

In general, a baseline electrophysiologic (EP) study should not be performed before randomization unless the arrhythmia diagnosis is in question. However, previous EP study will not preclude patient enrollment and randomization.

Previous Drug Therapy:

Previous antiarrhythmic drug therapy does not eliminate a patient from enrollment. Prior use of amiodarone requires special consideration. Other drugs, such as ACE inhibitors, aspirin therapy and beta blockers will be administered when medically indicated; these decisions should be made prior to randomization, and the patient should be maintained on steady doses throughout the Trial as much as clinically feasible.

Exclusion Criteria For Trial

Evaluate all Registry patients with inclusion criteria (A) through (G) for the presence of conditions which would eliminate them from the randomized Trial. Patients meeting criteria (D), (E), (F) or (G) should be evaluated for Trial exclusions even though they are not candidates for the randomized Trial. The study population could be expanded to include patients with one of these ((D), (E), (F) or (G)) conditions. To accurately assess the impact of such a change, we would need to know what proportion of these patients would otherwise be eligible for the trial.

Mark as many exclusions as are applicable. The exclusions are not prioritized. Use the exclusion checklist as a screening tool to identify patients who are Trial candidates. For patients with arrhythmia (A), (B), or (C), the presence of any of the exclusion conditions precludes the patient from further consideration for enrollment into the randomized portion of the AVID Trial. However, these patients are still eligible for and should be enrolled in the AVID Registry.

SCREENING FORM

Overview

Complete on all patients who are being evaluated for arrhythmia therapy and who have had arrhythmias (A)-(F) or condition (G) within the last 6 months, regardless of cause or ejection fraction. Much of the information requested on this form is readily found in the hospital records.

Initial Screening — Date you initiated screening process.

Site — The 2-digit number assigned to your AVID center.

Item 1 — *Index Arrhythmia* — Indicate the arrhythmia that occurred within the last 6 months to qualify this patient for the AVID study. If the patient had more than one arrhythmia episode that qualifies him/her for this study, mark the worst (first in list) arrhythmia and record that date. If more than one episode of the same arrhythmia occurred, choose the episode that brought the patient to your attention. Select the most recent arrhythmia if it is more serious than the first. Arrhythmias (A), (B), and (C) are all inclusion arrhythmias for the Trial as well as the Registry, while (D), (E), (F) and (G) are inclusion criteria for the Registry only.

Arrhythmias (A)-(E) can occur either in-hospital or out-of-hospital, provided they are considered primary. Primary means not associated with, or, if in-hospital, not occurring within 5 days after acute myocardial infarction (defined by new ECG changes, enzyme changes, or both) nor with transient or reversible causes. Arrhythmia (F) is the non-primary (i.e., transient or correctable) arrhythmia occurring out-of-hospital. See (F) below. Condition (G) represents possible undocumented primary VT. These patients will be included in the Registry for the purpose of assessing true risk for recurrence of arrhythmia in this population.

(A) *Primary cardiac arrest* — Ventricular fibrillation requiring defibrillation. There is no ejection fraction limitation for eligibility, unless the patient requires revascularization (CABG or PTCA). In this case, LVEF must be ≤0.40.

(B) *Documented sustained primary VT with syncope* — Monomorphic or polymorphic VT, at a rate ≥100 bpm, ≥30 seconds in duration, accompanied by syncope and documented by ECG rhythm strip, 12-lead ECG, "Quick-look" paddles, or verification by trained medical personnel on the scene. Syncope need not be witnessed, but rhythm documentation is necessary. If the patient requires revascularization, the LVEF must be ≤0.40 to remain eligible for the Trial.

(C) *Documented hemodynamically compromising sustained primary VT (systolic BP <80 mmHg, significant cardiac symptoms such as chest pain or near-syncope, but not simple palpitations or anxiety) with EF ≤0.40.* Sustained VT is defined as ≥30 seconds of polymorphic or monomorphic VT at a rate of ≥100 bpm or, if <30 seconds, requiring medical intervention to terminate the arrhythmia. Hypotension or other significant cardiac symptoms must accompany the VT, AND the EF must be ≤0.40.

(D) *Documented sustained primary VT, systolic blood pressure <80 mmHg or significant cardiac symptoms such as chest pain or near-syncope BUT EF >0.40* — These are patients with arrhythmias as defined under (C) above, but with EF >0.40.

(E) *Documented sustained primary VT, hemodynamically stable* — These include patients with polymorphic or monomorphic VT lasting ≥30 seconds at a rate ≥100 bpm with no EF limitations. The patient was clinically stable, i.e., no significant cardiac symptoms requiring emergent care.

(F) *Out-of-hospital documented sustained VT or cardiac arrest due to VF associated with a transient or correctable cause.* This includes patients with out-of-hospital VT, monomorphic or polymorphic, lasting ≥30 seconds and at a rate of ≥100 bpm, or patients with out-of-hospital VF. The arrhythmia is attributable to, but is not limited to, one of the following:

New MI — Arrhythmia occurs at the onset of MI prior to hospital admission for treatment of the MI. ECG changes and/or enzyme elevations are necessary to substantiate this finding as the cause of the arrhythmia. Specifics of enzyme and ECG abnormality criteria are left to local standards.

Antiarrhythmic drug reaction — occurring after initiation of antiarrhythmic drug or drugs which, in the investigator's opinion, was likely to be responsible for the arrhythmia.

Electrolyte imbalance — Severe hypokalemia or hypomagnesemia significant enough, in the investigator's opinion, to be primarily responsible for the arrhythmia.

Cocaine or other illicit drug — Ingestion of an illicit substance which, in the investigator's opinion and in the absence of other clinical cause, was likely responsible for the arrhythmia.

(G) *Out-of-hospital unexplained syncope in a patient determined to have structural heart disease and to have inducible VT during EPS with symptoms.* EP Study symptoms may include near syncope, dizziness, hypotension, or other significant cardiac symptoms. Discomfort or anxiety from simple palpitations alone is not adequate. These patients may be followed in the Unexplained Syncope Substudy. See Section 10.

Item 2 — *Registry Exclusion Checklist* — Checking any of the following 10 items excludes the patient from the Registry and any further consideration for the Trial:

(1) *Event occurred in-hospital within 5 days post MI* — The patient's index arrhythmia occurred while the patient was in the hospital within 5 days after the patient experienced myocardial infarction. Post MI patients whose arrhythmia occurred out-of-hospital within 5 days <u>are</u> Trial candidates.

(2) *Event occurred within 5 days after cardiac surgery or PTCA*.

(3) *Prior ICD implant or attempted implant* — Prior to index arrhythmia event, implant or attempted implant of any device that automatically operates as a cardioverter, defibrillator, or antitachycardia pacemaker excludes the patient from consideration for Registry and Trial. Atrial antitachycardia devices are acceptable.

(4) *On an intra-aortic balloon pump or other device or receiving an inotropic drug (not digitalis) necessary for hemodynamic support at the time of screening* — If the patient's condition stabilizes and this support is no longer required, he/she would then be considered an AVID candidate.

(5) *New York Heart Association (NYHA) Class IV congestive heart failure*.

(6) *Currently on a heart transplant waiting list* — If the patient is on an active transplant recipient waiting list (e.g., carrying a beeper, on-call to the hospital operating room), he/she is excluded. If, at any point, the patient experiences improvement in symptoms and cardiac function, and is no longer on the "active transplant list", he/she is now eligible for the Trial, provided it is within 6 months of the index arrhythmia event and the patient has no other Trial exclusions.

(7) *Life expectancy less than 1 year* — In the investigator's opinion, the patient has significant disease which would limit his/her life expectancy to less than 1 year.

(8) *Chronic serious bacterial infection* — History of active, chronic serious infection which would be a contraindication to the implantation of an ICD system.

(9) *Inability to obtain verbal assent due to severe neurologic impairment* (if assent required) — Unable either physically or mentally to comprehend the requirements of the Registry. This criterion may include comatose patients with severe anoxic brain damage.

(10) *Died during screening* — Screening is initiated but the patient dies before arrhythmia evaluation. In other words, the patient who never "stabilizes" from the index arrhythmia would not be registered. Patients who died during the process of evaluation for chronic treatment of arrhythmias should be included in the Registry.

If no Registry exclusion is checked, complete a Registry form. Copy the ID number from the top of the Registry form onto the space indicated on the bottom of the Screen form. FAX both Screen and Registry forms to the CTC.

REGISTRY FORM

Overview

Complete for all patients with an appropriate index arrhythmia (i.e., A through G) and no Registry exclusion. The Registry forms are pre-numbered to identify the patient. Use only forms sent from the CTC. To avoid the possibility of using duplicate numbers do not make copies of a blank form. You do not have to use the forms in sequence.

Item 1 — *Index arrhythmia date* — Record date of index arrhythmia. If a patient has more than one qualifying index arrhythmia, choose the date of the most serious event (e.g., date of VF versus date of syncopal VT). If two or more similar arrhythmias occurred, record the arrhythmia date that the patient was brought to your attention.

Item 2 — *Location of index arrhythmia:* Indicate the location where the arrhythmia diagnosis was made. If a symptomatic VT patient is driven to the Emergency Room prior to monitoring and diagnosis of VT, check the "ER" bubble. If a symptomatic VT patient or his family calls the paramedics, who find the patient in VT, check the "Out-of-hospital" bubble.

If the index event occurred while the patient was in the hospital or the Emergency Room, indicate whether the admitting diagnosis was cardiac (e.g., chest pain, CHF, etc.) or non-cardiac (e.g., pneumonia, elective hernia repair, etc.).

Also indicate if the patient was in a monitored setting prior to the event (e.g., ER, ICU/CCU, telemetry or other monitored bed).

Finally, note if the event occurred during or within 5 days after any invasive procedure, such as surgery or cardiac catheterization.

All index arrhythmias, particularly those occurring in-hospital or in the ER, must have clear documentation of the details of the index arrhythmia in the patient's AVID folder. (See Section 11, "Quick Reference".)

Item 3 — *Demographics*

Race — Enter the patient's predominant racial descent. When in doubt, ask the patient what race he/she considers him/herself. If the patient considers him/herself to be more than one race, check the one race that the patient considers predominant.

Hispanic origin — If this is not clear from the medical chart, ask the patient.

Health insurance — Mark all insurances that the patient/medical record report. VA/military includes active and retired military (e.g., Champus). Medicare/Medicaid includes a patient who is hospitalized emergently, has no insurance, and is "Medicaid pending."

Item 4 — *Was the patient taking antiarrhythmic drugs at the time of the index arrhythmia?* Indicate "Yes" if the patient was taking antiarrhythmic drug(s) for ventricular or supraventricular arrhythmias at the time of the event, whether or not the patient was taking the fully prescribed amount. This includes beta blockers prescribed for arrhythmias. It does not include drugs prescribed for their AV nodal blocking properties, such as digitalis.

Did the patient receive amiodarone in the 6 months prior to screening? — Check "yes" if the patient received any amount of amiodarone, IV or oral, whether before or after their index arrhythmia in the last 6 months.

Item 5 — *Clinical History* — Check all conditions present prior to the index arrhythmia. Categories include arrhythmias and antiarrhythmic therapy, cardiac risk factors, and life-limiting conditions.

Prior VF: History of primary VF without new MI. This does not include the index arrhythmia.

Prior VT: Includes history of primary monomorphic or polymorphic sustained VT prior to the index arrhythmia. Patient records that refer to a history of wide complex tachycardias or tachycardias of unknown origin without adequate ECG documentation should not be recorded here as VT.

Atrial fibrillation/atrial flutter: A history of spontaneous chronic or paroxysmal atrial fibrillation or flutter, with ECG documentation. Atrial fibrillation related to an intervention (e.g., patient shocked for VF which resulted in AF for several hours or days) should not be recorded here.

MI: History of Q wave or non-Q wave MI, documented by any combination of ECG changes, significant enzyme changes and/or clinical symptoms.

CHF: History of NYHA class I or greater CHF.

Bradycardia or AV block: Record any symptomatic or clinically significant bradycardia or AV block requiring intervention, including temporary pacing, unless in the setting of acute MI.

Hypertension: Persistent systolic BP >160 mmHg or diastolic BP >90 mmHg, and/or patient has been prescribed or received pharmacologic treatment for hypertension.

Diabetes: Either adult or juvenile onset, insulin dependent or requiring treatment by diet modification and/or oral medication and/or the patient has a written medical history of diabetes.

Present smoker: At the time of the patient's index arrhythmia, he/she was using tobacco, in any form.

Neoplasm: Defined as a malignancy of any type. Skin cancer is not included in this definition unless malignant (i.e., melanoma).

Unexplained syncope: Any unexplained complete loss of consciousness occurring in the year prior to index arrhythmia.

Hyperlipidemia: The patient has a measured elevation of a fasting plasma level of triglycerides or cholesterol, past or present.

Use of Class I or III Antiarrhythmic Drugs: History of Class I or III antiarrhythmic drug use for the treatment of any arrhythmia (supraventricular or ventricular).

Item 6 — *Organic Cardiac Disease:* Indicate all diseases that pertain to the patient, or "No identifiable heart disease" if, after the cardiac evaluation, no structural heart disease was identified.

Item 7 — *Cardiac Procedures Prior to Index Arrhythmia:* Indicate all therapeutic procedures ever attempted or completed prior to the index arrhythmia. Diagnostic tests such as heart catheterization, signal averaged ECG or EP study need not be reported here.

Item 8 — *Trial Exclusion Checklist:*

Cardiac:

(1) *CABG or PTCA planned or performed since index event and EF >0.40* — Any patient (VF or VT) with an EF >0.40 who is to undergo revascularization is excluded. However, if the decision to revascularize is reversed at any point during the patient's hospitalization, that patient again may be a candidate for the Trial.

(2) *Arrhythmia surgery or procedure planned or successfully completed* — Arrhythmia surgery/procedure includes aneurysm resection and catheter ablation. Patients who have undergone successful ablation for treatment of their ventricular arrhythmia are ineligible unless a second spontaneous qualifying arrhythmia occurs.

(3) Index event occurred on amiodarone.

(4) Exposure to amiodarone in last 6 months, unless total dose <10 grams, duration <2 weeks, or serum level <0.2 mcg/ml. This includes intravenous or oral amiodarone administered in the 6 months prior to screening unless you can document one of the following: (a) total dose was <10 grams, (b) total exposure was for <2 weeks, c) a serum level, at screening, of <0.2 mcg/ml.

(5) *Other contraindication to amiodarone* — Includes severe sinus node dysfunction causing marked sinus bradycardia, second or third degree heart block in the absence of a permanent pacemaker, or severe pulmonary, liver, thyroid, or neurologic disease.

(6) *Long QT syndrome* — This syndrome is characterized by a long QTc interval (usually 500 to 700 msec.), recurrent syncope, and ventricular arrhythmias. It should be documented by 12-lead ECG or Holter recording showing a long QT,

and/or a written medical record describing the existence of these findings. If any combination of these exist suggesting a long QT syndrome, the patient should not be enrolled.

(7) *Atrial fibrillation (AF) or other supraventricular arrhythmia requiring class I or III antiarrhythmics* — If a patient is taking class I or III antiarrhythmic drugs chronically for the prevention or control of supraventricular arrhythmias, he/she is excluded from this study. However, if the patient was on class I or III antiarrhythmics in the past, but has demonstrated absence of supraventricular arrhythmia for more than a year without the use of these drugs, he/she is eligible for the Trial. If the physician plans to institute class I or III antiarrhythmic drugs for AF, the patient should not be considered for randomization.

(8) *Symptomatic sinus bradycardia, second or third degree AV block in the absence of a pacemaker* — If the heart rate is less than 45 bpm or second or third degree AV block is present with symptoms of lightheadedness, dizziness, near syncope, or syncope, in the absence of permanent pacemaker the patient is excluded. The exception to this rule is the patient who has symptomatic bradycardia, has a temporary pacemaker, and a permanent pacemaker insertion is planned. In this instance, the investigator could postpone the procedure until the patient is randomized. If the patient is assigned to the ICD arm, the ICD would have pacemaker capabilities; but if the patient were assigned to the drug arm, a permanent pacemaker insertion would be performed prior to initiating antiarrhythmic drug therapy.

(9) *Antiarrhythmic therapy already determined* — If, after the index arrhythmia event, the patient's physician has firmly decided on a therapy for the patient (e.g., ICD implant), even if it has not yet been instituted, the patient is excluded. However, if a patient is on antiarrhythmic drug therapy and the physician agrees to discontinue the drug for entry into AVID, the patient is eligible.

(10) *Excessive arrhythmia making crossover likely* — If, in the investigator's opinion, the frequency and nature of the patient's ventricular arrhythmia is likely to necessitate the use of both antiarrhythmic drugs and implantable defibrillator, the patient should not be enrolled.

Noncardiac exclusions:

(11) *Condition likely to limit cooperation* — If, in the opinion of the investigator, the patient's condition precludes him from long-term compliance, (i.e., adherence to drug therapy and follow-up visits, and completion of the required quality of life forms and cost diaries), then the patient is not eligible for AVID. This may include patients with psychiatric problems, mild anoxia, or alcoholism.

(12) *Geographically inaccessible* — Patient lives at a distance which makes it impractical and/or too costly to return for the required follow-up visits. Note that it is not mandatory that patients return to the AVID site for each visit, depending on local circumstances (e.g., occasionally, some medical information may be transmitted via phone, FAX and mailed reports).

(13) *Current conflicting study* — Enrollment in any investigational trial where therapy or data collection for one trial might jeopardize or overlap with the other trial excludes the patient. When study conflict is in question, the investigator may approach the AVID Executive Committee for permission to enroll the patient.

(14) *Prisoner or ward of the state.*

Item 9 — *Trial eligibility* — Is this patient eligible for Trial inclusion? Indicate "Yes" if the patient meets the inclusion arrhythmia criteria (Arrhythmia (A), (B), or (C) and has no Trial exclusions (see Item 8). If the patient is randomized, carefully affix one of the clear, pre-printed ID labels where indicated. If the patient is eligible but is not randomized, indicate reason(s). If the patient is ineligible for the Trial, proceed to Item 10.

Item 10 — *LVEF* — For patients being considered for the Registry and not the Trial, a qualitative assessment of left ventricular function is allowed. The EF numerical value is preferred and is REQUIRED for patients who are randomized.

Date obtained: record the date of the most recent ejection fraction determination and the method used. An EF obtained within 6 months of the index arrhythmia without an interim event that may alter the EF (e.g., MI) is acceptable.

Method: If an EF was recently obtained by more than one method, record the results of the left-most listed test (e.g., if both an echo and RVG were obtained, record the RVG result).

Items 11-15 should be completed at the time of or shortly after the patient has been discharged from the hospital (if hospitalized during the evaluation) or at the time of evaluation if not hospitalized (and not randomized).

These items, which will document community practice for patients with serious ventricular arrhythmias, may be the most important variables in the Registry.

You may find it helpful to keep your partially completed Registry forms in a folder and review the patient charts once a month to complete this section of the form.

Item 11 — *Cardiac Procedures Since Index Arrhythmia* — Indicate all interventional procedures that were done from the time the arrhythmia occurred through the end of the evaluation and treatment of the arrhythmia. Do not record diagnostic tests, e.g., EP studies or cardiac catheterization here. If, at the time of discharge for the index arrhythmia evaluation, the patient is scheduled or intended for one of these procedures in the near future, you may delay completion of the Registry form to a time immediately after the procedure has been performed (e.g., CABG) for the purpose of collecting this information. Indicate all procedures, whether attempted or completed. The "Pacemaker" bubble refers to permanent pacemakers. For interventional arrhythmia surgery, indicate "other" and specify. Be sure to include the AVID ICD implantation for patients randomized to a device.

Item 12 — *Discharge Medications or Current Medications* (if not hospitalized) — this question is intended to elicit the out-of-hospital, at-home medication regimen as prescribed after evaluation and treatment of the patient's index arrhythmia. If this form is completed at the time of hospital discharge from the index arrhythmia evaluation, record the prescribed discharge medications. If this form is completed at a later date (but within 6 months from the index arrhythmia), record the medications the patient is prescribed after you evaluate him/her for the AVID study. If a patient dies prior to hospital discharge, record medications prescribed prior to onset of symptoms which preceded death. Indicate "Yes" to the drugs that are taken on a regularly scheduled basis and also drug categories taken on an "as needed" (PRN) basis (e.g., nitroglycerin sublingual). Do not include analgesics taken for occasional pain relief.

Item 13 — *Physical Exam* — Enter the most recent resting, sitting heart rate and blood pressure prior to hospital discharge if this form is completed at the end of baseline index arrhythmia evaluation; if the patient is being evaluated in an outpatient setting, enter today's resting, sitting heart rate and blood pressure. In the event of an inpatient death, omit this question.

Item 14 — *Were enzymes collected?* If yes, record the peak (or highest) CPK (Creatine phosphokinase) obtained within 3 days after the index arrhythmia. Note the number of hours after the index arrhythmia that the peak CPK was collected. Also record the peak (or highest) MB (CPK isoenzyme) if done. Record the peak MB, whether or not it occurred at the same time as the peak CK.

Item 15 — *Screening Hospitalization (admission when screened for AVID)* — Enter the hospital admission and discharge dates when the patient was evaluated for AVID. Note the vital status at discharge and, if the patient died, enter the date of death.

Complete this last page (item 16) but DO NOT FAX to CTC. File this page for future use. Retain this page even if the patient dies.

Item 16 — Enter the patient's last name, first name, middle initial and Social Security Number and birthdate.

When the Registry form is completed, fax pages 1 through 3 to the CTC. Make a copy of page 4 and retain the original and copy in two separate locations. The information on page 4 is crucial for obtaining vital status through the National Death Index, which will be done at approximately 2 years and 6 years after the study has started.

CONSENT THROUGH RANDOMIZATION

A. Overview

Once you have identified an eligible patient, the AVID physician and coordinator should approach the patient and his or her family for participation in the Trial. Signed informed consent is required before you can begin collecting baseline information and before you can randomize the patient. The following sections describe the process of obtaining consent, performing baseline tests and calling the CTC for a randomization assignment.

B. Informed Consent

It is worse to enroll a patient who drops out than never to have enrolled the patient.

To be enrolled in the AVID Trial, patients must sign the AVID Trial informed consent. In addition, if the patient is married or living in a spouse-like relationship, the spouse or partner should be approached to sign the Quality of Life consent. If the spouse/partner chooses not to participate, the patient can still be randomized.

Registry patients may need to sign a Registry informed consent, depending upon local IRB requirements.

Obtaining informed consent is a process that begins with your first contact with the patient. Your communication with the patient and his or her family will form the basis of their understanding of the study and their role. It is important that you take the time to make sure that the patient understands the purpose of the study and therapy alternatives. These patients have experienced a near fatal event, and will likely have many concerns and fears.

The consent form for this Trial is lengthy and, as with many legal documents, can be intimidating. Be sure to set aside sufficient time to go over the form carefully with the patient and his/her family. A lot may be happening to these patients, especially if you are recruiting them while they are still in the hospital. Because we will be relying on their continued participation for up to five years, it is important that the patient and family have a clear understanding of their commitment.

Hypoxia or anoxia is often present in this patient population, complicating the issue of informed consent. At a minimum, to be eligible for AVID a patient must be aware that he/she is participating in a research trial. If your IRB has further guidelines regarding this issue, they should be adhered to. Family support and understanding is important in these cases. Informed consent must be signed by the patient and may additionally be signed by a family member.

All consent forms must be signed and witnessed as designated on the form. They should be retained in the patient's AVID chart (or as stipulated by your institution).

C. Baseline Procedures and Forms

Once a patient has been carefully screened, is deemed a Trial candidate and has signed informed consent, you should focus on completing the baseline procedures necessary for randomization. Decisions regarding revascularization and decisions regarding the use of ACE inhibitors, antithrombotic therapy and beta-blockers should be made prior to randomization. The patient should be maintained on steady doses of the above drugs throughout the Trial (as much as clinically feasible).

Prior to calling the CTC for randomization, complete the following forms:

Screen
Registry (through item 10)
Baseline
ECG
*Patient QL - Baseline
**Spouse/Partner QL - Baseline
Patient Information
Randomization Worksheet

*Unless patient declines or is unable to complete the QL.
**Unless spouse/partner declines participation or completion of this form may delay randomization.

D. Outline of Randomization

Once an eligible patient has signed informed consent to participate in the AVID study, and baseline data have been collected and baseline forms completed (see section 2), the patient enters the study by being randomly assigned to receive an ICD (device arm) or to receive antiarrhythmic drug therapy (drug arm). A patient randomized to the drug arm and who has no known contraindication to sotalol will be further randomized to either amiodarone or sotalol. The method of cost/utilization data collection will also be assigned at time of randomization.

Given below is a brief outline of the steps to follow during the randomization process. A more complete description of these steps follows:

1) Complete the Randomization Worksheet.

2) Assign a patient ID number and acrostic.

3) Call the Clinical Trial Center (CTC) for randomization assignment(s).

E. Randomization Worksheet

The Randomization Worksheet must be completed (except for *'d items) before you call the CTC for randomization. This worksheet provides assurance of adherence to

protocol and gives information necessary for proper randomization of the patient. When you call, the CTC staff person will ask you for most of the information on the worksheet. During the randomization call, the CTC will provide the drug/device randomization assignment, the amiodarone/sotalol randomization assignment (if applicable), and cost/utilization method assignment. You will record this assignment on the worksheet.

F. Assignment of patient ID

You will assign the patient ID by taking the next available sheet of pre-printed transparent labels from the supply provided to your clinical center by the CTC. Each sheet has 30 labels for you to use on baseline forms. Each label looks like:

A A - B B B - C

where A A is your clinical center number, B B B is a unique patient number, and C is a check digit to protect against data entry or FAX transmission errors.

The patient numbers ("B B B" above) are assigned sequentially, one value per page of 30 labels, but there are occasional gaps in the sequence, so if a value is skipped from one page to the next, it is on purpose -- you aren't missing a page.

You will note that the patient ID boxes on each form have another set of four boxes. These are for the patient acrostic, which you assign. The acrostic, composed of the patient's first initial and the first three letters of the patient's last name, is to help you identify your patients in communications with the CTC.

You should now put the patient ID on each page of the baseline forms and Randomization Worksheet as follows: locate the patient ID boxes near the top right corner of each page. Carefully print the acrostic in the last set of four boxes, making sure each letter is contained within a box. Then carefully affix a transparent label so that the clinic number, patient number, and check digit are properly positioned within the first three sets of boxes. Note that you should print the acrostic FIRST, in case your pen doesn't like to write on the transparent label.

After the patient is randomized, be sure to add the Trial patient ID number to page 2 of the Registry form (Item 9).

Once the patient has been randomized, the CTC will print and send to you additional sheets of labels for that patient, with the acrostic included.

Patient labels should be attached to each page of all data forms and to other patient materials for AVID (e.g. ECG recordings).

G. Contacting the CTC for Randomization

With the Randomization Worksheet complete (except for CTC staff ID and randomization assignment(s)) and the patient ID assigned, you can now call the CTC for randomization. Normally the clinic coordinator calls, although anyone whom the clinic has authorized may, if necessary, call. The telephone call is made in one of two ways:

1) On working days (Monday through Friday, except Washington state holidays), between the hours of 7:00 am and 5:00 pm Pacific Time, call directly to the CTC. The phone number is:

(800) 253-1387

2) At other times, use the AVID digital pager to contact a CTC staff person who will be able to randomize the patient. Call from a touch-tone phone. The AVID pager number is:

(206) 989-5212

When you hear three quick beeps, punch in the telephone number where you can be reached (area code, phone number) and then hang up. A CTC staff person will return your call.

When you randomize the patient, the CTC staff person will ask for the information on the Randomization Worksheet. The CTC person will read it back for verification.

Once the information is verified correct, the CTC person will give you the drug/device randomization assignment. Mark the bubble on the worksheet corresponding to this assignment. If the drug arm is assigned, and the patient can receive sotalol, the CTC person will give you the randomization assignment between amiodarone and sotalol treatment. Mark the bubble on the worksheet corresponding to this assignment. If the drug arm is assigned but the patient cannot receive sotalol, the patient will automatically be started on amiodarone, so mark the "amiodarone" bubble. Finally, the CTC staff person will give you the cost utilization method assignment. Mark the bubble on the worksheet corresponding to these assignments.

At this point the randomization is complete. Therapy should be instituted as soon as possible following randomization. Amiodarone therapy should be initiated within 24 hours of the call for randomization. Baseline testing for administration of sotalol should begin within 24 hours for Holter recording, 72 hours for EP study. The patient should be scheduled for NTL device implantation as soon as possible after the call, but in any case within 3 days. Thoracotomy procedures should be performed within 5 days of randomization.

If you learn after you called to randomize that the patient died before you phoned to randomize, phone the CTC immediately.

The CTC will FAX a copy of the randomization information to your site, and you should carefully compare this copy with your worksheet to insure that all information was communicated and recorded accurately. If there are any discrepancies, call the CTC immediately.

You do not need to FAX the Randomization Worksheet to the CTC, but you should retain both it and the copy from the CTC in the patient file.

If it is later determined that any information recorded on the Randomization Worksheet and given at randomization is incorrect, phone the CTC for further instructions. Changes will NOT be made to the patient acrostic after randomization.

BASELINE FORM

Overview

The Baseline form should be completed prior to randomization, but only after the patient has been determined to be AVID eligible (i.e., inclusion and exclusion criteria met, ejection fraction obtained, revascularization decision made, and informed consent has been signed by the patient).

Information requested in this form will require abstraction of the medical records as well as direct elicitation from the patient and/or family. The baseline form includes arrhythmia history, clinical history, demographics and current clinical assessment.

Item 1 — *Date of patient interview* — This date should be on or shortly after the date of obtaining informed consent for the Trial and prior to phoning the CTC for randomization.

Item 3 — *Arrhythmia history (prior to, but not including, index arrhythmia)*

Answer "Yes" or "No" to each question. These questions pertain to arrhythmias prior to the index arrhythmia. Do NOT include the index arrhythmia.

Primary cardiac arrest due to VF cardiac arrest without any new MI.

Documented sustained primary VT with syncope — Monomorphic or polymorphic VT rate ≥100 bpm and lasting ≥30 seconds or requiring emergent intervention and accompanied by complete syncope.

Documented sustained primary VT, systolic BP <80 mmHg or chest pain or near-syncope — ECG rhythm strips or 12-lead ECG document sustained monomorphic or polymorphic VT at a rate ≥100 bpm, lasting ≥30 seconds or requiring emergency intervention, with palpable or auscultated systolic BP <80 mmHg or patient experiencing chest pain or other significant cardiac symptoms such as near-syncope to denote a hemodynamically unstable status. The severity of a person's symptoms (e.g., mild chest pain but severe dyspnea and diaphoresis) will help to differentiate the hemodynamically stable versus unstable patient.

Documented sustained primary VT, hemodynamically stable — Monomorphic or polymorphic VT rate ≥100 bpm lasting ≥30 seconds. Patient has an auscultatory or palpable systolic blood pressure ≥80 mmHg and is free of profound symptoms of chest pain or near-syncope.

Out-of-hospital documented sustained VT or cardiac arrest due to VF associated with transient or reversible cause — Out-of-hospital monomorphic or polymorphic VT rate ≥100 bpm lasting ≥30 seconds or requiring emergent intervention, or cardiac arrest due to VF requiring defibrillation which, in the investigator's opinion, is associated with any transient or reversible cause. Causes, as described on the Registry form, include but are not limited to:

Acute MI, either non-Q wave or Q wave
Antiarrhythmic drug reaction
Severe electrolyte imbalance (e.g., hypomagnesemia or severe hypokalemia)
Recent use of cocaine or other illicit drugs

Supraventricular arrhythmia — The patient has a history of a rapid, slow, or irregular heart rhythm arising in the upper portions of his heart and/or has a written medical history or ECG documentation of a supraventricular arrhythmia. If the supraventricular arrhythmia can be further characterized, indicate one of the following:

Chronic atrial fibrillation or flutter - The patient has a current 12-lead ECG recording of atrial fibrillation or flutter, and has been told or has written medical records to indicate that this rhythm has been present for >6 months without documentation of intervening sinus rhythm.

Paroxysmal atrial fibrillation or flutter - The patient has a history of one or more spontaneous episodes of atrial fibrillation or flutter that either terminated spontaneously or required electrical cardioversion and/or drug therapy for conversion to and maintenance of normal sinus rhythm. Atrial fibrillation related to an intervention (e.g., patient is shocked for VF resulting in AF) should not be included.

Other, specify - Record any other supraventricular arrhythmias here, or if unknown which specific type of supraventricular arrhythmia, record "unknown."

Other significant arrhythmia — record any other significant arrhythmia not mentioned above (e.g., symptomatic bradycardia). Asymptomatic junctional rhythms or bradycardias need not be reported.

Item 4 — *Family history of MI or sudden death prior to age 55* - Enter whether or not there is a history of myocardial infarction or documented sudden death occurring in the patient's direct blood relatives before the age of 55 years. Mark "unknown" if the patient has no knowledge of his blood relatives or of their medical history.

Item 5 — *Other clinical history* — Record medical information that is known by the patient or is accessible from the patient's chart and occurred prior to the index arrhythmia. Mark each item either "Yes" or "No."

Angina — The patient has experienced a visceral discomfort occurring anywhere in the anterior chest, back, jaw, neck, or shoulder but at some time

involving the substernal region, precipitated by exertion and requiring rest or nitroglycerin for relief; and/or the patient has a written medical record documenting a history of angina by clinical symptoms and/or cardiac anti-anginal drug therapy; and/or patient has undergone an invasive cardiac procedure resulting in a diagnosis of angina; and/or the patient has undergone a treatment such as CABG or PTCA for the treatment of anginal symptoms.

Peripheral vascular disease — The patient has impaired circulation of the upper or lower extremities and/or the patient has experienced cramping pain on exercise in the thighs, calves, or buttocks which is relieved by rest and reproduced by the same exercise. Non-atherosclerotic etiologies (e.g., Raynaud's and Buerger's diseases) are also included. Atherosclerotic and non-atherosclerotic conditions are considered present by written medical history when it has been recorded that the patient has lower extremity claudication, any of the peripheral pulses are absent or specific arterial disorders have been diagnosed.

Cerebral vascular disease — The patient has had either a stroke or transient ischemic attack that resulted in transient or permanent abnormalities in vision, speech, sensory, or motor functions.

Depression or other mental disorder — The patient has or has had clinical depression and/or other clinical psychiatric disorder which may or may not have required medication.

Renal disease — The patient has a history of renal disease, such as glomerulonephritis, acute tubular necrosis, renal insufficiency, chronic renal infections, or chronic renal failure. History of isolated bouts of hematuria, proteinuria, oliguria or renal calculi does not alone signify renal disease for purposes of this form.

Arthritis — The patient has inflammatory lesions involving the joints, marked by pain, heat, redness, or swelling due to inflammation.

Menopause — The female patient has experienced cessation of menstruation, occurring usually between the age of 45 and 50.

Chronic pulmonary disease — The patient has chronic obstructive pulmonary disease (COPD), chronic or frequent bronchitis, emphysema, or asthma and/or the patient has a written medical history of chronic lung disease (obstructive, infiltrative, restrictive, or fibrotic). Pulmonary hypertension, tuberculosis, or neoplastic disorders are not considered chronic pulmonary disease for the purpose of this form.

Seizure disorder — The patient reports, and/or was witnessed to have experienced one or more transient episodes of seizures with loss of consciousness, associated with a diagnosed neurologic disorder and frequently requiring prophylactic anti-seizure medication.

Hepatic disease — The patient has had clinically significant liver disease. Hepatic diseases may include cirrhosis, hepatitis (viral, drug-induced or toxic), infiltrative diseases, jaundice, biliary tract disease, or arterio-venous malformations. Chronic passive congestion of the liver, jaundice associated with pregnancy, and gallbladder disease are not considered hepatic disease for the purpose of this form.

Thyroid disease — The patient has a history of abnormalities of thyroid function, either hyperthyroidism or hypothyroidism.

Prostate disease — The patient has clinical evidence and/or has a written medical history documenting prostatitis, prostatism, benign prostatic hypertrophy, prostate cancer, or any other prostate disease. Simple elevation of the PSA level does not alone support prostate disease for the purpose of this form.

Treatment for alcohol or drug dependence — The patient reports having attended inpatient or outpatient treatment program for alcohol and/or drug dependence.

Other significant disease — Specify any serious, significant medical diagnosis which the patient has. Do not include the Clinical History items already recorded on the Registry form Item 5 (prior arrhythmias and cardiac risk factors). List other medical history items which do not fall within the categories listed above. Do not include usual childhood diseases, pregnancy, or myocardial infarction history.

Item 6 — *Is the patient currently being medically treated for hypertension?* Indicate "Yes" if the patient is being treated by a physician with medication. Diet, exercise, biofeedback and other non-pharmaceutical therapies are not included.

Item 7 — *Demographics*

Education level — Indicate the highest grade or degree the patient has completed. If the patient has attended a trade school, business school, or received post-secondary school training of any type (e.g., in the military, or on the job), indicate "College (with or without degree)."

Household living situation — Indicate the situation that best describes the patient's living situation where he spends the largest percentage of time.

Lives with another adult(s) includes adult family members or other non-related adults, but not an institutional setting.

Include under "other," nursing homes and other institutional settings.

Work status — Indicate the patient's level of work <u>at the time of the index arrhythmia</u>.

Full time — The patient was employed 40 hours a week or more.

Disabled — The patient was been forced to quit working prior to retirement because of health, either on his/her own accord upon recommendation of a physician, or upon requirement from the employer.

Unemployed — The patient was currently unemployed (by economic circumstance or choice) or is temporarily on sick leave secondary to a non-cardiac illness.

Part time — The patient is employed less than 40 hours per week.

Retired — The patient stopped working upon reaching retirement age, as opposed to quitting because of a physician's advice or incapacitation.

Missed Work — If the patient was employed either full or part-time in the last 3 months, ask him/her how many days were missed from work <u>because of their heart condition</u>. Enter zero if none.

Item 8 — *Clinical Evidence of Ischemia* — Specify if there is evidence of underlying or ongoing ischemia. If Yes, indicate all clinical or test indicators used to substantiate the ischemia within the last 6 months.

Specify anginal and CHF status at baseline. These determinations relate to your estimate of the patient's probable status as an outpatient prior to this hospital admission.

ECG FORM

Overview

ECG information must be recorded from a 12-lead ECG. Complete at baseline when the patient is free of antiarrhythmic drugs, immediately prior to baseline hospital discharge for patients who began drug therapy, and at each scheduled semiannual follow-up visit (6 month, 12 month, etc.). All ECGs and rhythm strips obtained during AVID should be retained in the patient's AVID record. Do <u>not</u> send any ECG recording to the AVID Clinical Trial Center.

Item 1 — *Date of recording* — Enter month/day/year.

Item 2 — *Reason for recording* — Baseline ECG should be recorded in an antiarrhythmic drug-free state. A second ECG should be obtained when the patient has achieved maintenance dose of antiarrhythmic drug, or at hospital discharge for patients on amiodarone. Mark the appropriate bubble for ECGs obtained during follow-up.

Item 3 — *Rhythm at time of recording* — Mark all rhythms documented during the ECG recording, e.g., if the patient has intermittent atrial fibrillation and intermittent pacemaker rhythm, mark "atrial fibrillation/flutter" and "paced." Heart block, if present, will be recorded separately in Item 6. "Sinus rhythm" includes normal sinus rhythm, sinus tachycardia and sinus bradycardia.

Item 4 — *Heart rate* — Record either the average beats per minute of the ECG or the average RR interval in milliseconds. If the rhythm recorded is irregular (e.g.,

atrial fibrillation or intermittent paced rhythm) the heart rate must be obtained by averaging the rate of at least 10 complexes.

Item 5 — *Intervals* — Record PR, QRS, and QT intervals in milliseconds, the average of at least three complexes if the rhythm is regular. For patients with atrial fibrillation or a paced rhythm, check "Not measurable" for the PR interval. QRS and QT should be recorded for paced rhythms.

Item 6 — *ECG Abnormalities* — If the patient is continuously paced, check "Yes" and leave this section blank. For patients without a pacemaker, complete the rest of the page checking "Yes" or "No" for each abnormality.

Presence of abnormal Q waves ≥300 msec (or abnormal R waves or R/S ratio) — Mark "Yes" if the patient has an abnormality as defined below:

(1) any Q waves in at least two contiguous leads excluding V1 and aVR (contiguous leads are V2-V6; I and aVL; II, III, aVF);
(2) >50% reduction in the R wave in each of at least two contiguous precordial leads as compared to a previous ECG or, in the absence of RBBB or RVH, the R wave amplitude in V5 or V6 is <25% of that in V3 or V4;
(3) R/S ratio of 1 or > in V1 or V2.

If abnormal Q waves are present, indicate all location(s); Anterior (leads V2-V4); Inferior (leads II, III and aVF) lateral (leads I, aVL, V5, V6) or posterior (lead V1).

Heart block — If "Yes" is checked, specify the degree. First degree has a PR interval ≥210 milliseconds. Mobitz 1 indicates progressive lengthening of the PR interval until the P wave is not conducted. Mobitz 2 denotes abrupt loss of conduction of the P wave without preceding PR prolongation. Advanced or high degree heart block is defined as between second and third degree block, with only rare intermittent conducted beats. Third degree block is non-conduction of any P waves. Idioventricular rhythm usually results.

LBBB — defined as QRS duration of ≥120 milliseconds, with a wide, notched R wave in the left precordial leads (V4-V6) and lead I or with a pattern of rR' in the same lead. The initial Q wave often seen in I and V6 disappear with the development of LBBB.

RBBB — Defined as QRS duration of ≥120 milliseconds, with a rsR' complex in the right precordial lead V1, a terminal R in aVR, and a terminal S in lead I.

LAFB — Left axis deviation (superiorly directed QRS axis, ≥30°) and initial small R wave and terminal deep S in leads II, III, and aVF, and a small Q wave in I and aVL.

LPFB — Right axis deviation (inferiorly directed QRS axis ≥110˚) and initial small Q wave and tall R in leads II, III, and aVF in the absence of RBBB, RVH, or lateral myocardial infarction.

IVCD — QRS ≥100 milliseconds but if ≥120 milliseconds, not in a typical BBB or fascicular block pattern.

LVH — The definition of LVH should be made by the individual investigator per local standards.

PATIENT INFORMATION SHEET

Complete for each patient enrolled in AVID and keep it in the patient's AVID chart. Do NOT send it to the CTC. It is a work sheet for your convenience to help you keep track of the patient. Record all applicable information. When the patient comes in for a follow-up visit, make sure that the information is still up to date.

RANDOMIZATION WORKSHEET

Overview

Complete (except *'d items) after obtaining informed consent and completing the baseline forms but prior to phoning the CTC for a randomization assignment. Retain this worksheet in the patient's AVID chart. Do not FAX it to the CTC.

Following randomization, you will receive written confirmation of the information given during the call for randomization. Check that information carefully against that on this worksheet. If there are any discrepancies, contact the CTC immediately.

Item 1 — *Today's date:* Enter the date you will be randomizing the patient (normally today's date); enter as two digits for the month, then two digits for the day of month, then four digits for the year (e.g., if today's date is June 3, 1993 enter 06, 03, and 1993).

Patient ID: Affix an ID label for the patient identification number you have assigned to the patient (see page 3-3).

Patient's name: Write the patient's name for your identification purposes. The CTC will not ask for this information, but will ask for the patient's first initial and first 3 letters of the last name (acrostic).

Name and code number of person placing call: If you will be calling the CTC for randomization, enter your name and two-digit code number, otherwise enter the name and code number of person who will be calling the CTC. The CTC provides a list of persons at your site, and their code numbers, who are authorized to randomize patients. If you forget your code number and cannot find the list, the CTC can tell you your code number when you call for the randomization.

Name and code number of person at CTC: Leave blank for now; enter at time of call.

Item 2 — *Is the baseline Quality of Life form completed and in hand?*: The baseline QL must be completed by the patient and collected prior to randomization. Even if the patient is unable to complete the baseline QL because he/she is too ill at present, the patient should be encouraged to complete the follow-up QL questionnaires.

If the Baseline QL form will not be completed, indicate the reason. If the patient is still working on the Baseline QL form, you can either delay the call for randomization until it has been completed, or you can collect the partially completed form from the patient before you discuss the randomization assignment with the patient.

Item 3 — *Randomizing Hospital:* Enter the name and two-digit code number of the hospital at which you are randomizing the patient: The CTC provides a list of hospitals at your site at which patients can be randomized and the associated code numbers. If you forget the hospital number and cannot find the list, the CTC person can tell you the hospital number when you call for the randomization.

Hospital where device would be implanted: If the patient would be admitted to a different hospital for implantation of a device, enter the name of that hospital and its two digit code here. Under the AVID IDE, investigators with minimal NTL experience, (i.e., fewer than three NTL implantations) must limit AVID ICD implantations to the "main" hospital for your center before an additional hospital may be added that has experience with fewer than 3 NTL implantations.

Item 4 — *Initiation of AVID therapy*

This section is to remind you of the time frames for initiation of AVID therapy following randomization.

Item 5, 6 — *Gender, race, and Hispanic origin:* These are the same as on the Registry form, so just enter the same information. The CTC must ask them at the time of randomization in order to be able to prepare up-to-the-minute tallies of recruitment for NHLBI.

Item 7 — *Age:* Enter patient's age (in years) at time of randomization.

Item 8 — *Health Insurance:* This is the same as on the Registry form, so just enter the same information. The CTC asks this at time of randomization in order to assign the method of cost/utilization data collection.

Item 9 — *QL form preference:* Indicate whether the patient would prefer an English or Spanish version of the QL form during follow-up. If the patient cannot participate in the QL portion of the trial, indicate why.

Item 10 — *Index arrhythmia date, type and location:* These are the same as on the Registry form, so enter the same information. Only arrhythmia types (A), (B), and (C) on the Registry form make a patient eligible for the AVID study.

Item 11 — *Decision regarding revascularization:* Before the patient can be randomized, the decision whether to perform revascularization (including CABG, PTCA, and atherectomy) must have been made. Mark the bubble corresponding to the decision – no or yes. You must mark yes to this first part of the question or the computer will stop the randomization process. Then, check what the decision was – no revascularization planned, revascularization performed since index event, or revascularization planned. If the patient has had revascularizaton since the index event, give the date of the procedure. If the patient is scheduled to undergo revascularization, enter the anticipated date for the procedure.

Item 12 — The ejection fraction (and date ejection fraction was obtained). If revascularization (CABG, PTCA, atherectomy) was performed or revascularization is planned, the EF must be $\leq$0.40 in order to randomize the patient. Be sure the EF is verified and not just estimated.

Item 13 — *Has the patient had other open heart surgery since the index event?* If the patient has had valve repair/replacement or other open heart surgery since the index event, give the date of the surgery. If the surgery included aneurysmectomy for treatment of the ventricular arrhythmia, the patient is excluded from trial participation unless another clinical index arrhythmia occurs postoperatively. Although there is no time requirements, the patient should be stable and at least able to take oral medications within the protocol time recommendation (one day after randomization) prior to randomization.

Item 14 — *Signed informed consent obtained:* Make sure that the informed consent has been signed before calling for randomization.

Item 15 — *The Screen, Registry and Baseline forms complete:* Make sure that you have completed the Registry form and all the Baseline forms (Baseline, ECG and Quality of Life) to the extent possible prior to hospital discharge.

Item 16 — *Are any exclusions checked?:* Double check the list of medical exclusions to make sure that the patient is eligible for the AVID study.

Item 17, 18 — *Patient/patient's physician advised regarding the use of aspirin, ACE inhibitors and beta blockers:* The protocol recommends using these cardiac medications, if appropriate. The decision should be made prior to randomization and the patient's physician should understand the importance of not changing these therapies during the AVID trial unless medically necessary.

Item 19 — *Known contraindication to sotalol:* If, at this time, there is a known contraindication to sotalol (e.g. from a previous workup), mark with an "x" "Yes"; otherwise mark "No." Contraindications to sotalol include: patients with bronchial asthma, severe sinus bradycardia, second and third degree AV block (unless a functioning pacemaker is present), uncontrolled congestive heart failure, or previous evidence of hypersensitivity to sotalol. If the patient has

already had a baseline EP study or Holter and was found to be non-inducible or with insufficient ectopy to guide therapy, this will be considered a contraindication to sotalol. If the patient has a history of clinical inefficacy, this will also be considered a contraindication. Patients with contraindications to sotalol will receive amiodarone.

Item 20 — *Spouse/partner Quality of Life*: See sections 7.B and 7.E of the *Manual of Operations*. Mark appropriate bubble ("Yes", "No", or "Not applicable"). If you marked "No", mark the appropriate "why" bubble; if you marked "other", please write in the reason.

INITIATION OF AVID THERAPY

A. Overview

After randomization, patients should be started on the assigned intervention as soon as possible. Prompt initiation of treatment is important because in an intention-to-treat analysis, all events "count" once a patient is randomized — whether the treatment has actually been started or not. Thus, if a patient dies while waiting for a scheduled ICD implantation, that event counts as a death in the device group.

B. Patients Assigned to Drug Therapy

Complete an Initiation of Antiarrhythmic Drug form on all patients assigned to drug, whether or not the drug is ever started. You must adhere to the following instructions for administration of amiodarone and sotalol.

1) Institution of Amiodarone

Amiodarone should be administered immediately after randomization, but in any case no more than 24 hours after randomization.

Prior to institution of amiodarone, the following tests are strongly recommended: liver function (AST, ALT, Alk Phosphatase), total or direct bilirubin, TSH and T_4 or thyroxine, hemoglobin corrected diffusion capacity and CXR. Which of these tests are performed is left to local standards. It is strongly recommended that these tests be repeated every 3-6 months to evaluate the patient's response to medication.

Dosing of amiodarone: Initiation and stabilization of amiodarone dosing should be performed in the hospital. 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 gram) 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 4 weeks and then a maintenance dose of 400 mg/day. Some patients may require higher maintenance doses. 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 should not be done.

If a patient fails amiodarone because of intolerable adverse symptoms, consideration should be given to reduction of the drug dosage first, then treatment with the alternative drug, sotalol.

If 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 obtaining the "baseline" Holter recording and/or performing an 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 combination) consistent with good clinical practice. Investigators are encouraged to keep patients in their assigned randomization groups, within the limits of good clinical practice.

For patients assigned to amiodarone, complete:

A Laboratory Data form prior to or shortly after initiating therapy.

An Initiation of Antiarrhythmic Drug form, completed at hospital discharge or completion of antiarrhythmic drug therapy determination. If amiodarone is discontinued prior to discharge, indicate the final therapy.

An ECG form prior to baseline hospital discharge.

2) Institution of Sotalol and Testing for Efficacy

All patients randomized to the sotalol drug therapy arm must have therapy guided by Holter 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) is not allowed.

Patients randomized to the EP/Holter guided sotalol therapy arm will be treated with empiric amiodarone if the requirement for Holter (≥30 VPDs/hr) or EP guidance (inducible sustained monomorphic VT with a maximum of triple extrasimuli) is not met. In this case, complete an Initiation of Antiarrhythmic Drug form marking "sotalol not started, insufficient ectopy" and, on the same form, indicate the antiarrhythmic therapy at discharge.

a) 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. However, if a patient has 10 or fewer couplets or 10 or fewer runs of VT on baseline 24 hour, drug-free Holter recording, all of the couplets or VT runs must be suppressed for the drug to be considered efficacious.

b) 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 extrastimuli must be used, both for the drug-free study and for drug testing. 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 for arrhythmia induction 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 after the first induction. Suppression is defined as the inability to induce >15 beats of nonsustained VT.

c) Dosing of Sotalol

Initiation and stabilization of sotalol dosing should be performed in-hospital. In general, the sotalol regimen should follow the package insert. The recommended initial dose is 80 mg 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.

If the patient never started sotalol because of failure to meet EP or Holter requirements or if the patient is not suppressed on sotalol or EP testing shows that the patient is still inducible, or the patient experiences intolerable adverse symptoms on sotalol, the next therapy evaluated will be empiric amiodarone. The period and method for washout should be handled as for change of therapy from amiodarone to sotalol (see page 4-1).

For patients assigned to sotalol complete:

A Holter form and/or EPS form for baseline test and, if appropriate, for documentation of efficacy or lack of efficacy.

An Initiation of Antiarrhythmic Drug form — complete at hospital discharge or completion of antiarrhythmic drug therapy determination. If sotalol is discontinued, complete a Laboratory Data form, if appropriate, for laboratory values obtained prior to starting amiodarone.

An ECG form prior to baseline hospitalization discharge.

C. Patients assigned to ICD

Overview

The AVID study will use state-of-the-art device technology. Implanted defibrillators will be inserted transvenously whenever possible, and tiered therapy will be used. Table 1 details those devices currently allowed in AVID, some of which are only available under the AVID IDE. Only AVID patients may receive devices under this IDE.

Decision to perform revascularization must be made prior to randomization. It may be desirable to perform the revascularization before randomization so that morbidity/mortality due to that procedure does not impact AVID. In that case, and if the revascularization is CABG, the physician should delay randomization to allow sufficient time to elapse to ensure the safety of a second surgery between randomization and implantation (if randomized to device). Patients randomized to an ICD and undergoing coronary artery bypass graft surgery and/or valvular surgery after randomization may have an epicardial device implanted during the operation with minimal intraoperative defibrillation testing to minimize operative mortality and morbidity.

Patients randomized to an ICD should have the procedure performed as soon as possible. Once a patient is randomized, that patient is considered a part of the study arm to which he is randomized, whether therapy is actually administered or not. Therefore, prompt implantation of a device is essential to avoid any events occurring prior to implantation. In all cases, the device should be implanted within 3 days of randomization if it is a non-thoracotomy implantation and within 5 days of randomization if the patient is undergoing surgery for CABG.

When more than one device is available, the choice of devices will be left to the individual investigator at each site. There will be no randomization of specific devices. Training in the implantation and programming of individual devices will be left to the device manufacturers and will follow each manufacturer's protocol.

Non-thoracotomy lead placement must be tried first, unless the patient is 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 a non-thoracotomy 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 which delivers only high energy shocks (non-tiered therapy) is a possible option in patients with a high defibrillation threshold, particularly for patients whose index

arrhythmia was ventricular fibrillation, where an NTL biphasic device is considered by the Device Committee to be superior to a thoracotomy device with antitachycardia pacing. The investigator is strongly encouraged to use a device with antitachycardia pacing capability in those patients whose presenting rhythm was ventricular tachycardia. Exceptions to this guideline will be allowed only as dictated by good medical practice. However, antitachycardia pacing can be used only if it can be demonstrated that VT is inducible and pace-terminable unless the patient is involved in the empiric ATP substudy (see Ancillary Studies).

Each device and lead system used must have been previously approved by the AVID Device Selection Committee. See Table 1 (page 4-4) or Operations Memo 1 for list of currently approved systems. Deviation from protocol will jeopardize participation at the clinical site.

Only test shocks, not "rescue" shocks, should be counted in the measurement of the defibrillation threshold. Shocks should be delivered 10 seconds after initiation of ventricular fibrillation (range 7 to 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 a loss of blood pressure, not simply either the beginning or end of rapid ventricular stimulation. Three successful DFT measurements are recommended; however, it is acceptable to obtain two successful DFT measurements, and then a third high energy defibrillation with the leads attached to the generator. It is recommended, but not required, that at least 3 minutes elapse between induced VF episodes. There should be no more than 20 high energy shocks at any evaluation.

If non-thoracotomy implantation is not possible, it is strongly recommended that the procedure be terminated and a 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.

If a minimum of 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 the maximum output of the unit. In other respects, implantation will be carried out according to general practice at the local site.

Post-operatively, the device should be turned "on" at least for VF/VT detection and therapy at ≥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 bradycardia pacing should be turned "on." Antitachycardia pacing should be "on" only for VT patients in whom the VT is inducible and is pace-terminable (unless the patient is to participate in the empiric ATP substudy, see page 10 - 1). Use of "shock only" programming in such patients is discouraged.

Details of the antitachycardia pacing therapy will be left to the clinical judgment of the investigator.

In patients randomized to ICD therapy, an ICD interrogation prior to baseline hospital discharge is performed. Electrophysiologic testing 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 and is considered a crossover (see Crossover Section, page 6 -1). Late follow-up testing of the device after hospital discharge is not required.

Completion of implant/registration/warranty data forms for each manufacturer will be required as specified by the individual manufacturer. In most cases, these data forms will be only abbreviated versions of the reporting requirements for the manufacturer's investigational protocols.

D. Hospital Discharge (Initial Hospitalization)

At hospital discharge the following procedures and forms must be completed.

- Schedule (at least tentatively) the next follow-up appointment.
- Complete a Concurrent Drugs form.
- Complete an Adverse Symptoms form to note any adverse symptoms occurring during the hospitalization.
- Complete a Hospitalization form for the initial hospitalization.
- Provide "shoebox" patients with an AVID labelled accordion folder and any materials (e.g., pocket calendar) that may aid in collecting health care utilization data (see 8. Economic Evaluation Component)
- Finish completing the Registry form (items 10-13)

Drug assigned patients:

- Complete Initiation of Antiarrhythmic Therapy and EPS or Holter forms as necessary.
- Obtain a 12-lead ECG after the loading phase for the antiarrhythmic drug. Complete an ECG form.
- For amiodarone patients, complete Lab Data for baseline liver, thyroid and pulmonary function tests.

ICD assigned patients:

- Perform an ICD interrogation prior to hospital discharge.
- Complete ICD Implantation, Lead/Generator Identification and ICD Evaluation forms.
- At 30 days post implantation or hospital discharge, whichever is later, complete ICD Complications form.

INITIATION OF ANTIARRHYTHMIC DRUG FORM

Overview

This should be completed when initial antiarrhythmic drug therapy determination is complete, (i.e., there is intended long-term drug therapy).

For the purpose of this form, antiarrhythmic drugs include:

amiodarone	phenytoin
disopyramide	procainamide
encainide	propafenone
flecainide	quinidine
mexiletine	sotalol
moricizine	tocainide

Item 1 — *Date first started drug* — Enter the month, day and year that the first antiarrhythmic drug was started.

Item 2 — *Drug assigned at randomization* — Complete either the amiodarone or the sotalol block. For the drug assigned at randomization, indicate what happened.

Amiodarone

If the patient was assigned to amiodarone at the time of randomization, complete this section. Choose one result of dosing. If the patient was not discharged on amiodarone or was discharged on amiodarone plus another antiarrhythmic or ICD, complete item 3. If the patient was assigned to amiodarone and discharged on it, complete only this section of item 2 (and sign the form).

Sotalol

Complete this section only if the patient was randomized to sotalol. Choose one result of dosing. If the patient was not discharged on sotalol, or was discharged on sotalol plus another antiarrhythmic or ICD, complete item 3. If the patient was assigned to sotalol and discharged on sotalol, complete only this section (and sign the form).

Item 3 — *Therapy at discharge* — Only complete this section for patients who are discharged on something <u>other than</u>, or <u>in addition</u> to their assigned drug treatment.

If, for example, a sotalol-assigned patient has insufficient ectopy to be tested, tries and fails amiodarone because of adverse symptoms and is discharged on mexiletine, complete the sotalol section of item 2 and complete item 3 checking "other antiarrhythmic drugs." Write in "mexiletine" and the dose at discharge.

If implantation of an ICD is contemplated in a drug-assigned patient, contact the CTC. This is a therapy crossover. See page 6-1.

LAB DATA FORM

Overview

This is completed ONLY for patients taking amiodarone. Which tests a patient receives is left to the judgment of the clinical investigator and local practice, but it is strongly recommended that liver and thyroid function tests and pulmonary evaluation (by DLCO or CXR) be done every 3-6 months.

Item 1 — *Date* — Enter the month, day and year that the tests were completed. This form is not required after discontinuation of amiodarone. If you are using results from tests completed on several different days but are considered to be part of the baseline (or follow-up) evaluation, enter the date (Item 1) that the last test was completed.

Item 2 — *Reason for completion* — If tests were done in conjunction with starting amiodarone, "Baseline" should be marked. "Baseline" is defined as occurring during the baseline hospitalization, post-randomization and preferably prior to initiating drug therapy, but no more than 2 days after initiating amiodarone therapy.

It is not required, but it is strongly recommended, that some or all of these baseline lab tests be repeated every 3-6 months to evaluate the patient's response to the medication.

An event is defined as a symptom or finding which may prompt you to obtain lab tests. Most likely these will be adverse symptoms reported by the patient or an abnormality found on a routine follow-up physical exam, etc.

Item 3 — *Current Antiarrhythmic therapy* — Indicate the type of therapy the patient is currently receiving. "No therapy" indicates that the patient is receiving no antiarrhythmic drugs for ventricular arrhythmias and does not have an ICD. "ICD" indicates that the patient currently has a functioning ICD in place. "Antiarrhythmic drug" is defined as the patient receiving an antiarrhythmic drug for his ventricular arrhythmias. If the patient is taking an antiarrhythmic drug, you need to specify whether it is amiodarone and how many mg/day the patient is taking. It is possible that baseline tests may be completed after drug is started, and if so, the dose should be noted. "Other" antiarrhythmics would be checked if the patient is taking other antiarrhythmics in addition to amiodarone in a combination therapy. That antiarrhythmic would be listed and the dosage in mg/day should be recorded.

Item 4 — *Tests* — The following tests are recommended for patients taking amiodarone and should be repeated every 3-6 months:

Check "not done" for those tests not completed during this evaluation period.

Clinical Chemistry

AST (SGOT)
ALT (SGPT)
Alk Phos (Alkphos)
Bilirubin (Total) or
Bilirubin (Direct)
TSH - thyroid stimulating hormone
Thyroxine (T4) or
Thyroxine (free)

Pulmonary Function Evaluation

Diffusion Capacity (Hemoglobin corrected) varies with age.
Chest x-ray

Using local laboratory normal ranges, if the patient's lab value falls outside this range, note that finding and specify a possible cause of the abnormality. If the probable cause is (1) amiodarone, (2) concurrent drug therapy, (3) concurrent illness, or (4) other known cause, please provide a brief explanation.

ELECTROPHYSIOLOGIC STUDY FORM

Overview

This is to be completed for any baseline EP study (required or not), i.e., if a patient randomized to receive amiodarone or an ICD patient receives a baseline drug-free EP study, that EP study should be recorded on this form. If a patient is randomized to the sotalol arm and the investigator chooses to use EP guidance, the form must be completed for the baseline and evaluation studies. It is not required that a patient receiving drug therapy other than sotalol have an electrophysiologic study performed.

See page 4-3 for description of the EP protocol.

Item 1 — *Date of EPS* — Enter the month, day and year that the EP study was performed.

Item 2 — *Reason for completion* —

Baseline — is defined as any drug-free electrophysiologic study done prior to starting an antiarrhythmic drug.

Initial testing for suppression on sotalol or other drug suppression — is defined as steady-state testing of an antiarrhythmic drug. Most commonly this form will be used to record testing efficacy of sotalol but rarely this form may be used for testing other conventional antiarrhythmic drugs and, even more rarely, amiodarone.

Item 3 — *Current antiarrhythmic therapy* —

No therapy — indicates that the patient was on no antiarrhythmic drugs for ventricular arrhythmias, i.e., a "baseline" study.

ICD — indicates that the patient has an ICD in place as well as needing evaluation for antiarrhythmic drug therapy. Patients receiving ONLY an ICD should not have this form completed.

Antiarrhythmic drug — If "antiarrhythmic drug" is checked, specify which drug therapy the patient is receiving. If the "other" antiarrhythmic drugs is checked, write in the specific drug(s) and total dose of drug in mg/day.

Item 4 — *Which ventricular arrhythmias were induced* — Mark the most serious clinically relevant ventricular arrhythmia noted with each induction attempt. If more than two attempts at induction, report the two which demonstrate inducibility (i.e., the most clinically relevant arrhythmia) or lack of inducibility.

HOLTER FORM

Overview

Holter monitoring is intended primarily for sotalol patients. This is to be completed for any baseline Holter obtained (ICD or drug assigned patient), even if not required for AVID, during the baseline hospitalization.

It also is to be completed for any Holter recording used as a means of evaluating drug efficacy. The investigator has the option of evaluating antiarrhythmic drug efficacy (sotalol or other drugs, but, rarely amiodarone) using either a Holter monitor or electrophysiologic study techniques. See page 4-2 for an outline of Holter monitoring guidelines.

Holter recordings (tape or cassette) should be labeled with the patient ID and date recording started. The tape or cassette should be retained with the AVID records at the clinical center for possible subsequent review. It should not be sent to the CTC.

Item 1 — *Date recording started* — Enter the date that the Holter was attached.

Item 2 — *Reason for recording* —

Baseline — is defined as any drug-free Holter. It should be at least 24 hours in length (at least 18 analyzable hours) done prior to starting antiarrhythmic drug therapy.

Testing for sotalol or other drug suppression — Is defined as a Holter recording done after steady-state dosing is achieved. Again, the tape must be at least 24 hours in length with at least 18 analyzable hours.

Item 3 — *Current antiarrhythmic therapy* — List the current therapy the patient is receiving.

No drug therapy — Is marked for patients who are undergoing baseline Holter evaluation.

Antiarrhythmic drug — Is marked if the patient is being tested for antiarrhythmic drug efficacy. Specify whether the drug is either amiodarone, sotalol or other antiarrhythmic drugs. If "Other antiarrhythmic drugs" is checked, supply the drug name(s). For all antiarrhythmic drugs, provide the dose in total number of mg/day.

Item 4 — *Length of analyzable recording* — Enter the total number of hours and minutes of interpretable recording.

Item 5 — *Total number of VPDs* — Record the total number of ventricular premature depolarizations observed on the tape.

Item 6 — *Total number of couplets* — Record the total number of ventricular couplets at a rate ≥100 bpm.

Item 7 — *Total number of runs of ventricular repetitive complexes (≥3 beats) at a rate ≥100 bpm* — Record the number of runs (defined as 3 or more consecutive ventricular beats) at an average rate of ≥100 bpm.

ICD IMPLANTATION FORM

Overview

This should be completed for:

- a successful ICD implantation
- an attempted unsuccessful implantation
- any subsequent lead or generator replacement
- any subsequent lead repositioning (after initial implantation procedure).
- explantation of an ICD
- a patient randomized to ICD in which no ICD will be implanted
- a patient randomized to drug who "crosses over" to ICD

If the patient has two procedures performed in one day, a separate form should be completed for each procedure. This form should not be completed for any testing which precedes the ICD implantation.

If the patient is randomized to the device arm, but no ICD will be implanted (e.g., due to deteriorating patient condition), complete this form leaving items 3 -11 blank. Use the date that the decision was made not to implant.

In conjunction with this form, complete the following additional forms:

	ICD Implant	ICD Complications at 30 days after implant or hosp disch	ICD Evaluation at hosp disch	Lead/Gen Ident
Original implantation or replacement	X	X	X (unless leads only implanted)	X
Unsuccessful attempt	X	X		X (only for items left in)
Explantation	X	X		X (for items explanted)
Lead reposition	X	X		X (for items repositioned)
Randomized to ICD, no implantation attempted	X			

Item 1 — *Date* — Enter the date of implantation: mm/dd/yyyy. If the procedure spans two days (e.g, starts at 8:00 p.m. and is completed at 1:00 a.m. the next day), enter the date that the procedure started. It is important that the time is recorded in case there is more than one attempt to implant on the same day. The procedure is considered to start with the introduction of anesthetic, either local or general, whichever comes first.

Item 2 — *Is this procedure?* — Indicate whether this implantation is: an original implantation involving leads only, generator only, or both leads and generator; or a generator replacement, a lead replacement or repositioning, or an explantation. If no implantation will be attempted, complete items 1, 2 and 12 only. A lead repositioning or lead replacement should prompt completion of this form only if it is done as a separate procedure from the original implantation. That is, if a lead needs to be repositioned during the original implantation, an additional form need not be completed. A procedure/operation is considered to have been completed when the patient is taken out of the procedure/operating room. If any object (lead and/or generator) is implanted and left in place, explanted or repositioned, complete a Lead and Generator Identification form to specify the items involved.

For example, if a lead requires repositioning after the initial implant procedure, you will need to complete a separate ICD Implantation form and a separate Lead and Generator Identification form for the second procedure. If, during that procedure, the generator fails, you would check both "Generator" and "Lead replacement/repositioning" on the second ICD Implantation form.

If this procedure is due to a generator or lead system failure other than normal expected battery depletion, notify the CTC immediately by FAX and verbally by telephone call. Notification is required within 10 working days of discovery of the malfunction. Any violation of this guideline may result in the termination of a site's participation in the study and could jeopardize the entire trial.

If the generator is replaced, indicate whether the replacement was for expected end of life of the unit or other reason (e.g., infection). Specify the number of months in use for units replaced for battery depletion. Round to the nearest whole month.

If any lead is replaced or repositioned, mark the appropriate bubble. Note that repositioning for simple dislodgement does not require special notification to the CTC. Lead replacement for a simple rise in defibrillation threshold likewise does not require special notification to the CTC. However, lead failure due to wire fracture or insulation failure must be reported immediately.

Item 3 — *Location of procedure* — Indicate whether the procedure was done in an operating room (OR) or EP or cath lab.

Item 4 — *Participating physicians* — Implantation of an ICD may be performed primarily by an electrophysiologist, primarily by a surgeon, or may be combined

and nearly equal effort. Furthermore, each aspect of ICD implantation may be performed by one of these individuals, while another aspect may be performed by someone else. In this section, simply check who was primarily responsible for the lead placement, repositioning or explantation, intraoperative electrophysiological testing (including device testing), and pocket formation and closure. This determination may be somewhat arbitrary. It is possible that another individual, for example, a physician's assistant, nurse, or a representative of a device company may be primarily responsible for one aspect of the procedure. If so, check "other."

If the procedure was a generator replacement only or explant and some of the procedures were not done, simply mark not done.

Item 5 — *Route of implantation* — Choose the one most appropriate description of the route of implantation. If multiple attempts were made to implant the device, a separate ICD Implantation form must be completed for each attempt. **Leave blank if lead repositioning or generator replacement only.**

Route of NTL insertion. Indicate which approach was used for insertion of leads. **Leave blank if generator replacement only.**

Mark the bubble describing the site for the location of the generator. **Leave blank if procedure only involved leads.**

Item 6 — Duration of *Procedure* — The duration of the procedure is defined from the start of the infiltration of local anesthesia or incision or percutaneous puncture, whichever comes first, to the end of the procedure, usually identified as the completion of the suturing procedure for the pocket. The procedure time is intended to capture the "skin-to-skin" duration of the ICD implantation. It should <u>not</u> include the time waiting in the operating room prior to the start of the procedure, nor time waiting in the operating room at the completion of the procedure until the removal to the recovery room. Usually this time can be obtained from the anesthesia notes, although the procedure time likely will be different than the anesthesia time.

Item 7 — A*nesthesia* — Check the type of anesthesia given. Check whether an anesthesiologist or an anesthetist was present for the procedure <u>and administered anesthesia</u>. Simply "standing by" or "on call" does not qualify as presence of an anesthesiologist or anesthetist.

Item 8 — *Use of antibiotics* — Antibiotics include oral and IV antibiotics given either prophylactically or because of infection related to the procedure. "Pre-op" includes any time up to the start of the operative procedure.

Item 9 — *Irrigation* — Specify whether irrigation of the pocket with antibiotics was performed. The specific type of antibiotic is unimportant. Antibiotic ointment placed on the skin does <u>not</u> qualify for a "yes" answer to this question.

Item 10 — *Procedures performed at the time of implantation* — Specify additional procedures which were performed at the time of the implantation of the device. List the number of distal anastomoses if coronary artery bypass graft surgery was performed. If heart valve repair or replacement was performed, indicate all valves repaired or replaced. Aneurysm surgery for nonarrhythmia purposes (e.g., management of severe CHF) is not an exclusion criterion for AVID. Time on cardiopulmonary bypass should be filled in as appropriate.

Item 11 — *Defibrillation threshold* —

Three energies should be tested and successful in converting ventricular fibrillation. Do not include energies used for cardioversion of ventricular tachycardia. Specify whether this testing was done or not.

Specify whether the 10 Joule safety margin was achieved. That is, was the defibrillation threshold at least 10 Joules below the maximum output of the device?

Item 12 — *Was implantation successful?* — Successful implantation means that a system capable of functioning resulted (i.e., both leads and generator were working). If this implantation was not successful, indicate the one reason which describes why.

Second attempts at implantation (even on the same day) should be recorded on a separate ICD Implantation form.

Leave this question blank for explanted devices.

ICD IMPLANTATION COMPLICATIONS FORM

Overview

This should be completed for any ICD implantation, explantation, repositioning or replacement of leads or generators. In other words, for almost every ICD Implantation form, there should be an ICD Implantation Complications form.

This form should be completed 30 days after the implant procedure. If the patient's baseline hospitalization extends beyond 30 days, complete the form at hospital discharge. Since early surgical complications are classified and reported within 30 days of the procedure (or at hospital discharge, if later), it is important to complete this form at 30 days even if it means deducing the complications at exactly 30 days. For example, the 30th day post-implant falls on a Sunday. You phone the patient on Monday and determine there were no complications since hospital discharge. You can therefore deduce that there were also no complications at 30 days either and date the form at that date.

The form should be completed even if the patient experienced NO complications of the procedure.

Item 1 - *Date of evaluation* - Enter the date that you contacted the patient (i.e., 30 days after ICD implantation or at hospital discharge whichever is later).

Item 2 - *Timing of the evaluation* - Indicate whether, at the time of the evaluation, the patient had previously been discharged from the hospital or was being discharged from the hospital (i.e., long hospitalization).

Item 3 — *Were there any complications* — If the patient experienced any complications related to the implantation procedure, indicate here. If there were no complications, sign the form and FAX to CTC.

Note that unexpected generator failure or lead failure must be reported to the CTC immediately both by FAX and verbally by telephone call.

Infection related to the implantation procedure is defined as a condition requiring either hospitalization or prolongation of hospitalization which requires antibiotics (not including prophylactic antibiotics). Administration of antibiotics on an out-patient basis does not qualify as an infection complication unless the patient is subsequently hospitalized for the infection.

The following complications need chart documentation sent to the CTC including operative notes, anesthesia notes, ICD implant notes, MD notes describing the complication, pertinent ECG/lab test and hospital summary:

- Bleeding requiring reoperation or transfusion
- Cardiac perforation
- Coronary laceration
- Death
- Erosion/extrusion

- Explantation
- Generator failure
- Hematoma that results in surgical evacuation/correction
- ICD infection
- Lead failure
- Pneumothorax
- Stroke

LEAD & GENERATOR IDENTIFICATION FORM

This must be completed whenever a generator, lead, adapter or connector is implanted, explanted or repositioned, including failed attempts or partial implants where any part of the system is left implanted when the patient leaves the OR or EP lab.

Item 1 — *Date:* Enter the date of the procedure. If leads and generator were placed on separate days, complete 2 forms indicating what was implanted on each day.

Item 2 — *Generator:* Specify the manufacturer and the model number and serial number of the unit. Indicate whether the unit was implanted or explanted.

Item 3 — *Lead systems implanted, explanted or repositioned at this time:* This section lists the lead systems implanted, repositioned or explanted during this procedure. Specify the manufacturer, model number, and serial number of each lead. Defibrillation leads/patches should be listed first. An "Other" manufacturer bubble is available for sensing electrodes, adapters or connectors approved for use with Ventritex devices only. Again, these sensing leads should be listed after the leads and patches that are used for defibrillation. It is not necessary to note the company name for these "other" manufacturers.

List the lead configuration. For a transvenous lead that has more than one electrode, specify the location of the most distal electrode of the lead. List each lead separately. Posterior position for subcutaneous patches includes subscapular. For an adapter/connector, check the appropriate bubble and record the manufacturer, model and serial number. These should be noted last.

Do not include such things as lead end pin caps (used to cap off old pacer leads) or the length of the lead. Do not record leads that weren't implanted due to extraneous reasons (e.g., wrong size or contaminated).

For attempted but failed NTL implantation where no lead is implanted, it is not necessary to record lead serial numbers unless the failure is due to a flaw in the lead. In this case check "explanted" and leave item 2 "generator" section blank.

For replacement due to generator or lead system failure other than normal battery depletion, FAX this form immediately to the CTC as part of your required notification of unexpected system failure. You must phone the CTC in addition to FAXing this form and any other required documentation.

HOSPITALIZATION FORM

Overview

The Hospitalization form is completed:

(1) At the time of discharge from the baseline hospitalization where the patient was randomized and AVID therapy commenced;
(2) At discharge for each subsequent hospitalization, whether or not the hospitalization is for cardiac-related reasons.
(3) Anytime a patient visits the ER for any reason.
(4) Anytime a patient has a "short stay" procedure.

Item 1 — *Date of hospital admission* — Enter the date that the patient was admitted to the hospital or visited the ER. If the patient was admitted to the emergency room on the day prior to the actual hospital admission date, enter the emergency room admission date.

For the baseline hospitalization, enter the date that the patient was admitted to the hospital where randomization occurred.

For subsequent hospitalizations, where the patient may be transferred from one hospital to another, include the entire hospital stay, beginning with the initial admission.

Date of hospital discharge or death — Enter the date the patient left the hospital (alive) or the date that the patient expired in-hospital. If the visit admission and discharge occurred on the same day, list as such. If the patient was discharged to a rehabilitation facility (even if in the same institution) or to a nursing home or other extended care facility, the patient is considered discharged. This information will be noted on the Healthcare Utilization Abstract form.

Item 2 — *Type of admission* — Note whether the patient had an ER visit only, a "short stay" admission (<24 hours) or an overnight hospitalization.

Item 3 — *Name of hospital* — Enter the name of hospital.

If the patient's hospitalization included a transfer, list the receiving hospital, that is, the hospital from which the patient was ultimately discharged.

Location — List the city and state where the hospital is located.

Item 4 — *Antiarrhythmic therapy at admission* — Specify the antiarrhythmic therapy. If the patient is receiving antiarrhythmic drugs, compute the total daily dose in mg/day.

Item 5 — *Primary reason for hospitalization* — Note whether the hospitalization is cardiac or non-cardiac related. For cardiac, check only one primary reason for hospitalization. For non-cardiac specify the primary reason.

For the baseline hospitalization, "Cardiac" and "Baseline hospitalization" will always be checked. Some patients' baseline hospitalizations will include acute treatment of their index arrhythmia. Other patients will have had their index arrhythmia several weeks or months prior to being admitted for baseline hospitalization and randomization. "Baseline" refers to the hospitalization(s) during which the AVID randomization and initiation of therapy occurred. If these occur on two separate hospitalizations (e.g., patient is randomized to ICD, discharged from hospital, and readmitted for the ICD implantation) both hospitalization forms would have "Baseline" checked.

The other reasons for hospitalization will be related to rehospitalizations, ER or "short stay" visits. Patients who are seen at the hospital after the initial baseline hospitalization will need to have the primary reason for their hospitalization, ER or "short stay" visit marked. If that reason is cardiac, only one of the following causes will be marked:

Recurrent ventricular arrhythmia-Recurrent ventricular arrhythmia, regardless of type of antiarrhythmic therapy, is defined as ventricular fibrillation requiring defibrillation, ventricular tachycardia or nonsustained ventricular tachycardia with symptoms requiring hospitalization. In patients who have an ICD, a recurrent ventricular arrhythmia is one that is either terminated by the ICD but results in hospitalization, or, if not terminated by the ICD, required other measures to terminate the arrhythmia (i.e., external cardioversion/pacing, IV antiarrhythmic drugs, and/or ICD reprogramming). A Recurrent Arrhythmia form must also be completed.

ICD shock(s) not related to ventricular arrhythmia — Check this bubble if a patient is admitted for evaluation of ICD shocks thought unrelated to a ventricular arrhythmia, e.g., atrial fibrillation or sinus tachycardia.

Presumed contributing factors:

No factors identified — Check here if, after medical evaluation, no contributing factors are identified.

New or worsened CHF — Mark if the patient advances by one or more NYHA classifications (e.g., from no CHF to Class I, from Class I to Class II, etc.).

New or worsened ischemia or MI — Mark if the patient's angina progresses to a more severe CCS classification, or if the patient rules in for an MI.

Supraventricular arrhythmias — If the patient was found to have atrial fibrillation or flutter that was felt to be responsible for the ICD therapies, this bubble should be marked.

Electrolyte imbalance — Mark if abnormal electrolytes, thought to be responsible for an arrhythmia, were found on admission.

Lead failure — If lead repositioning or replacement was necessary during this admission, this bubble should be marked. If lead replacement is performed for unexpected lead failure (e.g., wire fracture or insulation break), the CTC must be notified immediately.

Generator failure — If generator failure occurs for any reason except expected battery depletion, the CTC must be notified immediately.

Other — Other contributing factors should be specified here.

Information not available the patient was hospitalized at a remote location, and records identifying factors were unavailable, this bubble should be marked.

ICD evaluation not prompted by shocks — ICD patients will occasionally have ICD testing performed to evaluate device function.

Other arrhythmia (not resulting in ICD shocks) — Most often other arrhythmias will include atrial fibrillation and atrial flutter, but could potentially include less common arrhythmias such as heart block or bradycardia.

Syncope — Syncope is defined as transient complete loss of consciousness, thought to be cardiac in origin. Non-cardiac syncope would be recorded under "Non-cardiac, specify."

Confirmed MI — MI is defined by clinical symptoms, electrocardiographic changes, enzyme changes, or a combination of these findings, as diagnosed by the individual Investigator.

Angina or suspected MI - ruled out — If the patient advances by one or more CCS classifications (e.g., from no angina to Class I, from Class I to Class II, etc.).

New or worsened CHF — If the patient advances by one or more NYHA classifications (e.g., from no CHF to Class I, from Class I CHF to Class II, etc.). If yes, mark the NYHA class at admission.

Cardiac procedure or cardiac surgery — This category includes all cardiac procedures e.g., cardiac surgery, pacemaker implantation, etc. It does not include diagnostic procedures, e.g., catheterization without PTCA or EPS.

Adverse symptom due to antiarrhythmic drug — This includes any adverse symptom which, in the investigator's opinion, is likely related to antiarrhythmic drug treatment. Discontinuation of the drug or dose reduction should alleviate the adverse symptom.

Late adverse symptom due to ICD — This includes lead/generator failure not associated with shocks.

Other — Please specify the reason.

Item 6 — *Events during hospitalization* — Mark all the events occurring during hospitalization and complete the appropriate events form.

Death — Complete the Death form.

Recurrent ventricular arrhythmia — Check this bubble for any recurrent ventricular arrhythmia, regardless of type of antiarrhythmic therapy, requiring external cardioversion/pacing, IV antiarrhythmic drugs, and/or ICD reprogramming to terminate the arrhythmia. Complete a Recurrent Arrhythmia form.

MI — is defined by clinical symptoms, electrocardiographic changes, enzyme changes, or combinations of these findings.

New or worsened angina — If the patient advances by one or more CCS classifications (e.g., from no angina to Class I angina, from Class I angina to Class II, etc.).

New or worsened CHF — If the patient advances by one or more NYHA classifications, (e.g., from no CHF to Class I, from Class I to Class II, etc.).

Cardiac procedure or cardiac surgery — Be sure to mark all procedures that were done during this hospitalization, including pacemaker insertion.

Thrombolytic therapy — Mark this bubble if the patient receives intravenous or intracoronary thrombolytic therapy immediately prior to, or during this hospitalization.

CABG — coronary artery bypass graft surgery. Mark if CABG was initiated, whether or not successfully completed.

PTCA/atherectomy — percutaneous transluminal coronary angioplasty. This bubble should be marked if PTCA was attempted, whether or not successfully completed. Atherectomy includes laser atherectomy, Rotablator, excisional atherectomy, and other techniques.

ICD implantation — Include insertion or attempted insertion of any implantable cardiac defibrillator. ICD Implantation and related forms must also be completed.

Pacemaker implantation — Mark only if the patient is receiving a new or replacement permanent pacemaker.

Arrhythmia surgery/aneurysm resection — Arrhythmia surgery may include endocardial resection, cryoablation, encircling ventriculotomy, laser ablation, and other techniques. Aneurysm resection is a removal and/or plication of aneurysmal, dead, and/or scarred myocardium.

Patients scheduled for arrhythmia surgery of this sort on the baseline hospitalization are excluded from the randomized portion of the AVID study. Arrhythmia surgery is considered a "crossover." Complete a Change of Study Therapy form.

Ablation — successful or unsuccessful catheter ablation of any cardiac arrhythmia. This is considered a "crossover." Complete a Change of Study Therapy form as well.

Valve repair/replacement — Valve repair includes balloon valvuloplasty, as well as open heart valve repair. Valve replacement includes surgical replacement of one or more of the cardiac valves.

Other cardiac procedures —

Other cardiac events (specify) — Specify any other cardiac events which occurred.

Item 7 — *Procedures during baseline hospitalization only* — The section is completed only for the baseline hospitalization. Note whether the patient had coronary angiography, baseline (drug free) EPS and/or baseline (drug free) Holter done after the index arrhythmia. If Yes is checked, complete the appropriate form(s).

Although the AVID protocol requires EP and/or Holter guidance for sotalol —— patients only, we are collecting this baseline EP and Holter information, if performed, on non-sotalol assigned patients. Do not check "Yes" for any EP testing performed post-ICD implantation.

Leave this Section blank for subsequent hospitalizations.

Item 8 — *Was there an intended long-term change in study therapy?* — If a patient was discharged from the hospital with any of the following changes in AVID therapy, complete a Change in Study Therapy form:.

- Addition or discontinuation of an AAD (Class I or III) to a drug assigned patient
- Addition or discontinuation of an AAD (Class I or III) to an ICD assigned patient
- Addition of ICD to a drug assigned patient
- Explantation of an ICD
- Turning ICD from “on” to “off”

If the dose of antiarrhythmic drug was adjusted, do not complete a Change in Study Therapy form.

If a device was reprogrammed, complete an ICD Evaluation form.

CONCURRENT DRUGS FORM

Overview

The Concurrent Drugs form is completed at: hospital discharge (baseline AVID hospitalization); each scheduled follow-up visit; and for death. It should be completed even if the patient is taking no concurrent medications.

Item 1 — *Date* — Enter the date the drug information was obtained. In the event of death record the date of the onset of symptoms related to death. For example, if a patient is resuscitated from a cardiac arrest but never regains consciousness and dies 2 days later, the form would be dated the day of the arrest.

Item 2 — *Reason for completion*

Hospital discharge, baseline hospitalization — Record drugs patient was sent home on from the baseline hospitalization, i.e., where randomization occurred.

Scheduled follow-up — Record the specific follow-up month for which the patient is being seen. The date of this form should match the follow-up form visit date.

If the hospital discharge date coincides with the 1 month follow-up, check the bubble marked "Hospital discharge, baseline hospitalization." You will automatically get credit for both the baseline discharge and the follow-up.

Death — In the event a patient dies, record the medications prescribed at the onset of symptoms related to the death.

If the patient dies before baseline hospital discharge, check the bubble for death and record the medications at the onset of acute symptoms related to death.

Item 3 — *Current antiarrhythmic therapy* — Include any antiarrhythmic medications the patient is taking at the time the form is completed.

Item 4 — *Medications*

Indicate any concurrent medications. Include routinely taken medications (e.g., beta-blockers) and those prescribed "as needed" (e.g., nitroglycerin for angina or aspirin for osteoarthritis). If a particular drug is actually a combination of two therapies (e.g., Prinzide), mark "Yes" to both categories (e.g. Prinzide is an ACE inhibitor and a diuretic).

For concurrent medications at hospital discharge for the baseline hospitalization indicate all medications prescribed for the patient at the time of discharge.

Other cardiac drugs: write in any additional cardiac medications including mineral supplements that are specifically prescribed such as magnesium. Do not include such medications as antibiotics, pain medications, vitamins, stool softeners, inhalers, eyedrops, sedatives, etc.

Each drug group is defined below with a list of currently used drugs (by both generic and trade names).

Beta blocker other than sotalol — Medication that blocks the beta adrenergic receptors. These drugs are prescribed for multiple purposes, including the treatment of angina, hypertension, migraine headaches, arrhythmias in mitral valve prolapse, prophylaxis post MI, symptoms of hyperthyroidism, etc.

Generic — acebutolol, alprenolol, atenolol, betaxolol, carteolol, labetalol, metoprolol, nadolol, penbutolol, pindolol, propranolol, timolol

Trade — Blocadren, Cartrol, Corgard, Corzide, Inderal (LA), Inderide (LA), Kerlone, Levatol, Lopressor, Lopresor HCT, Normadyne, Sectral, Tenoretic, Tenormin, Timolide, Toprol XL, Visken

Calcium Channel Blocker — Also termed calcium antagonist, it acts on the slow inward current of the calcium channels. Prescribed for the treatment of reentrant arrhythmias, supraventricular arrhythmias, angina, and hypertension.

Generic — amlodipine, bepridil, diltiazem, felodipine, isradipine, nifedipine, nimodipine, verapamil.

Trade — Adalat, Calan SR, Cardene (SR), Cardizem (CD or SR), Dilacor XR, Dynacirc, Isoptin (SR), Nimotop, Norvasc, Plendil, Procardia (XL), Vascor, Verelan

Digitalis preparation — Cardiac glycoside preparation that is used to augment the force of myocardial contraction, suppress supraventricular arrhythmias, and limit ventricular rate response to atrial tachyarrhythmias.

Generic — digitalis, digitoxin, digoxin

Trade — Crystodigin, Lanoxicaps, Lanoxin

Inotropic agent other than digitalis — A drug which increases the force or the strength of contraction.

Generic — amrinone, dobutamine, dopamine, milrinone

Trade — Dobutrex, Inocor, Intropin, Primacor

Diuretic — Drug that increases urine volume by acting directly on the kidney to inhibit solute and water absorption. Prescribed primarily for the management of heart failure or hypertension, it reduces interstitial edema and intravascular volume.

Generic — acetazolamide, aldactone, amiloride, benzthiazide, bumetanide, chlorathiazide, dichlorphenamide, ethacrynic acid, furosemide, hydrochlorothiazide, hydroflumethiazide, indapamide,

methyclothiazide, metolazone, quinethazone, spironalactone, triamterene.

Trade — Aldactazide, Aldactone, Bumex, Capozide, Daranide, Diamox, Dyazide, Dyrenium, Diucardin, Diuril, Edecrin, Enduron, Esidrix, Esimil, Exna, Hydrodiuril, Hydromox, Lasix, Lozol, Maxzide, Midamor, Minizide, Moduretic, Mykrox, Oretic, Prinzide, Vaseretic, Zaroxolyn, Zestoretic

ACE inhibitor — Relaxes vascular smooth muscle, either directly or indirectly, and alters the loading conditions of the heart and the heart's mechanical performance.

Generic — captopril, benazepril, enalapril, fosinopril, lisinopril, quinapril, ramipril

Trade — Accupril, Altace, Capoten, Capozide, Lotensin, Monopril, Prinivil, Prinzide, Vaseretic, Vasotec, Zestoretic, Zestril

Nitrate — Organic nitrate compound that relaxes vascular smooth muscle, predominantly in the venous circulation, primarily reducing venous tone and preload, secondarily reducing afterload. Nitrate preparations are prescribed primarily for the acute or chronic control of angina.

Generic — erythrityl tetranitrate, isosorbide dinitrate, isosorbide mononitrate, nitroglycerin

Trade — Cardilate, Deponit, Dilatrate, Duotrate, Ismo, Isordil, Minitran, Nitro-Bid, Nitrodisc, Nitro-Dur, Nitrogard, Nitroglyn, Nitrolingual, Nitrong, Nitrol Ointment, Nitrostat, Peritrate, Sorbitrate, Transdermal-NTG, Transderm-Nitro

Other vasodilator or afterload reducing agent — Any agent other than ACE inhibitor or nitrate that relaxes vascular smooth muscle, directly or indirectly, and alters loading conditions of the heart and the heart's mechanical performance. These drugs are generally used in the treatment of congestive heart failure, hypertension, or angina, and may be termed venodilators or arteriolar dilators. Venodilators (or preload reducing agents) are those drugs that increase venous systemic vascular beds, thus decreasing pulmonary congestion. The arteriolar dilators (or afterload reducing agents) induce a fall in systemic vascular resistance, thus augmenting left ventricular function and increasing cardiac output. Many agents possess both venodilating and arteriolar dilating properties.

Generic — dibenzyline, doxazogin, flosequinan, guanadrel, guanethidine, hydralazine, minoxidil, nitroprusside, papaverine, phentolamine, prazosin, terazosin

Trade — Apresazide, Apresoline, Cardura, Esimil, Hylorel, Hytrin, Ismelin, Lonitin, Manoplax, Minipress, Minizide, Nipride, Pavabid, Regitine, Ser-ap-es, Unipres.

Other antihypertensive not listed above — Excluding diuretics, beta blockers, nitrates, venodilators and afterload reducing agents, any antihypertensive drug prescribed for the control of blood pressure.

Generic — clonidine, deserdipine, diazoxide, guanethidine, methylclothiazide, methyldopa, phenoxybenzamine, reserpine.

Trade — Aldoclor, Aldomet, Aldoril, Catapres, Combipres, Dibenzyline, Diupres, Enduron, Enduranyl, Esimil, Harmonyl, Hydropres, Ismelin, Minoxidil, Oreticyl, Serpasil.

Lipid lowering agent — A drug which acts to lower serum cholesterol or triglycerides.

Generic — cholestyramine, clofibrate, colestipol, dextrothyroxine, gemfibrozil, lovastatin, niacin, nicotinic acid, pravastatin, probucol, simvastatin.

Trade — Atromid-S, Colestid, Choloxin, Lopid, Lorelco, Questran, Mevacor, Niacor, Nicobid, Nicolar, Pravachol, Zocor.

Potassium supplement — Potassium compound prescribed for the purpose of preventing hypokalemia. Supplements are available in tablets, capsules, crystals, liquid, and multiple compounds (chloride, citrate, gluconate, bicarbonate). Potassium compounds prescribed for purposes other than treatment of the serum potassium are not included here (i.e., iodide preparations, phosphates, expectorants).

Generic — potassium chloride.

Trade — K-Dur, K-lor, K-Lyte, K-Norm, K-Tab, Kato, Klor-Con, Klorvess, Klotrix, Kolyum, Micro-K, Rum-K, Slow-K, Ten-K.

Hypoglycemic — Agent prescribed for the treatment of elevated serum glucose; may be administered orally or parenterally.

Generic — acetohexamide, chlorpropamide, glipizide, glyburide, insulin, tolazamide, tolbutamide.

Trade — Insulin: Humulin, Iletin, Insulatard, Lente, Mixtard, NPH, Novolin, Semilente, Regular, Ultralente, Velosulin.
Oral: DiaBeta, Diabinese, Glucotrol, Glynase, Micronase, Orinase, Tolinase

Anticoagulant — Compound which alters clotting, prescribed to prevent the development of microemboli or thrombus formation.

Generic — heparin, warfarin.

Trade — Coumadin, Heparin.

Anti-inflammatory agent, analgesic — Any agent assigned to provide analgesic by reducing inflammation: this may be aspirin, nonsteroidal anti-inflammatory, or a steroid preparation.

1) Aspirin-based anti-inflammatories:

Generic — aspirin, acetylsalicylic acid, salsalate, trisalicylate.

Trade — Anacin, Asacol, Ascriptin, Bufferin, Disalcid, Easprin, Ecotrin, Monogesic, Salflex, Trilisate and many other over-the-counter preparations.

2) Non-steroidal anti-inflammatories (NSAID):

Generic — diclofenac sodium, diflunisol, etodolac, fenoprofen, flurbiprofen, ibuprofen, indomethacin, ketoprofen, ketorolac, meclofenamate, nabumetone, naproxen, mefenamic acid, piroxicam, sulindac, tolmetin.

Trade — Advil, Anaprox, Ansaid, Clinoril, Dolobid, Feldene, IBU, Indocin, Lodine, Meclomen, Motrin, Nalfon, Naprosyn, Nuprin, Orudis, Piroxicam, Ponstel, Relafen, Tolectin, Toradol, Voltaren.

3) Steroids:

Generic — dexamethasone, prednisone, hydrocortisone, methylprednisone.

Trade — Decadvon, Deltasone, Depo-medrol, Hydrocortone, Medrol.

Antiplatelet — Platelet suppressive agent that inhibits platelet release reactions and aggregation, thought to be of value in improving platelet survival, reducing incidence of emboli, and impeding clot formation.

Mark the "ASA" bubble if patient is on aspirin post MI or post cardiac surgery; mark the "other" bubble, and specify, if patient is on antiplatelet other than aspirin.

Other antiplatelet medication:

Generic — dipyridamole, sulfinpyrazone, ticlodipine.

Trade — Anturane, Persantine, Ticlid.

Bronchodilator — An agent which relaxes bronchial smooth muscle, usually given for chronic lung disease.

Generic — albuterol, beclomethasone, cromolyn sodium, diphylline, epinephrine, flunisolide, ipratropium, isoetharine, isoproterenol, metaproterenol, oxytriphylline, pirbutelol, terbutaline, theophylline.

Trade — Aerobid, Aerolate, Alupent, Asoron, Atrovent, Beclovent, Brethaire, Brethine, Bricanyl, Bronkephrine, Bronkometer, Bronkosol, Choledyl, Decadron, Dilor, Intal, Isoetharine, Isuprel Hcl, Luphyllin, Marax, Maxair, Metaprel, Primatene, Proventil, Quibron, Respbid, Slo-bid, Sus-phrine, Tedral, Theodur, Thealair, Theo-X, T-Phyl, Tornalate, Vanceril, Ventolin, Uniphyl.

Antidepressant — An agent used to treat depression.

Generic — amitryptylline, amoxapine, bupropion, clomipramine, desipramine, doxepin, fluoxetine, imipramine, isocarboxazid, maprotiline, meprobamate, nortriptylline, phenelzine, protriptylline, sertraline, tranylcypromine, trazodone, trimipramine.

Trade — Adapin, Anafranil, Asendin, Deprol, Desyrel, Elavil, Endep, Etrafon, Limbitrol, Ludiomil, Marplan, Nardil, Norpramin, Pamelor, Parnate, Prozac, Sinequan, Surmontil, Tofranil, Triavil, Vivactil, Wellbutrin, Zoloft.

Phenytoin — An agent used to treat epilepsy.

Generic — phenytoin

Trade — Dilantin

Histamine antagonist — An agent which blocks histamine receptors, causing anticholinergic (drying) and sedative effects; used in the treatment of allergic reactions, motion sickness, peptic ulcers, & Parkinsonism. These are <u>not</u> antihistamines. Record antihistamines (e.g., Seldane) as "other."

Generic — cimetidine, diphenhydramine, famotidine, nizatidine, ranitidine

Trade — Actifed, Atarax, Axid, Benadryl, Pepcid, Tagamet, Unisom, Vistaril, Zantac.

Thyroid replacement — An agent used to replace thyroid hormones.

Generic — levothyroxin, thyroid, thyroxine

Trade — Cytomel, Euthroid, Levothroid, Levoxine, Synthroid, Thyrolar

Other cardiac, specify — List only other <u>cardiac</u> medications which do not fit into the categories of drugs in the list above. Using 15 or fewer characters, enter the generic name of the drug deemed most important by the investigator. If the patient is taking supplemental magnesium for low levels include here. DO NOT list over-the-counter medications, hormonal supplements, oral contraceptives, tranquilizers or sedatives.

FOLLOW-UP

A. Overview

All patients will be followed to a common termination date, August 31, 1998. The ability of the study to produce meaningful results depends, in part, on the completeness of follow-up information. This means that you need to keep careful track of the patients randomized, making sure that you see them for each follow-up visit and that you do not lose track of any patient.

Each follow-up visit is important. Even if the patient has had no medical problems, you should still arrange an in-clinic evaluation for each quarterly scheduled follow-up. This is important so that we assess symptoms and events uniformly.

Remember, ALL patients must be accounted for in 1998. If you are having trouble following a patient, phone the CTC to discuss ways of dealing with hard to follow patients.

If a patient is planning to move out of the area (or has moved), you may consider shifting follow-up to another AVID center that is more convenient. Contact the CTC if the patient moves or is planning to move.

Patients will continue to be followed whether or not they are taking their assigned AVID therapy. Their follow-up schedule will be unchanged. NO patient will be withdrawn from follow-up unless he or she specifically requests (i.e., withdraws consent for the study).

If you believe that you have truly lost a patient, contact the CTC immediately. You will need to complete a Lost to Follow-up worksheet and provide documentation of efforts you have made to locate the patient. The Principal Investigator will have to write a letter describing the situation.

The clinic follow-up contacts are your chance to keep the patient involved with the study. In a clinical study where long-term interest and cooperation are essential, the importance of good rapport with the patient cannot be over-emphasized. The patient has volunteered for this study. Your contact with the patient and his or her family should reflect our appreciation for their contribution. Make sure that the clinic visits are conducted in a comfortable location for the patient, that you spend enough time with the patient to address all of his or her concerns, as well as those of the family, and that you do not seem rushed.

The follow-up schedule is based on the date that the patient is randomized. All patients will be seen one month following randomization and then every three months in clinic.

The schedule for procedures and tests at each follow-up is:

Form to be completed	1 Mo	3 Mo	6 mo	9 Mo	12 Mo	every FU thereafter	every 6 mos there after
Follow-up	x	x	x	x	x	x	
Concurrent drugs	x	x	x	x	x	x	
ECG			x		x		x
Adverse symptoms	x	x	x	x	x	x	
Amiodarone patients only							
Lab data			x		x		x
ICD assigned patients only							
ICD evaluation	x	x	x	x	x	x	
QL forms for patient		x	x		x		x
QL forms for spouse/partner		x	x		x		x
Utilization Abstract (monthly)*	x	xxx	xxx	xxx	xxx	xxx	
Shoebox (bill/receipts)*		x	x	x	x	x	

* Selected patients only xxx = monthly

B. Scheduled follow-up

A follow-up schedule, like the one in Figure 5 (page 5-4) for each patient will be sent to you shortly after randomization. Keep this schedule in the patient's AVID chart to facilitate scheduling follow-up visits. In addition, on a monthly basis, you will receive a reminder list from the CTC of patients coming due for a scheduled follow-up visit. When QL forms are to be completed, the appropriate QL form will be sent with the follow-up reminder report.

Each scheduled follow-up visit (at one month and then quarterly) should be an in-clinic visit, whether the patient has an ICD or not. The study coordinator can conduct this visit. If there are medical problems that warrant additional attention, the AVID physician should, of course, see the patient. The one month follow-up should be recorded even if the patient is still hospitalized for initiation of therapy.

The follow-up visit should be conducted within two weeks on either side of the target date for that follow-up. If it is not possible to schedule an in-clinic visit during this time window, every effort should be made to complete as much of the follow-up as possible within the window including having a local cardiologist provide the information if the patient cannot come to clinic or by telephone. Schedule an in-clinic visit as soon as possible before or after the window to complete the rest of the forms. For example, if a patient is hospitalized in a different city when you contact him for follow-up, you should complete as much of the follow-up as possible over the phone during the follow-up time window. You may be able to enlist the assistance of the attending cardiologist. Complete the remaining forms when it is possible to see the patient in clinic.

An ECG must be obtained at 6 months, 12 months, and 18 months and every 6 months thereafter (see Baseline Section).

The data forms associated with the follow-up visit should be FAXed to the CTC within four weeks of the follow-up visit.

Procedures that must be performed at each scheduled follow-up for all patients include:

- Completing the Follow-up form which is basically a checklist of events or change in condition occurring since the last follow-up. This form triggers completion of other specific event forms (Hospitalization, Recurrent Arrhythmia, Change of Study Therapy).
- Complete a Concurrent Drugs form (see Section 4.C. Hospital Discharge)
- Complete an Adverse Symptoms form, whether or not the patient has experienced any adverse symptoms since the last follow-up.
- For all patients assigned to the economic shoebox evaluation, telephone the patient monthly to abstract health care utilization, complete a Health Care Utilization Abstract form, and at each follow-up, collect bills/receipts (see Section 8. Economic Evaluation Component).

Figure 5

AVID Trial Follow-up Schedule

Patient: 01-024-5 MBOL Clinical Center: Alabama

Randomized: 06/15/1993

Follow-up	Target Date	Time Window*	Date Scheduled
1 month	07/15/1993	07/01/1993 - 07/29/1993	_____
3 months	09/15/1993	09/01/1993 - 09/29/1993	_____
6 months	12/15/1993	12/01/1993 - 12/29/1993	_____
9 months	03/15/1994	03/01/1994 - 03/29/1994	_____
12 months	06/15/1994	06/01/1994 - 06/29/1994	_____
15 months	09/15/1994	09/01/1994 - 09/29/1994	_____
18 months	12/15/1994	12/01/1994 - 12/29/1994	_____

etc.....

* A follow-up done within this time window will be considered done on time.

Follow-up of Patients on Antiarrhythmic Drug

At each follow-up visit, you should assess the patient's adherence to therapy by interviewing the patient about how reliably he/she has been about taking study pills. We will not require pill counts.

Patients taking amiodarone should, additionally, have blood tests and pulmonary function evaluation performed every 3-6 months per standard practice at each local site. These tests are described in Section 4.

If the patient requires addition or deletion of antiarrhythmic drugs, fill out the Change of Study Therapy form to record the new therapy. Dose changes only are not considered a change of study therapy.

Follow-up of Patients with ICD

For patients with an ICD, an ICD Evaluation form must be completed at each follow-up. The various manufacturers of devices have stipulated schedules for interrogation of the device, charging the capacitors, and checking the battery. If the particular device requires more frequent checking than every three months (e.g., CPI PRx requires bimonthly checks), the patient may need to be seen separately for the AVID follow-up and for checking the device. Record the results of the evaluation immediately preceding AVID follow-up. In any case, adherence to the manufacturers' recommended device testing and follow-up guidelines is necessary.

In general, all routine ICD follow-up reporting will be to the CTC, not the manufacturers.

Any reprogramming of the device because of symptoms or other reason is left to the judgment of the individual investigator. The ICD Evaluation form addresses changes in programmed parameters.

Patients Capable of Completing Quality of Life questionnaire

Have all patients capable of completing the scheduled Quality of Life questionnaire do so.

Patient Spouse/Partner Quality of Life questionnaire

Have all consenting and capable spouse/partners complete the scheduled Quality of Life questionnaire.

Shoebox Patients

Collect all shoebox bills and check off on appropriate Utilization Abstract form. Send a copy of bills to the CTC.

C. Lost to Follow-up

The Lost to Follow-up form should be completed whenever all efforts to contact a patient have been exhausted and the search has been abandoned. This form should be needed for fewer than 1%, probably closer to 0.1%, of all patients. The form is not sent to the CTC, but is kept in the patient's AVID chart to document the search effort.

NECESSARY STEPS BEFORE A PATIENT IS DECLARED LOST TO FOLLOW-UP

The necessary steps to be taken before a patient is declared lost to follow-up, use all of the information on the most recent version of the Patient Information form, page 3-18 and 3-19. It is important that all of the information on the Patient Information form be reviewed periodically so that it is up-to-date.

Attempt to contact patient - Record the results of all attempts to contact the patient by telephone. Describe the number of calls made, at what time of day they were made, and any response received. If the patient has obtained an unlisted phone number, the telephone supervisor may consent to call the patient and leave a message. Record the results of all attempts to contact the patient by certified mail at home and at the business address. Attach the return form received from the postal service.

Attempt to contact employer - Record the result of the attempt to contact the patient's employer, by letter and by phone, for information on the patient's whereabouts. It is important not to reveal the fact that the patient is part of medical study. This is information that the patient may not want the employer to know.

Attempt to contact spouse's employer - Record the result of the attempt to contact the spouse's employer, by letter and by phone, for information on the spouse's (and thus presumably the patient's) whereabouts. It is important not to reveal the fact that the patient is part of medical study.

Attempt to contact personal doctor - Record the result of the attempt to contact the patient's personal doctor, by letter and by phone, for information on the patient's current address and/or vital status. The doctor's nurse or office staff may be a source of information about the patient.

Attempt to contact consulting doctor - Record the result of the attempt to contact the patient's consulting doctor, by letter and by phone, for information on the patient's current address and/or vital status. Again, the doctor's nurse or office staff may be a source of information about the patient.

Attempt to contact other people - Record the results of the attempts to contact the people listed as first and second contact on the *Patient Information* form, by letter and by phone. If these contacts will not reveal the patient's current address, the vital status may still be determined. Do not reveal that the patient is part of a medical study, as the patient may not want his relatives and friends to know.

Search of hospital records

Record the results of a search of all local hospital records on the patient. Hospital records may reveal referring doctors or other persons to contact who are not recorded on the *Patient Information* form.

Other search efforts

Other possible sources of information about the patient are outlined on pages 3 and 4 of the form. Attempt to obtain the patient's current address, or at least whether or not the patient is alive. Do not volunteer the information that the patient is part of a medical study. Record whether each search effort is done or not done. If done, record the results.

The sources listed below may or may not be a legal source of information, depending on local laws.

Local telephone directories - If the patient's phone number has changed, it may be listed in a current directory.

Other local directories.

State or local departments of vital statistics - Records of birth, death and marriage certificates may yield information.

Social security administration

State department of motor vehicles

Voter registration records

Neighbors - Neighbors can be identified from reverse directories. Next-door neighbors may be the best source of information

Veteran's administration - This may be a source of information if an veteran's identification number is recorded for the patient.

Employment security offices

Health and welfare agencies

Social service agencies

Federal and state tax agencies

Public housing and relocation agencies

Utility companies

Post office - The post office may have a forwarding address for the patient.

Life insurance or medical insurance companies

Banks

Department stores

Neighborhood merchants

Local libraries

Public schools - Children of the patient may be enrolled

Police department

Alumni organizations

Fraternal organizations or unions - The patient's recorded employment may suggest an appropriate union to contact.

Public health department records

Other search efforts - Include here any other search efforts which are not included in the list above.

This form should be signed by both the Principal Investigator and the Coordinator and kept in the patient's file to document the search effort.

FOLLOW-UP FORM

Item 1 — *Date of follow-up* — Record the date of the follow-up contact. If the patient is being contacted by telephone but will be seen in clinic later, record the date of the phone call.

Item 2 — *Which follow-up* — Indicate which follow-up visit is being conducted. If the patient is seen more than once during a follow-up window, record the *first* time that the patient is seen during the window. See Item 5, below. The 1 month follow-up actually may be conducted prior to hospital discharge.

Item 3 — *Type of contact* — Indicate how the follow-up visit is being conducted. If you are contacting the patient by telephone, to be followed by an in-clinic visit OUTSIDE the allowed follow-up time window, mark both the bubble for a telephone visit and clinic. If you will be able to schedule the patient for an in-clinic visit within the allowed follow-up time window, record the information from the in-clinic visit and mark the bubble for "clinic" contact. If you cannot see the patient, telephone contact with the patient is preferred to contact with the patient's physician.

Item 4 — *Was the originally scheduled date changed because of an event or adverse effect?* — If the patient is being seen EARLIER or LATER than the originally scheduled follow-up date because of a medical event or adverse symptom, indicate "Yes" to this question.

Item 5 — *Current Antiarrhythmic therapy* — Indicate the antiarrhythmic therapy that the patient is receiving coming into this follow-up visit. If the patient has an ICD implanted and is taking an antiarrhythmic drug, mark with an "x" both the "ICD" and "Antiarrhythmic drug" bubbles. If the patient is taking an antiarrhythmic drug at the time of this visit, record the type(s) and total daily doses.

Item 6 — *Did the patient report taking the study medication as instructed?* — This is the coordinator's assessment of whether the patient took antiarrhythmic drugs as prescribed. No pill counts will be required. If you suspect adherence to be poor, indicate the one most probable reason.

Item 7 — *Events since last follow-up* — During the follow-up visit, you will interview the patient regarding any clinical events that have occurred since the last follow-up visit. Record your assessment on the Follow-up form and complete the required event forms as necessary. Possible adverse symptoms of the study drug or ICD, recurrent arrhythmias or arrhythmia symptoms should prompt evaluation by the AVID physician. Other medical conditions should be referred to the patient's cardiologist or primary care physician.

Item 8-10 — *Physical Exam, Congestive Heart Failure and Anginal Status* — A brief physical exam should be conducted. Record the sitting heart rate and sitting blood pressure after the patient has been sitting quietly for 5 minutes.

The patient's *out of hospital* anginal and heart failure symptoms, if any, should be assessed using the Canadian Cardiovascular Society Classification (for angina) and New York Heart Association Classification (for heart failure). For a 1 month

follow-up conducted prior to hospital discharge for ICD implantation/initiation of drug, leave items 9 and 10 blank.

New York Heart Association Definitions of Congestive Heart Failure

Class Description:

I. No limitation of physical activity. Ordinary physical activity does not cause undue fatigue or dyspnea.
II. Slight limitation of physical activity. Comfortable at rest, but ordinary physical activity results in fatigue or dyspnea.
III. Marked limitation of physical activity. Comfortable at rest, but less than ordinary activity causes fatigue or dyspnea.
IV. Unable to carry on any physical activity without symptoms. Symptoms occur at rest. If any physical activity is undertaken, symptoms are increased.

Canadian Cardiovascular Society Classification of Angina

Class Description:

I. Ordinary physical activity such as walking and climbing stairs does not cause angina. Angina with strenuous or rapid or prolonged exertion at work or recreation.
II. Slight limitations of ordinary activity. Walking or climbing stairs rapidly, walking uphill, walking or stair climbing after meals, or in cold, or wind, or under emotional stress, or only during the few hours after awakening. Walking more than two blocks on the level and climbing more than one flight of ordinary stairs at a normal pace and in normal conditions.
III. Marked limitation of ordinary physical activity. Walking one to two blocks on the level and climbing one flight of stairs in normal conditions and at a normal pace.
IV. Inability to carry on any physical activity without discomfort-anginal syndrome may be present at rest.

Item 11 — *Has the patient been driving?* — Based on all available evidence (including asking the patient) has the patient been driving since the last contact?

Item 12 — *Is the patient currently employed?* Based on patient interviews is the patient currently employed (paid employment). For patients who are fully retired, unemployed or homemakers, answer "No."

ICD EVALUATION FORM

Overview

ICD evaluation form - This form is to be completed at hospital discharge from initial implantation, and each time the ICD is interrogated or programmed parameters changed after the initial hospitalization. The form should be completed whether the follow-up visit is a regularly scheduled visit or an unscheduled visit if the ICD is interrogated. Follow the manufacturer's ICD evaluation schedule. For example, the CPI P_2 is interrogated bimonthly on the odd month (1,3,5, etc.). Complete a form for each visit. Be sure that the counters have been cleared, or reset, after each interrogation to avoid double counting of ICD therapies. Also be sure that the date/time stamp on the interrogation printout is accurate.

Stored electrogram printouts and device interrogation printouts should be kept in the patient's AVID chart. If the print-out is likely to fade, please make a copy to save. You may be asked to send a copy to the CTC <u>especially for those patients who received spontaneous therapies</u>.

Item 1 — *Date of evaluation* — Enter the date that the device was evaluated.

Item 2 — *Reason for completion* —

Mark "Implantation hospitalization" to record status at discharge from the hospitalization where the ICD was implanted.

For scheduled follow-up visits, regardless of whether the patient has reported an event, mark the bubble associated with the appropriate follow-up visit. For example, if the follow-up is rescheduled because the patient is experiencing shocks, record the first evaluation that falls within the follow-up time window as the "Scheduled follow-up" evaluation. Subsequent visits still within the time window are considered "Unscheduled interim visits."

Mark the bubble for "Unscheduled interim visit" when evaluating the device between scheduled AVID follow-ups.

Mark the bubble for "Event" if the patient required additional evaluation and/or medical treatment for an arrhythmic event (such as shock or loss of consciousness) outside a follow-up window or if the patient died and the device was interrogated after the patient's death.

Item 3 — P*rogrammed parameters:* — If this form is being completed at implantation hospital discharge (the original final programming), check “original programming/implantation hospital discharge." If <u>re</u>-programmed (after initial hospitalization) choose the reason which best describes why. Reprogramming includes changes to ATP, energy or rate settings. If no parameters are changed, mark “Evaluation only.”

Item 4 — *New programming* — If this form is being completed at implantation hospital discharge during the original implantation or if the programmed parameters were changed (e.g., due to frequent shocks), record the new programmed parameters with which the patient will leave the hospital or clinic visit. Do not report here routine interrogations that do not involve reprogramming.

Item 5 — *Battery check* - Mark whether the battery is reported as adequate or inadequate, based upon the individual manufacturer's specifications. For the implantation hospital discharge evaluation, it is not necessary to repeat a battery check. If the interrogation printout does not contain this information, record the battery status from the implant procedure. This does not require that the battery be charged (capacitors reformed) at each interrogation.

Item 6 — *Complete this section for the 5 most recent spontaneous arrhythmia episodes the patient received* — Record the most recent arrhythmia episodes (up to 5) since the last ICD evaluation.

An episode is defined as a therapy or series of therapies used to treat the same arrhythmia. For an ICD that has a date/time stamp of the shock episode, therapies occurring less than 5 minutes apart are considered part of the same arrhythmic episode. Keep in mind that episodes may differ significantly from the total number of shocks. For example, a patient may receive several high energy shocks in one episode. The intent of the question is to record the number of clinical arrhythmias occurring. If the patient receives multiple shocks over a very brief time (for example, 5 or 10 seconds apart) these shocks will be counted as a single episode of multiple shocks. At times, it may be difficult for the patient to distinguish the occurrence of multiple arrhythmias, minutes apart, from a single episode which required multiple rapid sequence shocks. The investigator will have to determine this distinction as best as possible within the limits of the patient's memory and device interrogation

Enter the date and approximate time of each episode, listing the activity immediately prior to the episode. Enter the worst symptom experienced by the patient during the course of the episode. The items listed from 0 to 10 are roughly ordered by severity. For example, syncope is considered to be a more serious symptom than nausea, and syncope should always be listed as the worst symptom when it occurred. However, the patient may report that he has severe nausea but very mild chest pain, in which case nausea would be listed as the worst symptom. The worst symptom relates to the perception of the symptom by the patient and not necessarily by the sequence listed on this form. If the patient doesn't remember enter "unknown."

List the number of each therapy used in each episode – ATP, low energy shock and high energy shock, and external cardioversion. Do not include any therapies delivered during implantation or device testing. If external cardioversion occurred (unrelated to device testing), complete a Recurrent Arrhythmia form as well. Note whether the patient perceived the therapy received for each episode.

PI (investigator's) opinion of the cause of the ICD action: Utilizing available information (patient symptoms, activity, ICD interrogation printout, and electrogram recordings), indicate the most probable cause for the ICD therapy delivery. "Other inappropriate sensing" should be checked if the patient was shocked due to double counting or oversensing. "ICD malfunction" should only be checked when the lead and/or the generator is not sensing or delivering at their normal specifications. An example of this would include lead fracture

causing excessive shocks. If you cannot, with some certainty, ascertain the most likely cause of the ICD therapy, check “unknown.”

Item 7 — *If more than 5 episodes, record the total number:* — If more than 5 arrhythmia episodes occurred, record the total number of episodes that were ATP only and the total number of episodes that included any shock (with or without ATP).

Retain ICD electrograms and printouts. All printouts should be retained in the AVID chart. If therapies were delivered, the CTC will request a copy of these printouts and electrograms to be sent to the CTC for review. You may want to photocopy or print out a second copy for the CTC at the time you learn an ICD therapy was delivered.

VITAL STATUS SWEEP FORM

Overview

This study is monitored by a selected group of physicians, a statistician and an ethicist who are charged with assuring patient safety and reviewing the conduct of the study to make sure that it is being performed ethically and responsibly. This group, the Data and Safety Monitoring Board, meets approximately twice a year to review the study. In order for them to make the best decision possible, based on accumulated data to date, we will conduct a quick follow-up of all patients shortly before each of these meetings.

You will receive a report, as shown below, from the CTC listing those patients you are following. You will be asked to phone each patient to determine whether the patient is still living or has died. In addition, you will need to determine the patient's current antiarrhythmic therapy. On this form, you will record the date of your phone call and to whom you spoke.

Clinical Center: Alabama (01)						
	Vital Status		Antiarrhythmic Therapy			
Patient	Alive	Dead	ICD	Drug	ICD +Drug	Date of Contact	Person Contacted	Date of Death (if dead)
01-001-4 RMCB								
01-008-7 MBRO								
Please FAX to CTC no later than April 15, 1994								

If the patient has died, record the date of death. If there is any uncertainty about the date, make the best estimate that you can, but indicate on the report that the date of death is in question.

If you have seen the patient in clinic or contacted him/her by phone within 5 days prior to the date that you receive the Vital Status request, you may record that contact as adequate follow-up.

A statement from the patient's physician, spouse/partner or other reliable witness that they saw or talked with the patient within 5 days will also suffice. They must know the date they had this contact.

As soon as you have completed your phone calls, return the report to the CTC by FAX. The report MUST be received by the date specified on the report

The End of Randomization Status form is a one time form designed to document the vital status of each AVID patient on or after April 7, 1997. Additionally, it records the medical recommendations made and actions taken regarding the antiarrhythmic therapy of each patient. **Contact with each patient should occur between April 7, 1997 and May 6, 1997. Fax each completed form to the CTC by May 13, 1997.**

Item 1 — *Date of contact* — Enter the month, day, and year of contact. If contact occurred by phone and in clinic, enter the latest date.

Item 2 — *Type of contact* — Indicate whether you spoke with the patient by phone or saw the patient in clinic or both. In the rare event you were unable to contact the patient (i.e., lost to follow-up), skip the rest of item 2, and items 3 through 5. Do not forget to write the date, patient ID, your code number and signature on page 2 before faxing the form to the CTC.

Indicate whether you spoke to the patient or someone other than the patient. If you spoke with someone other than the patient, record the date this person last saw or spoke with the patient.

Item 3 — *Status of patient* — Note the vital status of the patient at the time of this contact. If the patient died, record the date of death. Death materials should be submitted to the CTC within 6 weeks.

Item 4 — *Antiarrhythmic therapy* — Record the antiarrhythmic therapy that the patient received on April 7, 1997. If the patient died prior to April 7, indicate the antiarrhythmic therapy (therapies) at the time of death. Supply the dose of each antiarrhythmic drug in total mg/day.

Item 5 — *Recommendation* — Indicate what medical recommendation was made regarding the patient's antiarrhythmic therapy. Check all applicable. If you mark 'Other', specify the recommendation (e.g., VT catheter ablation). If you mark 'Unable to make a recommendation' (e.g., the patient is on vacation and you talk with a relative who has verified vital status), skip the rest of item 5.

Enter the date when the recommendation was made.

Indicate to whom the recommendation was made. Check all applicable.

Indicate the action taken or planned regarding the patient's antiarrhythmic therapy after the recommendation was made. Check all applicable. If you mark 'Other', specify the action. Remember to complete a "Change of Therapy" form if the therapy changed.

Enter the date when action was taken or will be taken.

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EVENTS DURING FOLLOW-UP

A. Overview

The following section outlines the events which may occur during the course of the study. In general, the investigator is strongly encouraged to maintain the patient in the assigned arm of therapy, within the bounds of acceptable medical practice.

Adverse Symptoms — If a patient develops intolerable symptoms from an antiarrhythmic drug, consideration should be given to reduction of the dosage of the drug first, then treatment with the alternative drug. If neither sotalol nor amiodarone is efficacious, or if side effects preclude the use of both drugs (after appropriate dosage adjustment), then the investigator may choose another antiarrhythmic drug or drug combination consistent with good medical practice. Evaluation of drug efficacy can be made using electrophysiologic testing and/or Holter recording. Investigators are encouraged to keep patients in their assigned randomization groups. Adverse symptoms from the ICD can usually be handled by reprogramming the device. In the case of dislodged electrodes, malfunctioning electrodes, malfunctioning generator, infection, etc., all possible attempts should be made to revise or re-implant the device.

Change of therapy — Change of therapy involves starting or stopping an arrhythmia therapy (either drug or device). It does not include dose adjustments or reprogramming of devices. However, **crossover** is defined as the addition of an ICD to a drug-assigned patient or the addition of a class I or class III antiarrhythmic drug with the intention of long term therapy on that drug to a patient assigned to ICD. Crossovers need to be handled expeditiously:

If a crossover is contemplated, the AVID clinical investigator is *strongly encouraged* to contact Dr. Leon Greene at the CTC (800 253-1387) to discuss the situation prior to instituting the change.

When a crossover has been instituted, the AVID **Principal Investigator** is required to submit a letter to the CTC describing the clinical course that led to the change in antiarrhythmic therapy and alternatives explored prior to crossing the patient from his/her assigned AVID therapy. This letter must be FAXed to the CTC within 2 weeks of the instituted change in therapy.

The appropriate AVID forms (Change in Study Therapy, ICD Implantation, etc.) must be completed as quickly as possible and submitted to the CTC. In any case, the Change in Study Therapy is required within 2 weeks of the instituted change.

In the situation that a drug is temporarily prescribed to an ICD-assigned patient, this will not be reported as a crossover or change in therapy unless the decision is made to continue the patient on the drug on a long-term basis, or the patient is discharged on an antiarrhythmic drug.

Substitution of another antiarrhythmic drug in a drug assigned patient is not considered a crossover but should be reported on the Change of Therapy form. Dose adjustments are not recorded on Change of Therapy forms, but simply reported on the

appropriate follow-up forms. Reprogramming of the device is recorded on an ICD Evaluation form.

In the event that it is necessary to change antiarrhythmic drug therapy, the dosing and timing of conversion from one drug to another must be individualized. Investigators should use their own clinical judgment about: (1) the length of time the patient should remain off one drug before beginning the other; (2) the length of time off one drug before performing a "baseline" Holter recording and/or electrophysiologic study, if indicated; (3) the need, or lack of need, for hospitalization for the drug changes; and (4) appropriate initial dosages of drugs. 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 the drug which must be stopped; (3) the half-life of the drug being discontinued; (4) the interim arrhythmia and side effects. In general, conversion from sotalol to amiodarone will be easier because of the shorter half-life of sotalol and the empiric nature of the administration of amiodarone. If amiodarone must be stopped because of side effects or arrhythmia recurrence, a minimum of two weeks should elapse before starting sotalol, unless new life-threatening arrhythmia develops in the interim, and at least four weeks should elapse before assessing the efficacy of sotalol. Generally, discontinuation of amiodarone in a patient who cannot take sotalol or in whom sotalol had already been proved inefficacious will require a prolonged "wash-out" phase prior to instituting the alternative antiarrhythmic drug therapy. Care must be taken to avoid drug - drug interactions, particularly when initiating amiodarone.

Similarly, if an ICD is inadequately treating the patient's arrhythmia, the investigator is encouraged, within the bounds of good medical practice, to keep the patient on the assigned therapy, ICD, and not to add antiarrhythmic drugs. If the device requires reprogramming, this will be documented on the ICD Programmed Parameters form. If an antiarrhythmic drug is added, this will be documented on the Change of Therapy form. Ablation or arrhythmia surgery is considered a crossover for both drug and ICD-assigned patients.

New or Worsened CHF is tracked on the Hospitalization and Follow-up forms. MI and new or worsened ischemia are similarly recorded.

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

Recurrent Arrhythmias — All serious recurrent arrhythmias must be reported. In drug treated patients, all recurrent ventricular arrhythmias will be reported. In patients with an ICD, only arrhythmias which were not adequately treated by the device will be reported (i.e., the patient sought medical attention).

Cardiac arrest with resuscitation will be the most serious arrhythmia encountered. Consideration should be given to changing the drug or increasing the drug dosage in patients randomized to the drug arm of a trial. Patients initially assigned to sotalol could be given amiodarone. Patients initially given amiodarone could be given sotalol with electrophysiologic testing and/or Holter guidance. Patients assigned to amiodarone could also be given an increased dose of amiodarone if adverse symptoms are not limiting. In addition, other arrhythmic drugs could be used in place of, or in addition to amiodarone and sotalol, with electrophysiologic testing and/or Holter

guidance. Patients randomized to device arm of the study should have reprogramming of the device.

Sustained ventricular tachycardia can also be treated by many available alternatives 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 may require additional investigations to determine the cause. In addition to serious arrhythmias, investigation should include the possibility of postural hypotension related to other drugs, bradycardias, or tachycardias. Appropriate adjustment of concurrent drugs should be made, and alteration of drug therapy or device programming may be necessary as noted above.

Recurrent device intervention with low or high energy shocks may require reprogramming of the device. Successful pacing therapy may not require any further programming of the device. Addition of antiarrhythmic drug for recurrent device intervention is discouraged.

Atrial fibrillation requiring antiarrhythmic drug therapy is an exclusion criterion for entry into the study. However, 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 arrhythmia with either sotalol or amiodarone. Investigators are encouraged to consider whether anticoagulation and rate control alone would be appropriate for an individual patient. Patients assigned to the device arm of therapy will need to be treated as clinically appropriate, with consideration of 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.

Death — The CTC 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 CTC. These data should include

1. Detailed letter explaining circumstances surrounding the death, including a description of the documented and/or presumed sequence of arrhythmias and any information from interview of relatives, bystanders, or other persons who might have witnessed the event. <u>This letter must be written or approved by the Principal Investigator</u>. <u>It must be signed by the Principal Investigator.</u>
2. Medic notes/rhythm strips.
3. Emergency room notes/rhythm strips.
4. Hospital notes, including progress notes (admission history and physical plus physician progress notes for 3 days prior to death).
5. Nurses' notes for 3 days prior to death.
6. Physicians' orders and drug administration notes (for 3 days).

7. All relevant electrocardiograms, rhythm strips, enzymes, and other lab tests.
7a. ICD interrogations and electrograms.
8. Discharge summary.
9. Autopsy report, if performed.
10. Information from interview of relatives, bystanders or other persons who might have witnessed the event. Use the "Coordinator's Worksheet" for the information.

It will also include the Death form reviewed by the Principal Investigator. In the event that the investigator feels that the death is directly attributable to ICD or ICD electrode malfunction, the Clinical Trial Center must be notified immediately by both FAX and verbal telephone message.

Withdrawal — A patient remains in the AVID study once randomized. Even if a patient is switched to the alternative therapy or receives combination ICD and antiarrhythmic drug therapy, the patient continues to be followed as a member of the randomization group to which the patient was originally assigned. Only if the patient categorically refuses all further contact with the AVID study investigators will the patient be withdrawn. Patients who discontinue their assigned study therapy are not withdrawn. Withdrawal requires a letter explaining the circumstances of the withdrawal and documenting all efforts performed to keep the patient in the study. This letter must be signed by the Principal Investigator. Integrity of the study is dependent upon complete follow-up of all patients.

ADVERSE SYMPTOMS FORM

Overview

The Adverse Symptoms form is designed to document any adverse symptom including any new or worsened CHF the patient experiences after randomization severe enough to require a change of study therapy, a change in concurrent medications, or, in addition for ICD patients, requiring treatment for late complications of ICD implantation (see item 6, below). In reporting all serious adverse symptoms, including those not directly attributable to AVID therapy, we may over-estimate the frequency. However, such reporting will be less biased than reporting only those serious adverse symptoms believed by the investigator to be directly attributable to AVID therapy.

This form should be routinely completed at:

- baseline hospital discharge
- each scheduled follow-up

And in the event of an:

- Intended long-term change in dose of antiarrhythmic drugs due to adverse symptoms
- Intended long-term change in therapy if the reason for the change is an adverse symptom (i.e., ICD implant in a drug-assigned patient or antiarrhythmic drugs added to an ICD patient.)

When completing this form at routine follow-up, be sure to note any new or persistent adverse symptoms that may have occurred since the last completion of the form including:

- New or persistent adverse symptoms whether or not requiring stopping, starting or adjusting the dose of AVID or non-AVID medications
- ECG abnormalities requiring pacemaker or other treatment
- late ICD complications requiring treatment
- reprogramming of the ICD due to adverse symptoms

Adverse symptoms include, but are not limited to, all those listed on the opposite page. Example: a patient on amiodarone develops hypothyroidism and is started on L-thyroxine. Or, a patient develops a severe cough while taking enalapril for which the dose of enalapril is adjusted. Both these situations would be reported as adverse symptoms.

If AVID therapy is changed long-term (e.g., antiarrhythmic drug started or stopped and the change is intended long-term, or ICD implanted or explanted) due to an adverse symptom, also complete a Change of Therapy form.

Item 1 — *Date of evaluation* — Enter the month, day and year of the evaluation.

Item 2 — *Reason for evaluation* — Mark one bubble only. If a crossover occurs in conjunction with a scheduled follow-up, mark the appropriate follow-up bubble. If, at the one month follow-up the patient remains hospitalized, complete an Adverse Symptoms form at hospital discharge only and mark the "Baseline hospital discharge" bubble.

Item 3 — *Current antiarrhythmic therapy* — Indicate whether the patient is receiving no therapy, ICD therapy, antiarrhythmic drug therapy, or both ICD and antiarrhythmic drug therapy at the time of this evaluation. If antiarrhythmic drug therapy is marked, please specify the drug(s) and list the total dose(s) in mg/day.

Item 4 — *Has the patient experienced any clinical adverse symptom since last AVID contact?* — Typical symptoms are given on the facing page of the form. If no symptoms are present, mark "No" and skip to question 5.

Severity — Mild or moderate symptoms are those that are noticeable, bothersome, or uncomfortable, and will probably result in a minor change in dose of study therapy such as a dose adjustment of an antiarrhythmic drug or reprogramming the ICD, or may prompt a change in other concurrent medications. Severe symptoms are those requiring temporary or permanent discontinuation of a study therapy and/or change in other medications.

Study therapy related? In the investigator's opinion, is this symptom related to the AVID therapy?

Actions taken — More than one bubble may be marked. For example, a severe adverse symptom may prompt a discontinuation of the patient's study therapy as well as an addition of other concurrent medications. If an intended long-term change in study therapy was made, fill out a Change in Study Therapy form.

Item 5 — *ECG adverse symptoms* — Mark "Yes" if the patient had any new ECG adverse symptoms listed below prompting a change in study therapy or other concurrent medications or insertion of a pacemaker. If "No ECG was obtained or no newly noted abnormalities" is marked, proceed to item 6. If any ECG adverse symptom was noted, the action taken must be recorded as well. If the ECG symptom prompted an intended long-term change in study therapy, then complete a Change in Study Therapy form.

For each of these ECG adverse symptoms the investigator must decide whether the symptom was related to the study therapy. Examples include: (1) a patient taking amiodarone develops sinus pauses for which the dose of amiodarone is lowered; (2) a patient taking inderal develops severe bradycardia requiring the drug to be discontinued.

Bradycardia — Record if severe enough to prompt a change in therapy or insertion of a pacemaker.

Mobitz II 2˚AV block, advanced or 3˚AV block — Mark the highest level of AV heart block noted.

QRS ≥2 times baseline or ≥200 msecs — Measured by 12-lead ECG.

QTc ≥500 ms — Measured by 12-lead ECG

Item 6 — *Complications of implantation severe enough to require treatment* — All late complications of implantation severe enough to require treatment will be noted here. The only exception is patients who report feeling a shock but none is

noted on the ICD interrogation (i.e., phantom shocks). These phantom shocks will be noted under the "other" category.

A late complication is defined as one occurring after the patient has been discharged from the hospitalization during which the device was implanted, or 30 days after implantation, whichever occurs later. More than one may be marked if treatment was received for each one.

Erosion/extrusion — Includes surgical repositioning.

Fluid accumulation/seroma — Seroma around generator pocket resulting in a procedure to remove the fluid.

Generator failure — Failure other than normal battery depletion; CTC must be notified immediately, see ICD Implantation form.

ICD Infection — This includes infections believed to be related to the device requiring hospitalization or prolongation of hospitalization and treatment with antibiotics or other (surgical) treatment.

Lead failure — Includes lead replacement. CTC must be notified immediately, see ICD Implantation form.

Lead dislodgement/migration — Includes lead repositioning or replacement.

Chronic pain — Includes symptoms severe enough to warrant box repositioning or explantation.

Patch migration — Includes only those patch migrations requiring repositioning or replacement.

Other — Specify. The only time that a problem would be reported here that did not require a medical intervention is the case of a patient who reports feeling a shock but none is noted on the ICD printout (i.e., phantom shock).

Complete the following forms:

- Hospitalization form, if hospitalized
- Change in Study Therapy form if an antiarrhythmic drug is started or stopped (intended long-term), an ICD is implanted or explanted
- ICD Implantation, ICD Complications and Lead/Generator Identification forms if a device was implanted/explanted or lead(s) repositioned or replaced.
- ICD Evaluation form if an ICD was implanted or a generator replaced or device was reprogrammed.

The following table summarizes:

	Additional Forms Needed		
Adverse symptom prompted:	Change of Therapy	ICD Evaluation	ICD Implantation, Complications, and Lead/Generator Identification
Dose Adjustment only (antiarrhythmic or other drug)			
Addition/substitution of an AAD	X		
Discontinuation of AAD	X		
Reprogramming of ICD		X	
Implantation of ICD	X	X	X
Explantation of ICD	X		X
Addition/discontinuation of other drug			
ICD turned off	X	X	

CHANGE OF STUDY THERAPY FORM

Overview

The Change of Therapy form is used to document the following changes in AVID therapy:

- Intended long-term addition of an antiarrhythmic drug (Class I or III) to an ICD assigned patient (crossover)
- Implantation of an ICD in a drug-assigned patient (crossover)
- Explantation of a device (crossover)
- Intended long-term discontinuation of antiarrhythmic drug in a drug assigned patient (crossover)
- Addition or change of Class I or III antiarrhythmic drug in a drug assigned patient after the initial hospitalization. For example, when a drug assigned patient switches from amiodarone to sotalol because of adverse symptoms.

Item 1 — *Date of Change* — Enter the month, day and year that the change was initiated, i.e., the day current study therapy was changed to a different study therapy. If therapy "A" is stopped one day, and therapy "B" started another, enter the day therapy "B" was started.

Item 2 — *Current antiarrhythmic therapy* — Note the current antiarrhythmic therapy (prior to change) which could either be no therapy, ICD therapy or antiarrhythmic drug therapy, or combination of ICD and antiarrhythmic drug therapy. If antiarrhythmic drugs, please specify the drug or drugs the patient is taking and indicate the total dose in mg/day.

Item 3 — *Primary reason for change in therapy* — Choose the one primary reason for the change.

Intolerable adverse symptoms — Complete an Adverse Symptoms form as well. Since more than one adverse symptom may be noted on the Adverse Symptoms form, select the symptom which is considered the primary cause for therapy change.

Frequent ICD shocks — ICD shocks occurring frequently enough that, despite optimal programming, patient comfort and/or ICD battery life is a concern.

ICD Complications — Any of the complications related to the ICD (e.g., infection, bleeding, severe discomfort due to the generator, but not frequent shocks) severe enough to lead to explantation or addition of an antiarrhythmic drug. Complete an Adverse Symptoms form if the complication occurs >30 days after implant or after baseline hospital discharge. Otherwise, the complication will be recorded on the ICD Complications form.

Recurrent ventricular arrhythmia — Any recurrent ventricular arrhythmia prompting a change in therapy (addition or deletion of antiarrhythmic drug or implantation or explantation of an ICD). A Recurrent Arrhythmia form will also be completed.

Recurrent supraventricular arrhythmia — This includes patients who have antiarrhythmic drugs added to their current study therapy because of recurrent supraventricular arrhythmias, such as atrial fibrillation.

Patient request — Please specify why the patient requested a change in study therapy. If the change in therapy was prompted by a perceived adverse symptom, mark instead "Intolerable adverse symptom."

Physician request — Please specify the reason for change in study therapy. If it is due to a perceived adverse symptom, please mark instead "Intolerable adverse symptom."

New or worsened CHF — Complete an Adverse Symptoms form.

Bradycardia — There is no rate limit for bradycardia. Good clinical judgment will determine whether this condition should prompt a change.

Item 4 — *Therapy changed to* — Indicate the new therapy. If the patient is taking antiarrhythmic drugs, specify the type of drug and dose in total mg/day at hospital discharge.

A change in therapy includes surgical and other invasive procedures designed to ablate the arrhythmia.

Item 5 — *If therapy change involves ICD, was the ICD explanted, implanted or turned off?* Complete the ICD Implantation and Lead/Generator Identification forms if the device was explanted or a new device was implanted. For simple ICD reprogramming, do not complete this form; complete an ICD Evaluation form. If the ICD was turned off complete an ICD Evaluation form.

CROSSOVERS:

This form should be FAXed to the CTC within 14 days of a change in therapy constituting a crossover. The AVID Principal Investigator should submit a letter describing the situation leading to the change in the therapy which should be received by the CTC within 14 days. See 6-1.

RECURRENT ARRHYTHMIA FORM

Overview

This form will be completed for each episode (either a single event or a storm) of a documented, sustained recurrent ventricular arrhythmia where the patient survives, or for syncope due to a presumed ventricular tachyarrhythmia. Terminal arrhythmias are recorded on the Death form.

For all patients a recurrent arrhythmia is defined as a ventricular tachyarrhythmia that results in hospitalization or, if it occurs while the patient is hospitalized, requires termination by external cardioversion/pacing, intravenous antiarrhythmic drugs, or reprogramming the ICD. Frequent episodes of non-sustained VT resulting in hospitalization would only be reported on this form if they required one of these measures for termination.

A "storm" is defined as a closely sequenced series of arrhythmic events. If the patient is hospitalized and continues to suffer arrhythmias, the "storm" would include all events during that hospitalization unless a substantial period of quiescence is achieved. If the patient is discharged, but has another episode shortly after discharge, this would be presumed to be a new event.

This form should be completed for both in- and out-of-hospital events occurring anytime after the patient is randomized. It is completed for spontaneous arrhythmias not those induced in the EP lab or operating room.

Item 1 — *Date of initial arrhythmia* — This is the month, day and year that the symptoms started.

Item 2 — *Type of initial sustained ventricular tachyarrhythmia lasting at least 30 seconds or requiring medical treatment* —

Ventricular Fibrillation — This bubble is marked if emergency defibrillation or ICD shock was required for resuscitation and VF was documented by "quick look" paddles, rhythm strip or ICD printout.

Ventricular Tachycardia with syncope VT is defined as ≥30 seconds of monomorphic or polymorphic VT at a rate ≥100 bpm or, if <30 seconds, requiring medical intervention to terminate the arrhythmia. The onset of syncope need not be witnessed, but the rhythm itself must be documented.

VT without syncope — Any documented sustained VT without syncope, using the definition of VT above.

Torsade de pointes — Typical polymorphic VT with spindle-shaped twisting morphology, usually associated with symptoms of syncope or near-syncope. A long QT is often present, usually associated with antiarrhythmic drug administration, often with bradycardia and/or hypokalemia, and not previously seen in the patient off drug.

Syncope presumed due to ventricular tachyarrhythmias — Mark this bubble in the event a patient has one or more episodes of syncope that is identical in nature to a prior episode of syncope where VT was documented. Syncope of unknown etiology will be noted on the Follow-up and Hospitalization forms.

Other — Specify arrhythmia noted. An example includes a patient who develops nonsustained VT requiring IV antiarrhythmic drugs, external cardioversion or ICD reprogramming to terminate the episodes.

Item 3 — *Current antiarrhythmic therapy (at time of initial event)* — List the therapy at the time of onset of symptoms for this event or, in the case of a storm, the therapy at the time of the initial event. This may include no therapy, ICD therapy, antiarrhythmic drug therapy, or combination of ICD and antiarrhythmic drug therapy. If antiarrhythmic drug therapy is marked, please specify which drug(s) the patient is taking, as well as the total dose in mg/day.

Item 4 —*How was the arrhythmia* terminated? — Mark the one intervention which terminated the episode or, in the event of a storm, the intervention that terminated the initial event.

Spontaneously— is defined as any arrhythmia which converts prior to antiarrhythmic drugs or electrical cardioversion, and the patient is subsequently hospitalized. Arrhythmias for which the patient does not get hospitalized are not recorded on this form.

By IV antiarrhythmic drugs only — Any intravenous antiarrhythmic drug was used to convert the arrhythmia.

By non-ICD pacing — is defined as any non-ICD overdrive pacing that converts the arrhythmia, i.e., internal or external overdrive pacing.

By external cardioversion — requires external shock for conversion.

By ICD without other intervention — defined as an arrhythmia in an ICD patient that was converted by the ICD, and the patient is hospitalized as a result of the ventricular arrhythmia.

By ICD reprogramming — ICD reprogramming results in conversion of the arrhythmia.

By ICD and IV antiarrhythmic drugs — A combination of IV antiarrhythmic drugs and ICD therapies terminates the arrhythmia episode(s). If drugs alone convert the arrhythmia, check "by IV antiarrhythmic drugs only" bubble.

Other — Specify any other means used to terminate the arrhythmia (not subsequent treatments), e.g., VT catheter ablation, precordial thump.

Item 5 — *Location of the initial arrhythmia* — Indicate whether the arrhythmia episode or storm began in-hospital or out-of-hospital. In-hospital is defined as a patient admitted to either the emergency room or the hospital itself. Out-of-hospital

includes all other possible locations, including at home, at work, or in an automobile or ambulance. Visiting in the hospital or seeing a physician at a clinic located in the hospital is classified as "out-of-hospital."

Item 6 *Intended long-term change of study therapy* — If antiarrhythmic drug therapy was changed or an ICD implanted, explanted, or turned “off”, answer yes to this question. If yes, complete a Change of Therapy form and related forms (e.g., ICD Implant). If all that was done was adjust the dose of an antiarrhythmic drug, do NOT complete a Change of Therapy form. If a device was reprogrammed, complete an ICD Evaluation form.

Complete the following forms:

- Hospitalization form if hospitalized or occurred in-hospital
- Change of Study Therapy if arrhythmia therapy was changed (drugs started or stopped or ICD implanted, ~~d or~~ explanted or turned “off”)
- ICD Evaluation form if ICD was reprogrammed.

NOTIFICATION OF DEATH

Overview

Complete as soon as you learn of a patient death. Make your best guess of cause of death.

The questions at the bottom of the form are a reminder checklist. However, ascertaining whether these procedures were done should not slow down sending the form.

As soon as the CTC receives this form, a checklist will be sent to track collection of documenting materials.

DEATH FORM

Overview

The Death form should be completed in the event of any patient death, regardless of the cause, at any time after randomization, even if it occurred before the patient began taking the assigned medication or before the ICD was implanted. For the purposes of this form, the term death means a spontaneous cessation of respiration and blood circulation (pulse) without recovery. Transient arrhythmias which convert spontaneously are not included. Any arrhythmias which are converted successfully are not included. Sustained ventricular tachycardia is not included. If a cardiac arrest patient is successfully resuscitated, do not complete this form (complete a Recurrent Arrhythmia form). Patients whose resuscitation yields a comatose, unresponsive, or vegetative condition are not included, until the patient ultimately dies. In addition to this form, the Principal Investigator is required to forward to the CTC copies of the following reports, with patient identifying information deleted for confidentiality purposes, except for the AVID ID number.

1. Detailed letter explaining circumstances surrounding the death, including a description of the documented and/or presumed sequence of arrhythmias and any information from interview of relatives, bystanders, or other persons who might have witnessed the event. <u>This letter must be written or approved by the Principal Investigator</u>. <u>It must be signed by the Principal Investigator.</u>
2. Medic notes/rhythm strips.
3. Emergency room notes/rhythm strips.
4. Hospital notes, including progress notes (admission history and physical plus last 3 days of physician progress notes).
5. Nurses' notes for last 3 days.
6. Physicians' orders and drug administration notes.
7. All relevant electrocardiograms, rhythm strips, enzymes, and other lab tests.

7a. ICD interrogation electrograms and data output.

8. Discharge summary.
9. Autopsy report (if performed).
10. Information from interview of relatives, bystanders or other persons who might have witnessed the event. Use the "Coordinator's Worksheet" for the information.

Complete a Concurrent Drugs form for drugs taken at the beginning of the terminal event. (For example, a patient has an out-of-hospital cardiac arrest and survives for 2 days and then dies. The Concurrent Drug form would be filled out for the time of the arrest.)

If the patient had an ICD, complete an ICD Evaluation form. Follow ICD manufacturer guidelines regarding explantation and return of generator and leads. ICD interrogation information and autopsy information are desirable, if obtainable.

If the patient is hospitalized in conjunction with his/her death, complete a Hospitalization form.

Item 1 — *Date and time of clinical death* — Enter the date and time that spontaneous circulation and respiration ceased (the date and time on the death certificate when the patient was "declared" dead). In some circumstances the exact time may not be known. If the event was unwitnessed, enter the date and time the patient was found.

Record the location at the time of the onset of the death event. This location will not necessarily be the same location as the site of death which correlates with the date and time noted above. Many patients will have resuscitation attempts leading to emergency room or hospital admission with subsequent death. For these patients, the location at the time of onset of symptoms which led to the death event are recorded. If a patient is successfully resuscitated and awakens in the hospital but subsequently has another event and dies, record the location as "in-hospital." For unwitnessed deaths, give the location where the patient was found.

List whether the event was witnessed. An event is considered "witnessed" if the victim was actually in visual or voice contact with an observer within the last 5 minutes. For example, if an event occurs while someone is talking with the patient but in another room, but not actually able to see the patient, or while the patient is talking with someone on a phone, the event is considered to be witnessed. If the patient was witnessed by an observer within 5 minutes of a cardiac arrest, the event is considered to be witnessed, with the relevant observations occurring at the last time the patient was seen or the last time anyone talked to the patient.

Item 2 — *Symptoms prior to loss of consciousness* — If the patient had an instantaneous death, that is, no symptoms but simply collapsed without any prodromal events, mark the "asymptomatic until collapse" bubble.
If the event was witnessed, enter the date and time of the onset of new, persistent, or accelerating symptoms related to the event. This date and time should represent the onset of symptoms which either persist or recur until loss of consciousness and should mark the onset of this death event. For example, if a patient has had symptoms of shortness of breath on exertion for the past six months but suddenly develops severe shortness of breath at rest 30 minutes prior to collapse, the date and time of onset of new symptoms would be 30 minutes prior to collapse, rather than 6 months prior to collapse.

If the event was unwitnessed, leave this section blank.

Item 3 — *Current antiarrhythmic therapy* — Record all antiarrhythmic therapies being used by the patient at the time of onset of symptoms which led to the death. Supply the dose of each antiarrhythmic drug in total mg/day.

Item 4 — *Documentation of rhythm associated with event* — Indicate when the arrhythmias were documented at the time of the event or mark the "Never monitored" bubble if the patient was found dead and no resuscitation attempts were begun. The "Monitored before and during collapse" bubble should be marked for patients who had already had electrocardiographic monitoring attached prior to death. The "Monitored only after collapse" should be marked

for patients who collapsed and then had their rhythm monitoring begun. Record the estimated amount of time to initiation of monitoring. For the case of a patient who was initially resuscitated but never regained consciousness with or after the resuscitation attempt, these bubbles should relate to the initial rhythm which caused the collapse, not any subsequent event in the hospital.

List the approximate time from the onset of collapse to monitoring in minutes.

Characterize the one rhythm which best describes the onset of the event. Once again, if an event occurs outside the hospital and the patient is initially resuscitated, but never regains consciousness, these rhythm choices pertain to the event outside the hospital and not the terminal, agonal arrhythmia in the hospital. Choose "electromechanical dissociation" only if patient had QRS complexes at a rate ≥30 beats per minute.

Item 5 — *Summary - Cause of death* — This item is intended to differentiate cardiac from noncardiac death. If the death is noncardiac, list the primary cause. Vascular disorders such as ruptured abdominal aortic aneurysm, CVA, etc., should be included in the noncardiac category.

Item 6 — *Cause of Cardiac Death* — For cardiac deaths, in the opinion of the Principal investigator, was the primary cause of death CHF or shock without ischemia, arrhythmia without ischemia, ischemia leading to CHF or shock with or without arrhythmia, or ischemia leading to arrhythmia? For the latter two conditions, mark the evidence for ischemia: history, ECG changes, and/or enzyme changes. If the death was caused by another cardiac condition, specify.

Item 7 — *Cardiac Death - Associated Symptoms* — For cardiac deaths, the events will either be witnessed and arrhythmic, witnessed and nonarrhythmic, or unwitnessed. Complete one of the three sections on this page.

If the event was witnessed, arrhythmic, and symptomatic, review <u>all</u> of the bubbles under "new, accelerating or persistent symptoms" and mark only the <u>one</u> bubble which best summarizes the event. Many patients will have multiple symptoms, and the investigator must choose the symptoms which he/she thinks are most relevant to the event. If the investigator determines that the event was asymptomatic and instantaneous (characterized by either no symptoms whatsoever or stable chronic symptoms which did not change up to the time of death), mark the "asymptomatic" bubble.

The time frames (e.g., <5 minutes, >24 hours) refers to the time from onset of symptoms to beginning of symptoms related to death.

If the event was witnessed but nonarrhythmic mark the bubble in Section B.

If the event was unwitnessed (that is, the patient was not seen or heard for >5 minutes), mark whether the event was presumed arrhythmic or not. If not, specify the presumed cause. In some cases, autopsy will be useful for these patients. Deaths which are unwitnessed will be presumed arrhythmic, unless evidence to the contrary is found.

In general, if the investigator thinks that the terminal event was arrhythmic, it should mean that the patient did not have congestive heart failure, cardiogenic shock, or any other disease which would have been expected to limit the patient's survival to <4 months.

Item 8 — *Has this patient had surgery, either cardiac or noncardiac, within 30 days prior to death, or has the patient had an invasive cardiac therapeutic procedure (angioplasty, atherectomy, stent, pacemaker, ICD implantation, etc.)?* If yes, specify the type and specify the date. If the patient had multiple operations and/or procedures, list the date of the first of the series of surgeries or procedures which were related to the terminal event.

The Principal Investigator must then determine whether this death is the result of the surgery or procedure.

Item 9 — *In the opinion of the Principal Investigator, would this patient have survived 4 months if a terminal arrhythmia had not occurred?* — This determination is obviously very subjective, but allows the Investigator to specify whether the patient was on a terminal downhill course which could not have been reversed even if an arrhythmia could have been prevented or treated.

Submit to the CTC

1. Detailed letter explaining circumstances surrounding the death, including a description of the documented and/or presumed sequence of arrhythmias and any information from interview of relatives, bystanders, or other persons who might have witnessed the event. Using the death letter format provided, this letter should be written or approved and signed by the Principal Investigator. If details presented in the PI's letter do not agree with hospital or medic notes, the PI needs to indicate why one record should be considered correct and the other, incorrect, e.g., information was obtained directly from the person who observed the death. The patient's name must be omitted or blanked out from the letter and from all items below, and the patient's AVID ID must be included.

   The format for the Coordinator's interview with family and bystanders is included at the end of this section. The format for the Principal Investigator's letter is also attached.
2. Medic notes/rhythm strips.
3. Emergency room notes/rhythm strips.
4. Hospital notes, including physician's progress notes.
5. Nurse's notes.
6. MD's orders and drug administration notes.
7. All relevant ECGs, rhythm strips, enzymes, lab tests, ICD interrogations and electrograms.
8. Discharge summary.
9. Autopsy report (if performed).
10. Information from interview of relatives, bystanders or other persons who might have witnessed the event. Use the "Coordinator's Worksheet" for the information.

Complete the following forms, as appropriate

- Concurrent Drugs
- Hospitalization form, if hospitalized

DO NOT COMPLETE a Recurrent Arrhythmia form unless a discrete event occurred prior to death.

Coordinator's Worksheet for History of Death Event
(to be obtained from family, friends, and other medical sources).

Narrative:

Ask about these specific items:	Yes	No	Comments
Recent worsening of CHF			
Edema			
DOE			
Orthopnea			
PND			
Changes in medication for CHF			
Recent worsening of angina			
Chest discomfort			
Arm/shoulder discomfort			
Changes in medication for angina			
Recent ventricular arrhythmias			
Palpitations/dizziness			
Near syncope			
Syncope			
ICD pacing			
ICD discharges			
Changes in medication for arrhythmias			
Recent MI			
Symptoms			
Hospitalization			
ECG			
Enzymes			
Procedures			
Recent surgery			
Cardiac			
Non-cardiac			
Recent clinic/ER/hospital visits			
Other hospitalizations			
Drugs at time of event			
Other lab tests			

Principal Investigator's Outline for Detailed Letter Explaining Death Event

History prior to randomization
- Etiology of heart disease
- Hospitalizations
- MIs
- CHF/angina history
- Medications

History of index event

History of hospitalization/tests/procedures surrounding index event (include measurement of EF)

Randomization

Events between randomization and death, including detailed description of status prior to death
- Angina/MI
- CHF
- Activity/Symptoms
- Medication
- Arrhythmias - changes in ICD programming/drugs
- Hospitalization/clinic & ER visits
- Other events prior to death

Death event
- Symptoms
- Drugs at time of death
- Summary of events chronologically - include all data listed in Page 6-33 of *Manual of Operations*:

1. Paramedic notes, especially notes from the rescue squad if death occurred within 5 days of admission
2. Emergency room notes
3. Hospital notes (including admission history & physical and at least the last 3 days of physicians' progress notes)
4. Nurses' notes for the 3 days preceding death
5. MDs' orders and drug administration notes
6. Copies of all relevant ECG's (including last ECG prior to death), ICD interrogation, electrograms, rhythm strips, and enzyme & other lab results
7. Discharge summary
8. Autopsy report (if performed).

Withdrawal

A patient may withdraw from the study. This ethical principle is operative in all clinical studies and clearly stated in the Informed Consent which the patient signed. However, such an event should be extremely unlikely after the patient has been randomized. By the time the patient has been randomized, the patient has given informed consent, gone through the extensive baseline data gathering process and lived with the knowledge of random allocation of treatment, right up to the time of allocation. Thus, to change his/her mind after randomization should be very unlikely if the patient's needs are being met in an efficient and courteous manner. Any indication that a randomized patient is considering withdrawal should prompt intensive efforts on your part to keep the patient in the study. Find out if there are logistical problems, and if there are, see if they can be dealt with. For example, if transportation is a problem, can it be arranged? If logistical problems are not at issue but the patient perceives the study as too difficult, find out if there are ways to alleviate the burden of the study on the patient. Only as a last result, is it advisable to consider curtailing certain aspects of the study. For example, the quality of life component or the economic evaluation component could be eliminated if that were the principal cause of the patient's objections and those objections could not be allayed otherwise. If the patient's concern has to do with the value of the trial or of his/her participation in the trial or with the therapy that he/she is receiving, it will be necessary to go over carefully the rationale for clinical trials, the rationale for this particular clinical trial, and the justification for the treatments chosen. You will probably need to involve the Principal Investigator at this point, and it may be necessary to have discussions with the patient's private physician in hopes that he/she will also reassure the patient about the usefulness of the endeavor.

If, despite all efforts, the patient insists on withdrawing, the Principal Investigator must send a letter to the Clinical Trial Center, describing the circumstances in detail. This should include the reason or reasons why the patient is withdrawing, and the efforts made to dissuade the patient from withdrawal. If there is any indication that the withdrawal might have been motivated by inadequate performance at the Clinical Center, the letter should indicate what steps will be taken to ensure this is not likely to happen again. This letter should be sent to the CTC as soon as, but no sooner than, you have determined that no further action can be taken on your part to reverse the patient's decision. It is possible that the patient may insist that he is withdrawing from the study but if contacted diplomatically, four or five weeks later, may reconsider. Such an event is not a withdrawal. It is also possible that a patient will continue on his study therapy but refuse to return to the clinic. He may, however, be willing to be contacted by telephone periodically. Such an event is also not a withdrawal. A withdrawal only occurs when a patient insists that he no longer be contacted, and you accept that as a final decision.

QUALITY OF LIFE ASSESSMENT

A. Overview

Research conducted over the past twenty years has shown that we need to look beyond biological and physical indicators to adequately understand both the impacts of illness and the effectiveness of treatment. Quality of life questionnaires have been developed specifically for these purposes. Quality of life questionnaires assess a broad array of illness-related impacts on people's daily lives, e.g., performance of roles and physical, social and emotional functioning. These questionnaires are also helpful in assessing changes in quality of life that may result over the course of treatment.

Research has also shown that a major illness in one family member may influence the quality of life of other family members. Because of the seriousness of heart rhythm problems and potential impacts of their treatment, we will also assess the quality of life of the patient's partner.

B. Instructions for Completing Questionnaires

Quality of Life questionnaires will be administered at baseline, three months, six months, one year and every six months thereafter. Because some aspects of this assessment are likely to change more slowly than others, not all of the questions will be repeated at each administration. A separate form of the questionnaire will be provided for each of these administrations. Individual forms will be provided for the patient and for his/her partner.

The Quality of Life questionnaire is to be self-administered by the patient and by the patient's partner. Due to the difficulty of conducting an unbiased interview, the Quality of Life instrument will not be administered to subjects who are illiterate or cannot read because of eyesight problems. Also, at this point, the instrument will not be administered to subjects who cannot read English since the questionnaires were developed in English.

The baseline Quality of Life questionnaire for both the patient and patient's partner should be completed at the first visit after the patient has signed the consent form but before randomization to treatment. A patient may be randomized in the AVID study without completing the Quality of Life questionnaire; however, since quality of life is an important endpoint in this study, we strongly encourage all patients and patients' partners to complete the Quality of Life forms.

An AVID patient has an eligible spouse/partner if he/she lives with another adult (e.g., a spouse, significant other, adult child, close friend or relative) and does not live in a long-term care facility. It will be necessary to obtain informed

consent from the patient's partner prior to asking him or her to complete the questionnaire. The patient's partner and the patient must also understand that the partner is free to not participate and that the partner's decision will have no effect on the patient's care. If possible the partner should complete the baseline questionnaire at the hospital. If not, the questionnaire should be mailed out as soon as informed consent is obtained.

Each month the CTC will send the clinic a follow-up reminder list. This packet will include the appropriate Quality of Life questionnaires with envelopes addressed to the CTC. A patient or partner ID label will be affixed to each form. Make sure that the date of administration is correctly completed. Ideally, the patient and the partner should complete the questionnaires during the clinic visit and then return them to the coordinator in the sealed stamped envelope to be mailed not FAXed to the CTC. If this is not possible, the patient or partner can complete the form at home and mail it directly to the CTC. Since full payment for a follow-up visit depends on prompt submission of data, do not wait to send the Quality of Life forms. If the CTC does not receive a Quality of Life form, the CTC will contact you. You should call the patient or partner (i.e. the person who has not sent in the form) once to remind him/her of the importance of completing the questionnaire. If he/she does not intend to fill out the questionnaire, complete the Procedures Not Done form and FAX it to the CTC. The clinic will be paid when the patient Quality of Life form or a Procedures Not Done form is submitted. (Full payment does not depend on the partner's questionnaire).

If you are conducting a follow-up by phone, you have the option of mailing the Quality of Life questionnaire to the patient and the partner and having them complete the forms and mail them to the CTC, or, if you expect to see the patient in clinic (even outside the time window), you may administer the Quality of Life questionnaires at the clinic visit. In other words, for follow-ups completed by telephone, the Quality of Life questionnaire does not need to be completed within the two week time window.

C. Guidelines for Administrator

At this initial exposure to the questionnaire it is important to make the activity positive and enjoyable. You should provide an orientation consisting of components described below: Motivation, Instruction and Reassurance.

Motivation: First, explain why the questionnaire is being administered. This explanation should attempt to make the subject realize what an important contribution he or she is making by providing this information. The full impact of heart rhythm problems and the full impact of treatment can only be assessed by the patient and those whose lives are intertwined with the patient. Without his/her help, we would have little insight into day to day activities affected by their heart problem or day to day activities restored by treatment.

In addition to making this statement, you can increase motivation and involvement by emphasizing that "we want to be in touch with how you are feeling as the study goes along so we can improve medical care. We will ask you to complete portions of the questionnaire at regular intervals during the course of the study. The questionnaire is a quick and useful way for you to tell us what is happening in your life."

Instruction: After giving the above explanation, tell the subject how to proceed in completing the questionnaire. Because the questionnaire is designed to be self-administered, your involvement should be kept to a minimum. You should say:

> "I would like you to work on this form by yourself, without discussing your answers with me or anyone else. We are interested only in your feelings and opinions. There are no good/bad or right/wrong answers. If you have any questions as you go through the form, I will be happy to try to answer them. Remember, we want to know how you are doing. Your opinions are what's most important to us. Also, remember that the information you give us is confidential."

If there are family members or friends present, arrange for the questionnaire to be completed when these individuals are not in the room. The subject should be encouraged to:

1. work alone
2. work at his/her own pace (there is no time limit)
3. answer every question
4. mark his/her answers clearly

Be sure to tell the patient what to do with the completed questionnaire.

Reassurance: Occasionally, a subject will express concern about his or her ability to follow these directions. There are several standard concerns patients may express:

1. "Should I say how I feel NOW, or how I felt BEFORE the heart attack occurred?" Subjects should be told to respond on the basis of the directions to each question, i.e., most of the time, in the past 4 weeks and so on.

2. "This question doesn't apply to me." Occasionally, a subject will remark that a particular item on the questionnaire seems directed at someone whose life circumstances or problems are somewhat different from the patient's. Encourage them to give the answer that seems most appropriate for them.

3. Confidentiality. This is a concern that is formally addressed when the subject enters the study but which should be acknowledged whenever a questionnaire is handed to the patient. You should reassure the subject that "all information is confidential" and should mention steps taken to protect privacy, such as identifying the forms by code number only, storage in locked file cabinets, and so on.

D. Spanish Version of Quality of Life Form

The Spanish version of the *Quality of Life* form should only be offered to Hispanics who cannot do the English version. This is because a Spanish version is not available for all the components of the QL instrument. There is only one Spanish version (i.e., it is the same at baseline and each QL follow-up).

E. Spouse/Friend/Relative Quality of Life

A Spouse/Partner, close friend or relative who lives with an AVID patient should be approached about completion of the Spouse/Partner Quality of Life Questionnaire. Administration of the Spouse/Partner Quality of Life is identical to that of the patient. You need to obtain written informed consent from the spouse/partner. Attach the patient ID label to the Spouse/Partner questionnaire. Be sure to use the Spouse/Partner Quality of Life questionnaire (not patient QL), as the questions are worded in a slightly different fashion from those used on the patient questionnaire. The form is then mailed to the CTC. You may want to remind the spouse/partner that he/she should not write his/her name on the form and explain to them that this process assures anonymity.

Spouse/partners may participate even if the patient is not participating. There is an abbreviated Spanish version of the Spouse/Partner questionnaire. Spouse/partners who cannot read English or Spanish will not be enrolled.

Please read the overview of Section 7 for more specific details.

Spouse/Partner Quality of Life Form

1. Sample questionnaire
2. Sample consent form
3. Sample introductory letter for the baseline questionnaire
4. Sample letter for follow-up questionnaire
5. Script for telephone follow-up reminder

Sample Informed Consent

Date _____

_____ UNIVERSITY CONSENT FORM

INFORMED CONSENT TO PARTICIPATE IN A CLINICAL RESEARCH STUDY

Study Title: Antiarrhythmics Versus Implantable Defibrillators (AVID) Spouse/Partner Quality of Life Study (Substudy in Antiarrhythmics Versus Implantable Defibrillators (AVID))

Investigator:

phone _____

Co-Investigators:

Sponsor: National Heart, Lung, & Blood Institute (NHLBI)

PURPOSE:

The purpose of this research study is to evaluate the effect of treatment of severe heart rhythm disturbances on the quality of life in patient's spouses and close relatives or friends.

PROCEDURES:

You will be asked to complete a questionnaire. Some questions will ask you to rate your feelings of fear, discouragement and depression. This survey will take about 30 - 60 minutes to complete. The initial questionnaire will be completed when you are first enrolled in the study. Subsequent questionnaires will be mailed to you 3 months from now, 6 months from now, and every 6 months thereafter for up to 4 years.

RISKS AND DISCOMFORTS:

There is no risk to you for participating in this study. Some questions may be sensitive and may cause emotions which could be unpleasant.

BENEFITS:

There will be no direct benefit to you from participating in this study. However, the information obtained may be used to benefit future partners of patients with heart rhythm problems.

ALTERNATIVES:

Participation in this study is voluntary. The alternative is to refuse to participate. There are no penalties for not participating in this study. Your decision to participate will not influence the care your spouse/partner receives.

CONFIDENTIALITY:

Information gathered in this trial will be kept confidential to the extent provided by law. Questionnaires will be reviewed and retained by study investigators for at least 5 years. If information about you becomes part of a medical or scientific report, your identity will not be disclosed. Only the study investigators will have access to the data while the study is on-going. After the study is completed, the questionnaires will be destroyed, and the computerized data will not contain identifying information.

This study is legally authorized under 42 USC 285b-3. The records will be maintained under 42 USC 287a, 287b. The data collected under this study is covered by the Privacy Act System of Records 09-25-0126: Clinical Research: National Heart, Lung, and Blood Institute - Epidemiological and Biometric Studies, HHS/NIH/NHLBI, January 13, 1993, Federal Register, Vol. 58, No. 8.

ROUTINE USES:

The information gathered from these questionnaires may be used in related research projects in order to better understand the impacts of severe heart rhythm disturbances and their treatments on patients' partners.

COSTS:

There will be no cost for participating in this study.

LIABILITY:

It is not the policy of the U.S. Department of Health and Human Services or any agency funding the research project in which you are participating to compensate or provide medical treatment for human subjects in the event the research results in injury.

If you have any questions about your rights as a research subject or research related risks, you may contact__ ___ at ____.

The University is covered by liability insurance. If you suffer any injury from the research project, compensation would be available to you only if you establish that the injury occurred through the fault of the University, its officers or employees. If you have further questions, please call_____ at_____

RIGHT TO ASK QUESTIONS AND TO WITHDRAW FROM THE STUDY:

The doctors listed on this consent have offered to answer any questions you might have. You are encouraged to ask questions about the study, and the physicians in charge of the project will do their best to answer these questions. You are free to decide not to participate in this project, and you can withdraw from it any time without penalty and without affecting your relationship with or treatment at the University.

You will be given a copy of this consent form to take home.

You are making a decision whether or not to participate in this study. Your signature below indicates that you have read the foregoing and agree to participate in this study.

Print Name	Print Name
Signature of Participant	Signature of Witness
Date	Date

Print Name

Signature of Investigator

Date

Introductory Letter for Baseline Questionnaire

Dear _____

We would appreciate your completing the enclosed questionnaire. Major illness often influences the quality of life of the patient's spouse and close relatives or friends. The National Heart, Lung and Blood Institute is sponsoring a study called the Antiarrhythmics Versus Implantable Defibrillators (AVID) Spouse/Partner Quality of Life Study which is authorized under 42 USC 285b-3. The purpose of this study is to determine the impacts of heart rhythm problems and their treatments on patients' spouses and close relatives or friends. This questionnaire will be used to better understand ways to help partners of patients with heart rhythm problems.

We need your assistance in getting some information about whether your daily activities have changed, how you feel in general, how things are going for you right now and concerns you may have about your partner's health problems. Since we are interested in your opinions, we would appreciate your completing this form by yourself without consulting your partner. If you have any questions please feel free to call the study coordinator. We would appreciate your returning this questionnaire in the enclosed self-addressed stamped envelope within a week. This questionnaire should be mailed to: AVID Clinical Trial Center, 1107 NE 45th Street, Room 505, Seattle, WA 98105.

Participation in this study is voluntary. Be assured that there will be no penalties if you decide not to respond to the questionnaire as a whole or to any particular question. Your responses will have no impact on your spouse/partner's medical care. Your responses to this questionnaire will be anonymous, and the information will be kept confidential to the extent provided by law. In particular, your responses will not be available to your spouse/partner or medical staff. In order to protect your confidentiality, please do not enclose this letter, which includes your name, in the return envelope. The information gathered from these questionnaires may be used in related research projects that study the effects of heart rhythm disturbances and their treatments on patients' partners.

We are very interested in how you are feeling now and as the study goes along; therefore, we will ask you to complete portions of the questionnaire at regular intervals during the course of the study. The questionnaire is a relatively quick and useful way for you to tell us what is happening in your life.

Thank you very much for your help.

Sincerely,

_____
Study Coordinator

phone: _____

Follow-up Letter

Dear

Thank you for participating in the AVID Study. As we indicated at the time of the first questionnaire, it is important to provide information at regular intervals. This letter is to request that you complete the enclosed questionnaire. Major illness often influences the quality of life of the patient's spouse and close relatives or friends. The National Heart, Lung, and Blood Institute is sponsoring a study called the Antiarrhythmic Versus Implantable Defibrillators (AVID) Spouse/Partner Quality of Life Study which is authorized under 42 USC 285b-3. The purpose of this study is to determine the impacts of heart rhythm problems and their treatments on patients' spouses and close relatives or friends. This questionnaire will be used to better understand ways to help partners of patients with heart rhythm problems.

We need your assistance in getting some information about whether your daily activities have changed, how you feel in general, how things are going for you right now, and concerns you may have about your partner's hearth problems. Since we are interested in your opinions, we would appreciate your completing this form by yourself without consulting your partner. If you have any questions please feel free to call the study coordinator. We would appreciate your returning this questionnaire in the enclosed self-addressed stamped envelope within 30 days. This questionnaire should be mailed to : AVID Clinical Trial Center, 1107 NE 45th Street, Room 505, Seattle, WA 98105.

Participation in this study is voluntary. You may decline to respond to any particular question. Be assured that there will be no penalties if you decide not to respond to the questionnaire as a whole or to any individual question. Your responses to this questionnaire will be anonymous, and the information will be kept confidential to the extent provided by law. In particular, your responses will not be available to your spouse/partner or medical staff. In order to protect your confidentiality, please do not enclose this letter, which includes your name, in the return envelope. The information gathered from these questionnaires may be used in related research projects that study the effects of heart rhythm disturbances and their treatments on patients' partners.

We are very interested in how you are feeling now and as the study goes along; therefore, we will ask you to complete portions of the questionnaire at regular intervals during the course of the study. The questionnaire is a relatively quick and useful way for you to tell us what is happening in your life.

Thank you very much for your help.

Sincerely,

Study Coordinator

Script for Telephone Follow-up Reminder

Hello, this is _____ (nurse coordinator's name) from the _____ (clinical center). The AVID Clinical Trial Center in Seattle has not yet received your quality of life questionnaire. I wanted to remind you that the spouse/partner quality of life data is very important for our study, and we would greatly appreciate your taking the time to complete the questionnaire.

Thank you very much for all of your help.

ECONOMIC EVALUATION COMPONENT

A. Overview

Studies have shown the clinical efficacy of the implantable cardiac defibrillator (ICD) in the treatment of sustained ventricular tachycardia and ventricular fibrillation, leading to enthusiasm for widespread use of the device as a substitute for pharmaceutical treatments in the secondary prevention of sudden arrhythmic cardiac death (SCD). Recent retrospective studies have suggested the potential cost-effectiveness of ICD compared to conventional drug treatment, however, no prospective economic evaluation has been conducted to date.

The Economic Analysis Subcommittee has identified a method, based on experience gained during the pilot, for assessing cost-effectiveness which is described in the AVID Economic protocol. Detailed health services utilization will be collected monthly on a sample of 4 to 10 patients per site. These will constitute the **shoebox subsample** since most of these patients will contribute more detail about health care utilization by keeping all their medical bills and receipts in an AVID "shoebox." For all patients, length of stay, reason and total charges will be collected for all hospitalizations. Reminders to obtain total charges will be sent monthly from the CTC. Also, for all patients, work status and work days missed due to poor health of any cause will be assessed at each follow-up. The clinical and cost data will be combined to assess the cost effectiveness of the ICD compared to drug treatment.

At baseline, you may want to have the patient sign a "Release of Billing/Medical Records" authorization. This may be helpful in obtaining charge data in certain instances. A sample Request for Release of Billing/Medical Records follows.

Briefly, the procedures and forms to be completed for the economic evaluation component are:

Baseline

- Have the patient sign a Release of Billing/Medical Records authorization.
- Provide "shoebox" patients with the AVID "shoebox" and instruct them to put all their medical bills in it and bring the "shoebox" (with bills inside) to every follow-up visit. The “shoebox” patients should also keep track of all hospitalizations, ER visits, clinic/lab/physician visits, and medications. Health care diaries and calendars are available as aids.

Follow-up

For ALL patients (randomized on or after 3/20/95)

- On an ongoing basis obtain total charges for all hospitalizations. It is not necessary to obtain the actual bill. Collecting the total charge by phone is acceptable. Often there is a significant lag in compiling of the total charges. If the hospitalization occurred at a VA hospital or an HMO affiliated hospital which does not generate bills, there is no need to obtain total charges.

For Shoebox patients:

- Monthly, contact each patient in the shoebox subsample and complete a Health Care Utilization Abstract form . This will be done by phone unless the patient is seen in clinic for follow-up. The CTC will provide monthly reminders of evaluations due. If the patient dies or otherwise withdraws from the study, complete a Health Care Utilization Abstract form for the period from the last economic evaluation until the time of death/withdrawal. Details about completing this form are discussed later in this section. A new form should be used for each contact and then faxed to the CTC.

- At each follow-up visit, collect the shoebox from "shoebox" patients, make two copies of the contents (one copy to be sent to the CTC, the other copy to be kept with the patient's records), return the originals to the patient in a manila envelope and reissue the empty "shoebox." Reconcile all bills/receipts (except medications) with the items noted on the Health Care Utilization Abstract form(s). Keep notes regarding the status of the bill in the right column of the Health Care Utilization Abstract form. If items remain unaccounted for, remind the patient about the specific items. In extreme cases you may need to obtain copies of the bills from the source (e.g., the clinic office, hospital, etc.). Once a month you will receive a list of items you noted (if any) on the Health Care Utilization Abstract form. We ask that you indicate whether you have sent a copy of the bill to the CTC.

1

Request for Release of Billing/Medical Records

RELEASE RECORDS TO:

DR:_____, an AVID Trial Investigator

ADDRESS: _____

_____

_____

Please Print

RELEASE FROM: _____

I, _____, (Patient's Name) am participating in a National Clinical Trial, *A Randomized, Controlled Trial of Implantable Cardiac Defibrillators Versus Antiarrhythmic Drug Therapy in Survivors of Ventricular Tachycardia or Fibrillation (AVID).*

I hereby give my permission to release any medical records and billing records from any clinical, medical office or hospital visits/stays from this date _____/_____/_____ until the closure of the study on January 1, 1999.

Patient SS#: _____/_____/_____ Patient DOB: _____/_____/_____

_____ _____

Patient's Signature Witness

Health Care Utilization Abstract Form

This form will be used by the study coordinator to collect information about health care utilization by telephone call monthly between follow-ups and in the presence of the patient at follow-up visits. It is to be completed monthly on each patient assigned to "Shoebox", whether or not he/she continues to be an active shoebox participant. An abstract form should also be completed for the interval between the last economic evaluation and death or withdrawal when appropriate.

Item 1 — *From (Begin) Date* — Record the beginning date for this economic period. This date will normally be one day after you filled out the last Economic Abstract form or the randomization date if this is the 1 month Economic Abstract form.

— *To (End) Date* — Record the date the abstract form was completed. This date should correspond to the date the patient or his/her designee was contacted by phone or seen for the scheduled follow-up visit.

Item 2 — *Type of contact* — Check whether you contacted the patient by phone or saw the patient at follow-up in order to complete the abstract form. Also check whether you spoke with the patient or with someone other than the patient.

Item 3 — *Hospitalizations* — Check whether there were any hospitalizations. If yes, record the date of admission, the hospital code or the name and location of the hospital, the primary reason for admission and the number of days spent in the hospital for each self-reported hospitalization. Be sure and complete a Hospitalization form for each hospitalization.

Item 4 — *Emergency room or non-overnight hospital visits* — Check whether there were any ER or non-overnight hospital visits. If yes, record the date of the visit, the hospital code or the name and location of the hospital and the primary reason for the visit for each self-reported emergency room or non-overnight hospital visit.

Item 5 — *Homecare* — If the patient has received home health care, indicate whether the provider is a nurse and/or other. Estimate the average hours per day for those days when care was provided and record the total number of days that care was provided since the last economic evaluation.

Record the total number of days since the last economic evaluation that the patient spent in a nursing home, rehabilitation and/or extended care facility.

Item 6 — *Physician/clinic/lab visits* — Check whether there were any visits including any AVID visits. If yes, record the date of the visit, whether physician, clinic and/or lab, the primary reason for the visit and the tests performed (use codes from the back of each page 1 of the form if applicable, otherwise write in). For shoebox patients only, record the name and city of the physician/clinic/lab unless the bill is at hand. The purpose is to provide a starting point for tracking down the bill if it does not ultimately show up in the patient's shoebox. If the bill is at hand, fill in the bubble at the right.

Item 7 — *Medications* — Check whether the patient is on any prescription medications. If yes, record the code (on the back of page 1), if available, or write in the name of any new or refilled prescription medications and the quantity received. Record only those medications obtained by prescription order. Over-the-counter medications should not be included unless ordered by prescription. Free study medications or other medication samples given to the patient should be recorded here as well.

Use the appropriate lines for medications that come in inhalers, bottles or tubes.

Item 8 — *Is there another page?* — If it is necessary to use the third page because of extensive physician/clinic/lab visits and/or medications, check yes and fill in the additional information on page 3. Otherwise, check no.

The form should be faxed to the CTC as soon as the evaluation is completed. As bills are brought in by the patient, you will need to access this form to reconcile the bills against the items on the form (except medications). Keep track of the status of the bill in the column labeled “Status of Bill”. This column is for your own use, but we suggest that you write the date the bill was sent to the CTC. Once a month, you will receive a list of all non-medication items you noted (if any) on this form. You will need to indicate which bills you have sent to the CTC. If a bill has not been obtained for a service that was performed over 4 months prior, the coordinator should actively pursue it. Also if the patient does not have an itemized bill for a hospital stay, one should be obtained directly from the hospital.

Note that you only need to FAX the form to the CTC <u>one time</u> (when you originally complete it). If you make updates to the form <u>*other* than in the “Status of Bill” column</u>, you should make a phone correction or refax the form.

COMPLETING AND FAXING DATA FORMS9. COMPLETING AND FAXING DATA FORMS

A. Orientation to FAX data entryA. Orientation to FAX data entry

We use a FAX-based data entry system. You FAX your data forms to the CTC where special software, called Teleform, automatically reads, interprets and loads the data into the computer. In order for the computer to recognize the data forms, you need to be particularly careful in how you fill out the forms. In the section that follows, we will discuss how to fill out and send the forms to the CTC.

The CTC has two FAX lines, one for sending your data and the other for routine messages. The two numbers are:

(800) 253-6404 Sending forms

(206) 543-0131 Sending routine messages ONLY

Be sure to use the correct number when sending the forms; furthermore, use this number exclusively for forms and notes regarding forms.

The forms contain information that allow the software to recognize the FAX as a data form. The information is contained in the black squares found in each corner of every page and also in the black and white rectangle found in the upper left corner of every page as shown here:

These markings should not be damaged. Stray pen marks or staple holes over these areas will make the forms uninterpretable.

B. How To Fill Out A FormB. How To Fill Out A Form

In order for the computer to interpret data correctly, forms must be carefully completed. This section provides guidelines for completing forms.

There are two main types of data fields which make up the forms. The most common is a "choice" field where you need only mark an "X" on the bubble (or small circle) which corresponds to your choice. For example:

○ Yes ○ No

The other type requires you to write in an appropriate response, for example the name of a drug or the dose in mg/day. For example:

○ Sotalol mg/day

The basics of letters and numbers:

The software system is capable of recognizing letters and numbers printed in the boxes provided; however it will have trouble interpreting characters which are not printed clearly or characters which touch the lines of the box. Print characters in upper case block format as follows:

Numbers also need to be printed clearly in block format as in this example:

Here are some examples of data fields which Teleform had trouble interpreting. Contained inside the boxes are the characters as the user wrote them. Given above and below the box are what Teleform interpreted them as. A question mark indicates that Teleform could not interpret the character at all.

Filling in bubbles:

In the bubbles which correspond to the choice fields, you should either fill in the bubble or put an "X" through it. Avoid check marks since it is difficult to center the check mark in the bubble. Teleform did not consider the following bubbles as marked:

The perfect pen:

A felt tip or ball point pen are acceptable if they don't skip on the page as you write. Never use pencil. The main concern here is that there are no gaps in your characters leaving white spaces. The best colors are blue or black.

Identifying forms and pages of forms:

Since you will have to put each page of a multi-page form into the FAX machine (and they could get mixed up), we ask that you affix a patient ID label to each page of each form and that you write in the date of the form where indicated at the top of each page of the form.

At the end of the form there is room for your signature and your code number. These are also required fields.

To the right of your signature is a gray box for internal CTC use. Please do not complete or make stray marks in this area.

What to do if you make a mistake:

The data that you FAX to us does not go directly into the AVID database. It is first processed by a data entry operator who will interpret problematic characters and marked bubbles. The operator will see the image of the form on the screen; therefore if you realize you made a mistake and want to correct it, put a line through the incorrect data and write the correct data above it. If you filled in a circle which should not be filled, clearly indicate that it was a mistake and should not have been filled in. Be sure to date and initial any corrections. Never use white out to make corrections. This is illustrated in the next example:

C. Procedures For FAXing DataC. Procedures For FAXing Data

Review your form before you FAX it

Make sure that each form you are FAXing contains all of its pages. Note that each form has a page number at the bottom of the page which states "page 1 of 5", "page 2 of 5", and so on. Check that the patient ID number and date of the form is on every page.

It is also important to verify that all pages of a form for a particular patient are together. Suppose you FAX us the Adverse Symptoms form for 2 patients. If we receive the first two pages of the Adverse Symptoms form for the first patient and next receive the third page of the Adverse Symptoms form for the second patient, Teleform will assume that the third page completes the form for the first patient. We will not be able to correct this type of ordering problem and will have to ask that the form be re-FAXed for proper interpretation.

The following list of items is a checklist of other details which you should pay attention to before you FAX your form:

— Are all the required data items on the form completed?

  Most of the items on each form are required. If any of these required fields are blank, we will not be able to process the form.

— Are the data items in the specified ranges?

  If you fill in a value which is out of the specified range for that variable, and you have verified that it is the true value, supply a cover sheet with the form which includes the form type, patient ID, date of form, the data item with the "out of range" value, and a brief description of the circumstance.

— Double check that the date that you supplied on the top of the form is correct.

— Did you sign the form and write in your code number?

— Are the data that you supplied readable?

  Visually scan the form for any unreadable characters or marked circles which could be misinterpreted. If Teleform cannot interpret it, will the data entry operator be able to identify the response?

FAX Machine Specifications

All data forms should be FAXed to this number at the Clinical Trail Center:

(800) 253-6404

Any G3 FAX machine will be adequate. However, a document feeder will make the process less of a chore. Please notify the CTC if you change your FAX number or purchase a new FAX machine.

If you notice that your forms were actually FAXed to (206) 727-8133, don't be alarmed: We have automatic rerouting in case our FAX line is busy.

When to FAX your forms

So that everyone can get a chance to send their forms without getting a busy signal, we are setting aside Monday, Tuesday and Wednesday mornings (Pacific time) for sending new data. Please send your data during these times. Afternoons, as well as all day Thursday and Friday, will be primarily used for communications regarding data cleaning. We would like to have all data cleaning completed by Friday morning so that all new and cleaned data can be entered into the AVID data base that afternoon.

Exception:

If you learn of a patient death or a failure in an ICD, you must notify the CTC immediately. To notify us of a patient death, fill out the Notification of Death form and FAX it to us immediately.

To notify us of an ICD failure, FAX a memo to (206) 543-0131 addressed to the CTC giving us the ID number of the patient, the date that the malfunction was discovered and a brief description of the failure. (See Section 4 on the ICD Implantation procedure and form for further description.)

D. Data CleaningD. Data Cleaning

Each Tuesday evening, a verification log will be sent indicating which forms were received and processed during the previous week. If a form you sent does not appear, please check with the CTC. You may need to re-FAX the form. When a form fails the validation checks the log indicates that there is a problem with the form and a brief description of the problem. Appearing at the bottom of the log is a list of unresolved form problems (forms with problems which appeared on a previous verification list but have not been re-FAXed to the CTC yet). A typical daily verification log looks like:

Section 1: The forms which the Clinical Trials Center received on June 24 and successfully transferred to the AVID database are listed here. Consider these forms as "data entered successfully" and file them.

Section 2: The forms listed here were not put into the AVID database due to problems on the form. Do not consider a form in this section as "successfully sent" to us until you correct the problem(s), re-FAX the form, and see it in section 1 of the verification log. (See the above section "What to do when you make a mistake").

Section 3: These forms were FAXed to us previously could not be put into the AVID database due to problems. The clinic was notified of the problem on an earlier verification list, but the form has not yet been re-FAXed to the Clinical Trials Center.

E. Re-FAXing A Form Which Has Already Been Merged Into The AVID DatabaseE. Re-FAXing A Form Which Has Already Been Merged Into The AVID Database

Even after a form has been merged into the AVID database, you may discover that a data field was in error. Suppose that one month after a form appeared in section 1 of the verification log, you discover that a field was in error. For example, the heart rate that you filled in on the ECG form was 78, but the correct value was actually 87. You should correct the field in the same manner as described in the section "What to do if you make a mistake" in section B above. Do not white out or erase the value that was in error; rather, put a line through it and write in the correct value on top of the boxes along with the date and your initials. Then re-FAX your form to the Clinical Trials Center. You do not need to indicate that this form was FAXed in the past. It will be merged into the AVID database and the old data will be replaced with the new.

Correcting the date of a form and requesting data to be deleted from the AVID database

If you discover at a later date that the *date* which you supplied at the top of the form was in error, you must correct the date and re-FAX the form. Additionally, you need to indicate to us that the form with the wrong date should be deleted. We call this a "deletion request" and have designed two forms for this purpose. One is used when you need to delete a REGISTRY form. The other allows you to delete a form on a patient in the randomized trial. Note that event forms cannot be deleted in this way. If the date of an event form is in error, you should notify the CTC by FAX memo or by phone. You may FAX the forms to us along with your other forms.

Caution: Only use the deletion request forms when the date of a form is in error or when you FAXed a form which was unnecessary and should be deleted. Do not use deletion requests for correcting non-date items on the form.

PROCEDURE NOT DONE FORM

Overview

Complete each time a *required* procedure is not done or a required data form will not be submitted. The purpose of this form is to notify the CTC that a procedure was not done and why. For example, if a patient declines to complete the Quality of Life at one follow-up, you will need to complete a Procedure Not Done form for that QL questionnaire.

Where payment is an issue (e.g. ECG required at follow-up), the reason that the procedure was not done will be taken into account when determining whether payment will be made.

Complete a separate Procedure Not Done form for each data form that will not be submitted unless the entire follow-up was not done in which case the "Entire follow-up visit" bubble would be checked.

The schedule of required forms is given Page 5-2.

After completing this form, FAX it to the CTC *in place of* the specific procedure form.

Item 1 — Date — Enter the date which you decided that the patient could not undergo the procedure or that the patient refused. If a form was not completed due to clinic oversight, use the target date for the form.

Item 2 — Type of procedure not done - Check one of the procedures/forms listed. Note that this form may be filled out for only those procedures/forms listed.

Item 3 — Time frame — Check the time frame for which the procedure was required. This should match the reason which you would have checked on the specific procedure form (i.e. if you would have checked "6 months" on the ECG form, check "6 months" on this form). Only one reason may be checked (i.e. if a patient refuses to complete the Quality of Life form at both the 3 month and the 6 month follow-up, you should fill out two Procedure Not Done forms.

Item 4 — Reason not done — Check the reason why the procedure was not done. If the reason is not listed here, check "other" and write in the specific reason.

Item 5 — Comments — Use this area to further explain the circumstances dealing with the omission of the specific procedure.

DELETE REQUEST FORM

Overview

Delete Request Form — This form is to be completed when you want to delete an existing form from the database. There are primarily two reasons for deleting a form: First, the date on the top of the form was wrong. Second, the form should not have been filled out (e.g., a DRUGS form before randomization).

Note that when you reFAX a form with a data correction (other than date), it replaced the form in the database and there is no need to fill out a Delete Request Form. If you are in doubt as to whether this form is needed, ask your CTC programmer.

Item 1 — Date of form to be deleted — This is the date on the top of the form which you are deleting.

Item 2 — Number of form to be deleted — This is the (old) form number (found on the bottom of every form).

Item 2 — Type of form to delete — Check the form type which should be deleted. You may delete only those forms listed. If you need to delete a form which is not listed here, contact your programmer.

Item 3 — Reason for deleting form — Fill in the reason why the form should be deleted (e.g.,"Wrong date," "Form not required").

SUBSTUDIES10. SUBSTUDIES

A. AVID Substudy: Empiric ATP TherapyA. AVID Substudy: Empiric ATP Therapy

Purpose:

The purpose of this study is to examine the efficacy and safety of programming empiric antitachycardia pacing (ATP) in patients with tiered implantable cardioverter defibrillators in whom successful pacing algorithms could not be demonstrated in the electrophysiology laboratory.

Background:

Implantable cardioverter/defibrillators (ICDs) have become accepted therapy in the treatment of patients with sustained ventricular tachycardia and fibrillation.[1] The first generation of implantable ICDs was able to deliver cardioverting/defibrillating shocks only, but the currently available commercial and investigational third generation devices have antitachycardia pacing capabilities as well.[2-4] These devices have a wide range of pacing algorithms that can be programmed. Optimal programming of ATP therapy is thought to require induction of ventricular tachycardia and demonstration of a successful pacing algorithm. The ability of ATP to terminate ventricular tachycardia successfully has been shown to correlate directly with tachycardia cycle length and inversely with interval variability.

Disparity in successful termination of tachycardia by ATP, depending on whether the tachycardia was induced or spontaneous, has been recently reported.[5,6] In patients with ventricular tachycardia , ATP can successfully terminate *induced* ventricular tachycardia 60-80% of the time.[5,7-9] In patients with implantable defibrillators in whom ATP has been turned on, ATP can successfully terminate *spontaneous* ventricular tachycardia 90-95% of the time.[2-5] The reason for this disparity is not known but may relate to 1) the observation that the cycle lengths of induced tachycardia are often shorter than the spontaneous tachycardia,[5,7,9,10] 2) the complex-to-complex variability in cycle length of induced tachycardia may be greater than spontaneous tachycardia,[10] and 3) the duration of tachycardia prior to initiation of therapy may be longer during induced tachycardia than spontaneous ones (if the investigator has to manually interact with the device)[5]. In addition, it has been noted that even when ATP has been demonstrated to terminate induced tachycardia successfully in the electrophysiology laboratory, most patients required reprogramming of ATP during follow-up.[11]

Thus, it is possible that in some patients in whom ATP could not terminate induced tachycardia, ATP might still successfully terminate spontaneous, clinical tachycardia. Programming empiric ATP therapy in these patients would increase the number of patients who would benefit from ATP and decrease the number of shocks required. On the other hand, programming of empiric ATP therapy might lead to acceleration of ventricular tachycardia, delay of appropriate therapy, and increased number of VT episodes requiring multiple shocks for termination of tachycardia. The efficacy and safety of programming empiric ATP therapy in patients in whom a successful pacing algorithm is not demonstrated in the laboratory is unknown.

References:

1. Nisam S, Mower M, Moser S: ICD Clinical Update: First Decade, Initial 10,000 Patients. PACE 1991; 14: 255-262.

2. Leitch JW, Gillis AM, Wyse ED, Yee R, Klein GJ, Guiraudon G, Sheldon RS, Duff HJ, Kieser TM, Mitchell LB: Reduction in Defibrillator Shocks With an Implantable Device Combining Antitachycardia Pacing and Shock Therapy. J Am Coll Cardiol 1991; 18: 145-51.

3. Bardy GH, Troutman C, Poole JE, Kudenchuk PJ, Dolack GL, Johnson G, Hofer B: Clinical Experience With a Tiered-Therapy, Multiprogrammable Antiarrhythmia Device. Circulation 1992; 85: 1689-98.

4. Fromer M, Brachmann J, Block M, Siebel J, Hoffman E, Almendral J, Ohm OJ, den Dulk K, Coumel P, Camm AJ, Touboul P. Efficacy of Automatic Multimodal Device Therapy for Ventricular Tachyarrhythmias as Delivered by a New Implantable Pacing Cardioverter-Defibrillator. Circulation 1992; 86: 363-374.

5. Gillis AM, Leitch JW, Sheldon RS, Morillo CA, Wyse G, Yee R, Klein GJ, Mitchell LB: A Prospective Randomized Comparison of Autodecremental Pacing to Burst Pacing in Device Therapy for Chronic Ventricular Tachycardia Secondary to Coronary Artery Disease. Am J Cardiol 1993; 72:1146-1151.

6. Porterfield JG, Porterfield LM, Smith BA, Bray L, Voshage L, Martinez A: Conversion Rates of Induced Versus Spontaneous Ventricular Tachycardia by a Third Generation Cardioverter Defibrillator. PACE 1993 16: 170-173.

7. Cook JR, Kirchhoffer JB, Fitzgerald TH, Lajzer DA: Comparison of Decremental and Burst Overdrive Pacing as Treatment for Ventricular Tachycardia Associated with Coronary Artery Disease. Am J Cardiol 1992; 70:311-315.

8. Calkins H, El-Atassi R, Kalbfleisch S, Langver J, Morady F: Comparison of Fixed Burst Versus Decremental Burst Pacing for Termination of Ventricular Tachycardia. PACE 1993; 16:26-32.

9. Newman D, Dorian P, Hardy J: Randomized Controlled Comparison of Antitachycardia Pacing Algorithms for Termination of Ventricular Tachycardia. J Am Coll Cardiol 1993; 21:1413-8.

10. Ip JH, Winters SL, Schweitzer P, Lotvin A, Tepper D, Gomes AJ: Determinants of Pace-Terminable Ventricular Tachycardia: Implications for Implantable Antitachycardia Devices. PACE 1991; 14: 1777-1781.

11. Porterfield JG, Porterfield LM, Smith BA, Bray L: Experience with Three Different Third-Generation Cardioverter-Defibrillators in Patients with Coronary Artery Disease or Cardiomyopathy. Am J Cardiol 1993; 72: 301-304.

Status of Devices/Procedures:

It is the standard of care for patients who have had a tiered therapy defibrillator implanted to have an electrophysiologic study at the time of implant or prior to hospital discharge at which time the patient's tachycardia is induced in order to program the defibrillator settings. A separate clinical consent form will usually be obtained for this electrophysiologic study, although some centers may have included this aspect of testing in the AVID consent form. The particular devices that the patients will have implanted may be investigational, but they will have already signed a consent form for implantation of the device. A separate consent will be needed for randomization of ATP therapy, however.

Study Proposal:

Inclusion Criteria:

The study population consist of all patients enrolled in AVID in whom: (1) monomorphic VT is induced but no successful ATP algorithm is identified and (2) patients without inducible monomorphic VT.

Exclusion Criteria:

Patients in whom monomorphic VT is induced and a successful ATP algorithm is identified.

Description of Study:

Patients in whom monomorphic ventricular tachycardia is induced but no successful antitachycardia pacing (ATP) algorithm is identified and patients without inducible monomorphic ventricular tachycardia (including those who have only inducible VF) will be randomized as follows:

One half will be randomly assigned to have empiric ATP therapy turned on for the first 3[1] months of follow-up; one half will be randomly assigned to have empiric ATP therapy turned off for the first 3 months of follow-up. At the 3-month follow-up visit, each patient will be "crossed over" to the alternate therapy, i.e., ATP off for the first group and ATP on for the second. Follow-up will continue for the second 3 month follow-up period.

At the end of the first 6 months follow-up, patients will be maintained in the study for another 6 months (two additional 3 month periods of alternative therapies) unless the patient or physician refuse to continue. The order of ATP on /ATP off will remain as randomly assigned. In particular, if the patient has experienced NO episodes requiring shock therapy in either 3 month interval, the patient will be maintained in the study for another 6 months, similar to the first two 3 month

[1] Due to manufacturer's requirements, follow up periods for patients with CPI PRx devices will be 2 months. Thus, observation will continue in 4 month blocks for these patients.

periods as long as the physician and patient are willing to complete a 6 month block.

The study will be conducted in a "single-blind" fashion. That is, the patient will be unaware whether ATP therapy is turned on or off for a particular period. This blind is needed for an unbiased measure of the effect on quality of life[2] and a comparison of the relative cost in terms of the number of hospitalizations, physician visits and number of times the device was reprogrammed. The physician and AVID coordinator cannot be blinded but should "forget" the current therapy mode to the extent possible.

Data to be collected in each period will include:

(1) The total number of shock therapies delivered;
(2) The number of episodes requiring a single shock;
(3) The number of episodes requiring multiple shocks;
(4) The number of syncopal episodes and shocks perceived by the patient.

Since the information provided in print-outs from the various devices varies greatly, no attempt will be made to collect prospectively and subsequently analyze any measure of termination or "acceleration" of VT. Instead, print-outs of stored electrograms and recordings of intervals and therapies will be copied and sent to the CTC for possible later analysis.

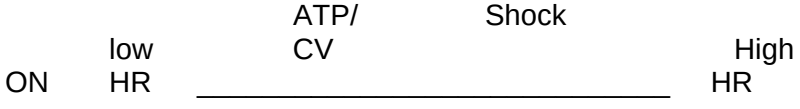
Electrophysiology study at implant or prior to discharge:

Ventricular tachycardia detection parameters and therapy will be turned on (if not already done). Non invasive programmed stimulation via the implanted defibrillator will then be done to induce monomorphic ventricular tachycardia.

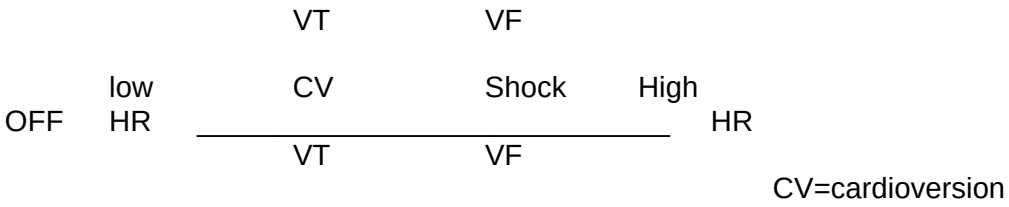
For the patients in whom monomorphic ventricular tachycardia is induced, an attempt will be made to find a pacing algorithm that successfully terminates ventricular tachycardia. All patients in whom ventricular tachycardia can be terminated by pacing will be discharged with ATP programmed on.

Randomization to "ATP on" or "ATP off" as the initial therapy will be made after demonstration that arrhythmias are not inducible or not pace terminable and after consent is signed. It will be made clear to the patient that participation in this substudy is voluntary. Participation in this substudy must not interfere with or adversely affect the patient's continued follow-up in the trial.

Programming of empiric pacing therapy should conform to the following schematic of heart rate (HR):



[2] There is no 9 month QL so there would be no QL comparison in the second 6 month follow period.



General guidelines are as follows: A lower rate of 150 be imposed on ATP. In patients who do not have inducible or clinical ventricular tachycardia, the VT detection should be set at a minimum of 15 beats/minute slower or 40-50 msec longer than VF detection. The empiric ATP programming may be ramp or burst, 5-8 complexes, 80-90% of tachycardia cycle length, and 1-3 trains. The remaining VT therapies will be programmed to cardioversion. Other programming specifics will be left to the individual investigator.

Benefits:

Patients who have empiric ATP turned on may have a decreased need for cardioversion which may in turn increase the quality of their life.

Risk:

Patients who have empiric ATP turned on may have an increased risk of having syncope due to the delay (10-20 seconds) to first shock or having more than one shock during a given episode.

Analysis:

The primary endpoint for this study will be a comparison of the total number of shocks delivered with empiric ATP on vs empiric ATP off. Secondary endpoints will include a quality of life and an economic (health utilization) measure. Descriptive endpoints will include the number of syncopal episodes, the number of episodes requiring one shock, and the number of episodes requiring more than one shock. In periods where ATP is turned on, a further descriptive endpoint will be a measure of the number of times that ATP apparently successfully terminated the VT and the number of times that ATP apparently accelerated the VT.

The primary endpoint will be shocks delivered. Let n_{ij} be the number of shocks delivered to patient i under therapy j[j=1(ATP on) or j=0(ATP off)]. Then the outcome measure will be $d_i=n_{i0}-n_{i1}$ and the null hypothesis is that d=0. The alternative is that d>0.

Censoring will occur. The magnitude of censoring due to death, change in other antiarrhythmic therapy or dropout can be expected to be substantial. However, if the censoring is unrelated to the intervention (and we expect censoring due to death or dropout to be so), the effect will only be to inflate variance (not cause bias). Treating n_{ij} as number of shocks/unit time will help keep the variance low. If the censoring is related to intervention (e.g., adding an antiarrhythmic drug might be such and certainly turning ATP off or on would be) this will require consideration of a bivariate or of a composite endpoint. One approach would be to test d=0 by a rank test where if d_1, d_2, ..., d_k are the ordered values of d for patients without intervention related censoring, then a value

$d_0<d_1$ or $d_{k+1}>d_k$ would be assigned to each intervention related censored patient depending upon whether ATP was "positive" or "negative."

If censoring occurs after the first 6 month period, d could be restricted to the uncensored 6 month intervals. This would be unbiasing but might ignore substantial information.

Of approximately 500 patients randomized to ICD in the main study, about 200 (say 150 VF and 50 VT) may be eligible and entered into this substudy. Approximately 100 might have episodes in the first 6 months while perhaps 80% might have episodes if maintained in the substudy for the duration of the trial. Perhaps 10% will be censored (death etc.) in the first 6 months and probably 50% over the duration. There is no information about the variance of d to allow power estimates, but generally variation within individuals is small and many crossover trials succeed with sample sizes on the order of 100.

Limitations:

If it was thought that the results of this substudy could affect the major outcome of this trial (survival), it would be an insurmountable limitation to doing this study; however, it is extremely unlikely that this study could affect outcome in the main trial. Published reports detailing the efficacy and safety of tiered devices have shown that there is no difference in sudden cardiac death or survival in patients implanted with devices capable of ATP therapy as compared to previously reported survival of patients implanted with "shock only" devices. This study could conceivably have a small impact on the quality of life study; however, this effect is minimized by having patients crossover from one limb to another.

If it was thought that this substudy would cause significantly increased work at either the coordinating center or the individual sites, it would be a significant limitation to doing the study. In fact, most of the information need for this substudy is already requested in the ICD implant and follow-up forms. The only extra work for the coordinating center is the randomization process.

Because AVID is a study of patients with resuscitated sudden death and syncopal VT, the patient population is skewed toward patients with rapid ventricular tachycardia. Since the overall efficacy of ATP is decreased in patients with tachycardia cycle lengths less than 300 msec, it may be more difficult to demonstrate the efficacy of empiric ATP in this population.

CONSENT FOR PARTICIPATION IN A CLINICAL RESEARCH PROJECT

TITLE:

COMPARISON OF EMPIRIC ANTITACHYCARDIA PACING + SHOCK THERAPY TO SHOCK ONLY THERAPY IN AVID PATIENTS: A SUBSTUDY OF A CONTROLLED TRIAL OF IMPLANTABLE CARDIAC DEFIBRILLATORS VERSUS MEDICAL ANTIARRHYTHMIC DRUG THERAPY

Investigators:

Name	Title	Dept/Division	Mail Stop	Phone

24-hour Emergency Phone Number _____ Ask for Cardiologist on-call

PURPOSE:

As part of your treatment in the AVID Study you have had an implanted cardioverter defibrillator (ICD) placed for treatment of your heart rhythm disturbance (arrhythmia). The ICD can stop your arrhythmia by giving the heart a small electric shock, but may be able to stop your arrhythmia by pacing the heart (making the heart beat a little faster than the arrhythmia for a few beats).

It is standard procedure after ICD implantation to test both methods of stopping your arrhythmia (pacing and shocking) while you are heavily sedated in the electrophysiology laboratory. If the ICD can stop your arrhythmias by pacing during testing, it is considered good medical practice to turn the pacing mode "ON". If it is not possible for the ICD to stop your arrhythmias by pacing during testing it is not known whether it is better to turn the pacing mode "ON" or "OFF".

In your case, it was either not possible to trigger any arrhythmias during testing or the pacing used during testing did not stop your arrhythmias. The goal of this study is to determine the best method of programming your ICD, that is, whether the pacing modes should be turned "ON" or "OFF".

PROCEDURES:

If you decide to participate in this study, the pacing mode will be turned "ON" half the time and "OFF" half the time. The decision whether to start with the pacing feature "ON" or "OFF" will be made randomly (like flipping a coin). You will not know whether the pacing is turned "ON" or "OFF", but your physician will know. Regardless of whether the pacing feature is used, your ICD will be programmed to deliver shocks as needed. If you decide not to participate in this study your ICD will have the pacing mode turned "OFF", in accordance with standard clinical practice.

You will be seen one month after leaving the hospital and then every three months until the end of the study, which is standard routine, even for patients who are not participating in a study. At each visit, your device will be checked and its memory read. Every three months, the pacing feature of your ICD will be programmed to the opposite of what it was before (if it was turned "OFF", it will be turned "ON"; if it was turned "ON", it will be turned "OFF"). The shock therapy will be unchanged.

If, during the course of this study, it becomes clear that having pacing "ON" or having pacing "OFF" is better for you, your participation in the study will end and your physician will set the pacing mode to what is best for you. If you ever decide to withdraw from this study and there is no clear evidence of whether or not the pacing mode is best for you, the pacing mode will be turned "OFF".

At the completion of this trial your physician will program the pacing to whatever (s)he thinks is best for you. Throughout this study, the pacing function for slow heart rates will remain turned "ON". Other procedures, such as completion of Quality of Life questionnaires, will remain unchanged.

RISKS, STRESS OR DISCOMFORT:

There is no known risk to having the pacing function of your ICD turned "ON" to treat rapid arrhythmias. If the pacing is turned "ON" but cannot stop your arrhythmia, there may be an increased likelihood of you becoming dizzy or needing to receive more than one shock, since your arrhythmia may last for a longer period of time before you receive the first shock.

BENEFITS:

There is no known benefit associated with participation. If the pacing is turned "ON" and can stop your arrhythmia, you may not need to receive as many shocks from your defibrillator and may feel better.

ALTERNATIVE TREATMENTS:

The alternative therapy would be to have your defibrillator programmed to deliver shocks only with the pacing unit in the "OFF" mode.

COSTS:

There will be no payment to patients for participating in this study. Since the treatment and tests being utilized in the study are standard for this problem, the costs of such tests and treatments will be borne by you and your insurance company. However, there are no additional tests or charges associated with participating in the substudy.

CONFIDENTIALITY:

Your identity will remain confidential. Results of this study will be given to your primary physician. The Food and Drug Administration (FDA) and the National Institutes of Health (NIH) reserve the right to review study data as well as your medical records, which may contain identifying information. Study data will be kept for at least five years with access limited to the investigators, the FDA, and the NIH. Some of the information gathered in this study may be used for medical publications. In the event of a publication, your identity will remain confidential.

LIABILITY:

In the event of an injury which is the direct result of participating in this substudy, you will be cared for by a member of the investigating team. You or your insurance company will be responsible for the cost of reasonable medical treatment. Financial reimbursement for such things as lost wages, disability, or discomfort due to injury is not available. For eligible veterans, medical care and treatment for any injuries sustained will be provided by the Veterans Administration. For eligible subjects, compensation may be payable under Title 38 USC 351 as outlined under the Federal Torts Claim Act. Further, no assurance can be made regarding the results that may be obtained from this study. With all studies, there may be beneficial or adverse effects which are still unknown.

For information regarding your rights as a research subject or research related risk you may contact _____ at _____ .

VOLUNTARY PARTICIPATION:

You can choose not to participate in this trial, or may withdraw from the trial at any time without penalty or loss of benefits to which you are otherwise entitled. Any significant new findings that develop during the course of this research study which may relate to your willingness to continue your participation will be communicated to you. Your participation may also be stopped without your consent if it is determined by the investigator that it is in your best interest.

Your signature below indicates that you have read this information, that you have discussed this study with one of the investigators and that you have decided to participate in the study based on all the information provided to you.

A copy of this consent form will be given to you.

I have read this consent form and my questions have been answered. I agree to participated in this study.

1) _____ _____

Participant name (print)

Investigator name (print)

Participant signature

Investigator signature

Date

Date

Witness name (print)

Witness signature

Date

ATP ANCILLARY STUDY RANDOMIZATION WORKSHEET

Overview

Complete for patients randomized to ICD who will enter the ATP substudy. The form should be complete *after* a baseline EPS demonstrating either that the patient was non-inducible or that monomorphic VT was induced but was not pace-terminable and after you have obtained consent for this substudy. The baseline EPS can be performed after implantation. Complete the form before calling the CTC for ATP assignment.

Item 1 — Enter the date you will be calling the CTC to randomize the patient to this substudy protocol. Enter the name and code number of the hospital at which this patient will be randomized to the ATP protocol. Each hospital must have separate IRB approval for this substudy protocol.

Item 2 — Check only one bubble, either that monomorphic VT was induced by not found to be pace terminable or that no monomorphic VT was induced by EPS.

Item 3 — A separate consent is required for this substudy. Make sure that the informed consent for the ATP substudy has been carefully discussed with the patient and the patient's physicians before enrolling the patient in this substudy.

Item 4 — At the time of your call to the CTC, you will be given the randomization assignment for the first 3-month period.

B. The Perfusion and Arrhythmia Ancillary StudyB. The Perfusion and Arrhythmia Ancillary Study

Background

There is evidence that arrhythmias may be triggered or facilitated by ischemic myocardium, thus it can be conjectured that the degree of perfusion to infarcted zones may be inversely related to the frequency or severity of arrhythmia. Many AVID patients, who by inclusion criteria must have had at least one serious arrhythmia have had prior infarcts. AVID patients will be carefully followed for arrhythmic events. With only minimal additional baseline data regarding infarct location and infarct area related perfusion, it will be possible to explore relationships between perfusion to infarcted areas and frequency of arrhythmic events. An inverse relationship would support the concept that ischemia promotes or facilitates arrhythmia.

Methods

Patients randomized in AVID with a history of remote myocardial infarction, i.e. prior to their index arrhythmia; with a catheterization adequate to determine the location of the infarct (and hence reasonable indication of the culprit vessels), and provided the clinical center is willing to participate in this ancillary study, will constitute the population of interest. At the time of discharge from the index hospitalization, measures of perfusion to the infarcted zone will be recorded based on collateral flow, successful PTCA, and/or successful bypass grafts. Endpoints will be episodes of VT or VF. In ICD-treated patients, frequency of arrhythmic events will be tabulated from the ICD evaluations during follow-up as well as from the Recurrent Arrhythmia form. For drug-treated patients, the frequency of arrhythmic events will be tabulated from the Recurrent Arrhythmia form. In the case of death, the Events Committee will determine whether the death was presumably due to arrhythmia or not.

Analysis

The basic analysis will compare the occurrence of arrhythmic events in the group with perfusion versus the group without perfusion to the infarcted zone. Refinements to this analysis may consist of time to the first arrhythmic event (which will reduce somewhat the censoring problem of non-arrhythmic fatal events), frequency of events and within sub-groups identified by location of the infarcted zone. In all analyses, adjustments would be made for baseline covariates since it can be expected that patients with and without perfusion may well differ on a number of important baseline clinical risk factors. Analyses will be stratified by whether the patient is receiving an antiarrhythmic drug (alone) or has an ICD implanted.

Sample Size

We can assume that at least half of the AVID patients will meet the criteria. If half of the clinical centers participate, we can expect approximately 400 subjects for this ancillary study. This will be adequate to detect a strong relationship between perfusion and arrhythmia frequency.

CORONARY PERFUSION FORM

Overview

Complete at baseline hospital discharge for AVID patients with evidence of MI prior to the index arrhythmia who undergo coronary angiography *after* initial index arrhythmia. MI is defined by symptoms, ECG changes enzyme abnormalities and/or segmental wall motion abnormalities.

Item 1 — Date of procedure: Enter the month, day and year that the angiography was done.

Item 2 — Angiography:

Coronary patency of the native vessel: refers to the major epicardial vessel and not to branch vessel(s) or distal segment(s). Percent maximum stenosis refers to the degree of stenosis in this major native vessel.

TIMI flow: refers to the perfusion beyond the maximum stenosis in this major native vessel and into the majority of the intended myocardial distribution of this vessel. Do not refer this question to flow into branch vessels or the flow of the distal segments of the major native vessel.

Coronary patency of graft vessels (from prior surgical procedures): refers to venous or arterial grafts that have been placed distal to sites of maximum stenosis. The stenosis in this graft vessel, if present, is indicated with a maximum stenosis percentage.

TIMI flow: refers to the perfusion beyond a stenosis, if present, in the graft vessel, or the native vessel immediately beyond the site of anastomosis.

TIMI flow grade:	Definition:
0	**No perfusion**
I	**Penetration with minimal perfusion.** Contrast material passes beyond the area of obstruction but "hangs up" and fails to opacify the entire coronary bed distal to the obstruction for the duration of the cine run.
II	**Partial perfusion.** Contrast material crosses the obstruction and opacifies the coronary bed distal to the obstruction, but the rate of entry of contrast material into the vessel distal to the obstruction and/or its rate of clearance from comparable areas not perfused by the previously occluded vessel is reduced (e.g., opposite coronary artery or coronary bed proximal to the obstruction).
III	**Complete perfusion.** Antegrade flow into the distal bed from the obstruction occurs as promptly as flow into the bed proximal to the

obstruction, and clearance of the contrast material occurs as promptly as clearance of material from an uninvolved bed in the same vessel or the opposite artery.

Reference: TIMI Study Group. The Thrombolysis In Myocardial Infarction (TIMI) Trial. Phase I findings *N Engl J Med* 1985;312:932-936

Location(s) of infarcted myocardium: Using ECG, wall motion and/or arteriographic findings, if there is evidence of prior infarction(s), indicate the location(s).

Suspected culprit arteries: The culprit, or infarct, artery is the native vessel supplying the zone of a previous MI.

Collateral circulation: Indicate to which vessel(s) there is collateral circulation, defined as angiographic evidence of alternate perfusion from a vessel that is not critically stenosed (i.e., <70% stenosis).

Distal flow impairment: Indicate whether a major region of myocardium supplying a significant myocardial distribution served by a major branch of one of the three major coronary arteries has less than TIMI III flow. Do not include small branch arteries that supply only small myocardial segments. A "significant myocardial distribution" is estimated to be ≥20% of the left ventricular myocardium. This definition will obviously be somewhat arbitrary by its very non-quantitative nature. This question is designed to capture impaired perfusion zone(s) not captured by other questions on this form.

Item 3 — Revascularization: Indicate if, after the index arrhythmia and baseline angiography, successful CABG and/or PTCA and/or atherectomy was performed.

CABG: If successful CABG was performed since the index arrhythmia, indicate the vessels bypassed. "Success" may simply be defined by the knowledge that a vessel was bypassed at surgery — most patients will not have follow-up angiography. If angiography was performed after CABG, success is defined as no lesion in a major graft/vessel ≥50%.

PTCA/atherectomy: Check all arteries that had successful PTCA or atherectomy performed since the index arrhythmia. Success is defined as residual lesion of <50% that restores flow to the distribution of all major downstream vessels. In the case of multiple lesions of major branches of a coronary vessel, all lesions must be dilated to <50% residual stenosis to be considered successful.

Note: If a patient undergoes cardiac catheterization or revascularization during a ***subsequent*** hospitalization, it need only be listed on a Hospitalization form under "Events during hospitalization," and this Coronary Perfusion form should not be completed.

C. AVID Substudy: QT Dispersion Substudy TC "C. AVID Substudy: QT Dispersion Substudy" \f C \l "2"

The goal of the QT Dispersion Substudy is to determine whether measures of QT dispersion are predictive of subsequent events in patients treated with an ICD and in patients treated with antiarrhythmic drug, and also to determine whether the administration of amiodarone and sotalol impact the measures of QT dispersion. To accomplish these goals, it is necessary to have a good quality copy of the 12-lead ECG, an original is preferable but a clean, clear photocopy is acceptable. A copy of a faxed ECG is not acceptable because the process of faxing distorts the intervals enough that the measurement won't be accurate. It is important that the ECG be clear and clean as the ECGs will be digitized at a central laboratory for reading. These ECGs will be collected at:

- baseline (while off antiarrhythmic drugs);
- near hospital discharge;
- approximately three months (±1 months) post discharge;
- approximately six months post discharge.

The CTC will send you preprinted patient ID labels (see below) to affix to the back of the 12-lead ECG. These labels will be sent to you attached to the cover sheet in your randomization packet. You need to indicate on the label the date of the ECG, whether it was obtained at baseline, hospital discharge, or follow-up. You should also check the cardiac drugs the patient was on at the time; write in any additional antiarrhythmic drugs the patient is on. The ECG should not be faxed to the Clinical Trial Center. Instead, approximately monthly, they should be batch mailed. If an ECG was either not done or unavailable during a given time period, simply note that on the cover sheet and mail it to the CTC after all ECGs are accounted for.

Predictive Value of QTd for Sustained Ventricular Tachyarrhythmias and Mortality in AVID Patients Treated with the ICD or with the Class III Antiarrhythmic Drugs Amiodarone or Sotalol

Specific aims:

The specific aim of this study is to determine the predictive value for future arrhythmic events of QT interval dispersion (QTd) on entry ECG in patients with malignant ventricular tachyarrhythmias in the AVID study undergoing therapy with either the ICD or class III antiarrhythmic drugs (amiodarone or sotalol). A secondary objective is to evaluate the predictive value of changes in QTd (and QT or QTc alone) caused by antiarrhythmic therapy on these outcomes in the drug treatment arm.

Background and significance:

Prolongation of the QT interval has been found to predict an increased risk of ventricular arrhythmia and sudden death in patients with coronary artery disease (1,2), alcoholic cirrhosis (2,3), and in normal, apparently healthy individuals (4). QTc prolongation as a risk factor for sudden death was also independent of age, history of myocardial infarction (MI), heart rate, and drug use (2). Another index of ventricular repolarization that may be even more useful as a predictor of risk is inter-lead variability in the QT interval (QT dispersion, or QTd). This index reflects regional variation in ventricular repolarization (5,6), and may indicate a substrate predisposing to serious ventricular tachyarrhythmias (7-11). Increased QT dispersion has been observed in patients with acute MI who develop ventricular tachyarrhythmias, compared with those with a benign course (12). Similarly, QT dispersion is increased in patients with long QT syndromes at risk of ventricular arrhythmias (10). Patients with hypertrophic cardiomyopathy who die suddenly have increased QT dispersion (13). In patients with chronic heart failure, increased QT dispersion has recently been associated with a high risk of sudden death (14).

Certain therapies have been shown to affect QT dispersion. Moreno et al. has recently reported reduction in QT dispersion by successful thrombolytic therapy in acute MI (15). Sotalol in one study was found to be associated with similar QT interval prolongation as congenital long QT syndrome, but QT dispersion was reduced after sotalol, whereas it was increased in the congenital long QT syndrome (10,16). In another study, sotalol given after MI increased QT interval (compared with placebo), but decreased QT dispersion (10,17). In another study (11), precordial QT dispersion was found to be a marker of torsade de pointes. A disparate effect of class IA antiarrhythmic agents versus amiodarone (class III) on QT dispersion was found. Whereas both drugs prolonged QT interval to the same degree, class IA therapy increased QTd in 9 patients with torsade de pointes, whereas in 29 patients without torsade, no increase in QTd was found. With amiodarone therapy (in the same patients), no increase in QTd was observed in any patients, and none developed torsade. These findings suggest that QTd may be a predictor of torsade de pointes with antiarrhythmic therapy, and may be a better marker than QT prolongation.

The cause and importance of the U wave during repolarization has been controversial. A recent study (18) suggests that the U wave may reflect after-depolarization in a unique subpopulation of cells in subepicardial and mid myocardial

regions, the “M cells”. Antezelevitch and Sicouri (18) further suggested that a QTu/QT dispersion ratio may even more accurately predict heterogeneity of recovery within the heart than QT dispersion alone, but their conjecture remains to be confirmed.

The predictive value for arrhythmic events (sustained VT or VF, torsade de pointes VT, appropriate ICD shocks, syncopal shocks, sudden arrhythmic deaths) and total mortality of QTd at entry, as well as QTd (and change in QTd) after loading on amiodarone or sotalol (predischarge ECG) in the drug arm, will be explored in the present study.

Hypothesis:

An increased QTd (> 80ms) at baseline predicts increased risk of arrhythmic events (i.e., reduced time to first sustained VT or VF event, cardiac arrest, or sudden death), but not non-arrhythmic deaths, in AVID patients. QTd on drug therapy in the drug treatment arm also will be predictive of arrhythmic events.

Experimental Design and Methods:

The study will require a 12 lead electrocardiogram of high quality (if not the original) for analysis taken at baseline (off antiarrhythmic therapy) and at early steady state (i.e., after in-hospital drug loading, pre-discharge), and around the 3 month and 6 month follow-up periods. These ECGs will be collected on patients in both the drug arm as well as the ICD arm (to serve as a control). Some of these ECGs are already being obtained by study centers, but they are not being forwarded to the CTC as part of the main study database. This substudy will request that high quality copies (if not the original) of the ECGs be sent to the CTC. The CTC will forward the ECGs (in batches) to the substudy core laboratory at LDS Hospital, Salt Lake City, Utah.

QT dispersion will be assessed on the ECGs (noted above) and the following analyses made: 1) Baseline (also, pre-discharge and at 3 & 6 months, when available) QTd (versus QT and QTc) will be assessed and compared in patients who experience events versus those who do not; the predictive value for arrhythmic events of baseline QTd will be the primary question of interest. 2) Effect of drug therapy on QTd (and QT and QTc alone); the predictive value for events of QTd and change in QTd on drug therapy will be the main secondary question of interest.

Method of QT dispersion determination:

Standard 12 lead electrocardiograms will be recorded at 25 mm/sec speed (or, if at 50 mm/sec, will be designated as such). High quality reproduction of electrocardiograms obtained in this study will be used by the LDS Hospital core electrocardiography laboratory by one or two validated observers (15), blinded to the patients’ drug and clinical status.

Measurements of QT, QRS, JT and RR intervals will be performed using a commercially available computer program (Configurable Measurement System, Salt Lake City, Utah) interfaced with a Calcomp 9000 digitizer. Using this measurement system, intraobserver, interobserver, and interstudy variability have been shown to be small in our laboratory (15). QT interval will be measured from the onset of the QRS

complex to the end of the T wave, defined as its return to the T-P isoelectric baseline (as determined by the intersection with the baseline of a line drawn tangent to the downslope of the T wave). The QT will ignore the U wave when the latter is present. QRS interval will be measured from the onset of the Q wave (or the R wave, if the Q wave is absent) to the end of the S wave, defined as its return to the T-P isoelectric baseline. JT interval will be computer-calculated by obtaining the difference between the QT and QRS for each QRST complex measured. Whenever possible, the average measurement of three complexes for each lead will be taken. If the end of the T wave cannot be reliably determined, or when the T wave is isoelectric or of very low amplitude, the QT measurements will not be made and these leads will be excluded from analysis. A lower limit of 5 or more technically adequate leads per electrocardiogram will be set for inclusion in this study.

QT dispersion will be defined as the difference between the maximum and minimum QT interval measurements occurring among any of the 12 leads on the standard electrocardiogram. QTc (or heart rate - corrected QT interval) will be calculated according to Bazett's formula as follows: (QTc=QT/square root of the RR interval. QTc dispersion will be calculated in a manner similar to QT dispersion. JT dispersion will be defined as the difference between the maximum and minimum QT interval measurements occurring among any of the 12 leads on a standard electrocardiogram. Bazett's formula will be applied to obtain JTc, substituting JT for QT in the formula derived.

Alternate methods for defining QTd will be to 1) assess the standard deviation of QT intervals as a measure of dispersion (20), 2) measure QTd only in the precordial leads, and 3) include the U wave in the analysis (18).

Statistical analysis:

Results will be expressed as a mean $\pm$ standard deviation for each group. Paired t testing and repeated measures analysis of variance will be used to test for effects of drug as compared with baseline, and on QT, QTc, and QTd. T-testing or one way analysis of variance will be used for comparisons between or among groups for QT (i.e., those who do versus do not experience events). Analysis of variance and covariance will be used to assess whether QTd was influenced by any of several baseline factors, including age, sex, type of underlying heart disease, type of presenting arrhythmia, the number of measurable leads per ECG, or the choice of leads where maximum and minimum QT intervals were measured. Time to first event in groups with QTd $>$80ms vs $<$ 80ms will be compared using the log rank statistic.

Impact:

This study will demonstrate whether increased QT dispersion at baseline is an important, independent predictor of arrhythmic risk in the AVID population both overall and in patients assigned to the ICD and drug treatment arms separately. Second, the study will test whether amiodarone and sotalol (two class III antiarrhythmic drugs) reduce or increase QT dispersion, and how this affects the risk of future arrhythmic events. It will specifically test if increases in QTd to $>$80-100 ms predict an increased risk of arrhythmic events with drug treatment. If for example, QTd is shown to remain high or to increase (i.e., to $>$80 ms), with therapy (whereas the intended response is a

reduction in dispersion to <60 ms with therapy), then chronic treatment can be avoided or dosage adjusted. Patients with persistently increased QTd should perhaps be more carefully monitored or selected for alternative therapy (i.e., ICD, etc.). The study may thus provide the basis for improved prognostic and treatment algorithms.

Costs:

To be negotiated, but primarily for technical help (technician time) for QTd analysis, estimated at 15 min. per ECG.

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D. AVID Substudy: Unexplained Syncope SubstudyD. AVID Substudy: Unexplained Syncope Substudy

Purpose:

The purpose of this substudy is to describe the treatments of and subsequent outcomes in patients who have out-of-hospital unexplained syncope, structural heart disease, and EP inducible ventricular tachycardia with symptoms

Background:

The VT recurrence rate in patients with unexplained syncope who have structural heart disease and EP-inducible VT may be equivalent to patients with documented VT, suggesting that VT was the arrhythmia responsible for the syncope. If it is suspected that the EP laboratory-induced arrhythmia is identical or similar to the clinical arrhythmia presumed responsible for syncope, patients may be treated with drugs or ICD to prevent VT recurrence. The AVID study plans to register several hundred patients with arrhythmia type "G" (unexplained syncope and EP-inducible VT). Semi-annual follow-up of these patients will make it possible to yield important treatment, morbidity, and mortality information.

Methods:

Patients registered in AVID category "G" will constitute the population of interest: Out-of-hospital unexplained syncope with structural heart disease and EP-inducible VT with symptoms. Patients will be followed at 6 month intervals. Data to be collected will include: baseline drug-free EP results; subsequent arrhythmia therapy; methods of testing used to establish arrhythmia therapy; semi-annual patient evaluation for development of recurrence of sustained arrhythmias, syncope, ICD therapies, rehospitalization, or death. All patients, regardless of treatment, will be approached for enrollment into the substudy. These patients, especially if untreated with antiarrhythmic drugs, will allow us to observe the natural history of the primary arrhythmic event. A recurrence rate that is consistent with or identical to an event rate in matched patients with documented primary arrhythmias would provide support of the hypothesis.

Analysis:

Primary outcomes we wish to measure are overall risk of death (total mortality) and evidence that syncope is due to ventricular tachycardia (either documented ventricular tachycardia obtained from monitored events or appropriate ICD interventions, either shock or antitachycardia pacing for presumed ventricular tachycardia).

Sample Size: Estimated minimum number of patients 300
Duration: Estimated duration 18 months enrollment with an additonal 18 month follow-up.

UNEXPLAINED SYNCOPE SUBSTUDY FOLLOW-UP FORM

Overview

Unexplained syncope substudy candidates include all arrhythmia category "G" patients who have consented to participate in this substudy, i.e., those with out-of-hospital unexplained syncope with structural heart disease and EP-inducible ventricular tachycardia with symptoms who have signed an informed consent.

Complete this form at:

- Baseline hospital discharge
- Half-yearly telephone or clinic follow-up visits, and
- Death.

Item 1 – *Date of contact* – Record here the date that either the patient went home from the baseline hospitalization, or that a telephone or clinic follow-up evaluation was conducted (at semi-annual intervals). Upon discovery of the patient's death, record the date of death here.

Item 2 – *Reason for completion* – Record here the nearest time interval for patient evaluation. Follow-up intervals plus or minus three months of the target time are acceptable.

Item 3 – *Baseline drug-free EP results* – Complete this section only at the baseline hospital discharge, when the patient has had a drug-free EP study. Indicate all of the clinically relevant ventricular arrhythmias induced in the EP lab. If none of these arrhythmias was induced at baseline EP, the patient should not be included in the substudy.

Item 4 – *Current arrhythmia therapy* – Indicate here which therapy (or therapies) the patient is receiving for treatment of his/her syncope. If the patient is on drug therapy for treatment of syncope, specify which antiarrhythmic drug(s) were given as long-term therapy. Examples of "other" medication a patient may be taking specifically for syncope may include ephedrine, disopyramide, fludrocortisone, etc. "Beta blockers" should be checked if used for any reason even if not specifically related to an arrhythmia.

If an antiarrhythmic drug was either started or changed since the last follow-up (or during admission for baseline hospitalization), check all methods that were used to establish and/or guide therapy. If a patient had more than one therapy initiated (e.g., Class I antiarrhythmic drug guided by EP study, then switched to empiric amiodarone), check both the EP and the empiric bubbles. In the case of an ICD implant, if EP testing is done pre-hospital discharge for induction and termination of arrhythmia, check the EP bubble.

Item 5 – *Recurrent sustained arrhythmia or syncope since last follow-up* – Semi-annual contact with the patient and/or patient's physician will include a careful evaluation of recurrences of sustained ventricular arrhythmia or syncope since

the last follow-up. If the patient was free of serious arrhythmias or syncope, check "no" here and proceed to the next question. If a sustained ventricular tachyarrhythmia (≥30 seconds or requiring an intervention to terminate), SVT, or bradyarrhythmia was noted, check "yes" here and indicate: the date and the type of arrhythmia, if known, whether this arrhythmia was accompanied by syncope; and whether this arrhythmia or syncope resulted in a subsequent hospitalization. Up to five arrhythmia/syncope episodes may be recorded on this form. If a patient had syncope without accompanying documented arrhythmia, check syncope as "yes" and arrhythmia "unknown". If a patient had a documented arrhythmia, it is important to talk with the patient, family members, and local physician to ascertain whether or not syncope accompanied the arrhythmia.

If more than five episodes of arrhythmia or syncope occurred since the last follow-up, select the five most serious events to report here. If a "storm" of arrhythmias occurred over a short period of time, report as one date/one episode, indicating the most serious arrhythmia that was documented during the "storm."

Item 6 – *Events since last follow-up (or since baseline hospital discharge)* – Report here all significant events since the patient was last evaluated. These include rehospitalization for either cardiac or non-cardiac reasons, implantation of either a permanent pacemaker or an implantable defibrillator, patient receiving ICD therapies (ATP and/or shock therapies), or patient death.

Hospitalized patients would include those who were admitted to a hospital for overnight care; do not include same day procedures, emergency room visits, rehab or extended care stays.

Pacemaker or ICD implantation will be checked "yes" when a new generator or complete system is implanted, either as a first time therapy, or as a replacement.

ICD therapies – Report the number of episodes where the patient received ATP therapy only. For example, for an ICD interrogation showing four ATP therapies treating one episode of ventricular tachycardia, record the number "one". Next, report the number of episodes of any shock (with or without ATP therapy). For example, a patient receives two ATP therapies, a low energy shock, then two high energy shocks all for one episode of ventricular tachycardia, you would report "one" in the box provided.

Patient death – Upon discovery of a patient's death, report the date of the death, and whether it was cardiac or non-cardiac. Write a brief summary of the details (e.g., preceding symptoms, specific cause if known, autopsy results).

E. AVID Substudy: Driving and Arrhythmias SubstudyE. AVID Substudy: Driving and Arrhythmias Substudy

Purpose:

The purpose of this study is to describe driving habits of patients with serious ventricular arrhythmias who are treated both medically and with an ICD. In addition such events as symptoms of arrhythmias while driving, accidents, and ICD shocks will also be collected. These reported events will be correlated with recurrent arrhythmias and ICD shocks reported on AVID forms.

Background:

Of the approximately 50,000 deaths that occur each year related to motor vehicle accidents, most are due to trauma incurred by the accident. Some deaths, however, occur as a result of natural causes. Although no complete record exists as to the actual number that were due to CAD, in two reports (1,2) the incidence ranged from 1-5%. In all of these, minor accidents resulted.

Patients who have already survived at least one episode of a serious ventricular arrhythmia are at higher risk for recurrence. One article estimates the risk of hemodynamically significant rhythm recurrence to be 16.5% in the first year; arrhythmias were most frequent the first 2 months after hospital discharge and stabilized after 7 months (3). It is unclear, though, how many of these events would have occurred while driving.

Recently an article was written concluding that motor vehicle accident rates caused by discharge from an ICD is low and that the fatality rate for patients with an ICD (7.5/100,000 patient-years) is significantly lower than the population in general (4). These numbers only represent those patients treated with an ICD. The accident/fatality rate for patients treated medically is not reported.

Study Design:

A driving survey will be administered to all patients at 3 months and semiannually for the duration of the AVID study. The driving survey can be completed with the help of family/friends and may be completed by patients not currently participating in QOL.

There are **two questionnaires**.

The **Initial survey** will be given to patients at a minimum of three months post randomization. For patients at the 3 month F/U, the survey will be sent to the patient only after the QOL survey has been completed so that any alteration in feelings this survey may prompt will not affect the QOL results. To accomplish this, the CTC will only send out the Driving Survey if we have received the QOL form or a Procedure Not Done form at AVID. Each month the CTC will enclose the survey with the patient ID and F/U code completed. An introductory letter is included if needed as well as a return envelope. The completed surveys will be mailed to the CTC for data entry.

For patients that are already past the 3 month F/U the Initial survey will be completed at the next scheduled F/U so everyone can “catch up”. Again, the survey will only be sent out once the QOL form has been accounted for.

The **Follow-up survey** will be completed only by those patients that indicate they have driven sometime in the year prior to joining AVID. The survey will be given every 6 months when the QOL survey is not being given (i.e. at 9mo, 15mo, 21mo, etc.). Each month, the CTC will send out individualized surveys, F/U reminders, and return envelopes. Completed surveys will be mailed to the CTC for data entry.

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