Appendix I

Table 1 – Inclusion and Exclusion Criteria for Defibrillator Trials

Study Sample Size	Inclusion Criteria	Exclusion Criteria	Baseline	Outcome
CAT 2002 ICD tx n=50; control n=54.	Age 18 to 70years; NIDCM ≤ 9 months; LVEF ≤ 30%; NYHA II-III.	CAD, prior MI, myocarditis, symptomatic bradycardia, VT, VF, sign. valvular disease, etc.	Mean f/u 23 mos, mean age 52 yrs, LVEF 24%, 65% NYHA II.	13 deaths in ICD group compared to 17 in the control group (p-value=0.554).
AMIOVIRT 2003. ICD tx n=51; Amio n=52.	NIDCM; LVEF ≤ 35%, NSVT, NYHA I-III.	Syncope, pregnancy, contraindications, NIDCM < 6 mos, etc.	Mean f/u 24 mos, mean age 59 yrs, LVEF 23%, 83% NYHA II-III.	No significant difference in survival between groups.
DEFINITE 2004. ICD tx n=229; control n=229.	Age 21-80 yrs; NIDCM; LVEF < 36%; NSVT/PVCs, VT, VF.	CAD, prior MI, symptomatic VT/VF, syncopy, arrest, NYHA IV, etc.	Mean f/u 29 mos, mean age 58 yrs, LVEF 21%, 57% NYHA II.	28 deaths in ICD group compared to 40 in control (hazard ratio= 0.65; 95% CI =0.40-1.06; p=0.08).
DINAMIT 2004. ICD tx n=332; control n=342.	Age 18-80 years, MI 6-40 days, LVEF ≤ 35%, depressed HRV.	NYHA IV, CABG w/I 4 wks, 3v PTCA, sustained VT/VCF, etc.	Mean f/u 30 mos, mean age 62 yrs, LVEF 28%.	62 deaths in ICD group compared to 58 in control (hazard ratio=1.08; 95% CI, 0.76-1.55; p=.0.66).
COMPANION 2004. CRT n=617; CRT-D n=595; control n=308.	Age ≥ 18 yrs., LVEF ≤ 35%, QRS ≥ 120 ms., PR > 150ms, NYHA III-IV.	MI within 60 days, syncope, unstable angina, indications for pace/ICD, etc.	Mean f/u variable, mean age 67 yrs, LVEF 21%, 86% NYHA III	77 death (25%) in the pharmacologic therapy group; 131 deaths (21%) in the CRT group; and 105 deaths (18%) in the CRT-D group (p=0.003 compared to control).
SCD-HeFT 2004. Amio n=845; ICD n=829; control n=847.	Age ≥ 18 yrs., LVEF ≤ 35%, NYHA II-III, CHF ≥ 3 mos.	LVEF > 35%, unable to conduct activities of daily living such as patients with NYHA Class IV CHF, cardiac arrest, pregnancy, patients likely to die from any non-cardiac cause within 12 months, etc.	Mean f/u 40.2 mos, mean age 59.5 yrs. Men comprised 77%, mean LVEF 24%. Approximately 52% ICM, NYHA.	244 deaths in placebo; 240 amiodarone (hazard ratio compared to control=1.06; 97.5% CI=0.86-1.30; p-value=0.529); 182 deaths in ICD (hazard ratio compared to control=0.77; 97.5% CI=0.62-0.96; p-value=0.007).

Appendix II

Table 1 – Inclusion and Exclusion Criteria for Defibrillator Trials (from June 2003 decision)

Study Sample Size	Inclusion Criteria	Exclusion Criteria	EP study	Outcome
MADIT I, 1996. Tx n=95; Conventional n=101.	age 25 to 80 years; myocardial infarction 3 wks or more; episode of asymptomatic unsustained VT unrelated to MI; LVEF ≤ 0.35; NYHA I-III; inducible, nonsuppressible VT on EPS; no indications for CABG or angioplasty.	prior cardiac arrest or VT causing syncope not associated with AMI; symptomatic hypotension; MI within past 3 wks; CABG within 2 months; angioplasty within 3 months; women of childbearing age not on med. contraceptives, adv cerebrovascular; noncardiac condition with reduced likelihood of survival.	all patients.	60% of defibrillator patients had shock discharge within 2 years. 15.8% (15 deaths) mortality rate in defibrillator group; 38.6% (39 deaths) in conventional therapy. hazard ratio=0.46; 95%CI=0.26-0.82.
CABG-Patch, 1997. Tx n=446; Control n=454.	scheduled for CABG; age < 80 years; LVEF < 0.36; Abn. signal averaged electrocardiogram.	h/o sustained VT or VF; diabetes m with poor control or infections; prior valve surgery; concomitant cerebrovascular surgery; serum creatinine >3mg/dl, emergency CABG; noncardiac condition with ex survival < 2 years; inability to attend f/u visits.	not required.	57% of defibrillator patients had shock discharge within 2 years. 22.6% (101 deaths) mortality rate in defibrillator group; 20.9% (95 deaths) in control group. hazard ratio=1.07; 95% CI=0.81-1.42.
MUSTT, 1999. EP tx n=351; No tx n=353.	had coronary artery disease; LVEF≤ 40%; asymptomatic unsustained ventricular tachycardia; EP induced sustained VT, VF.	H/o syncope or sustained ventricular tachycardia or fibrillation more than 48 hours after myocardial infarction; unsustained ventricular tachycardia only in acute ischemia, metabolic disorders, or drug toxicity.	all patients.	42% (132 deaths) overall mortality in antiarrhythmic therapy; 48% (158 deaths) in no antiarrhythmic therapy. Relative risk=0.80; 95%CI=0.64-1.01. Relative risk=0.45; 95%CI=0.32-0.63 for patients with defibrillators.
MADIT II, 2002. Tx n=742; Conventional n=490.	age >21 years, MI ≥ 1 month, LVEF ≤ 0.30.	had FDA approved indication for ICD; NYHA Class IV; coronary revascularization within 3 months; MI within past month; advanced cerebrovascular disease; were of childbearing age not using med contraceptives; condition other than cardiac disease with high likelihood of death; unwilling to consent.	not required.	19% of defibrillator patients had shock discharge within 2 years. 14.2% (105 deaths) mortality rate in defibrillator group; 19.8% (97 deaths) in conventional therapy. hazard ratio=0.69; 95% CI=0.51-0.93.

Appendix III

General Methodological Principles of Study Design

(Section VI of the Decision Memorandum)

We divide the assessment of clinical evidence into three stages: 1) the quality of the individual studies; 2) the generalizability of findings from individual studies to the Medicare population; and 3) overarching conclusions that can be drawn from the body of the evidence on the direction and magnitude of the intervention's potential risks and benefits.

The methodological principles described below represent a broad discussion of the issues we consider when reviewing clinical evidence. However, it should be noted that each coverage determination has its unique methodological aspects.

1. Assessing Individual Studies

Methodologists have developed criteria to determine weaknesses and strengths of clinical research. Strength of evidence generally refers to: 1) the scientific validity underlying study findings regarding causal relationships between health care interventions and health outcomes; and 2) the reduction of bias. In general, some of the methodological attributes associated with stronger evidence include those listed below:

- Use of randomization (allocation of patients to either intervention or control group) in order to minimize bias.
- Use of contemporaneous control groups (rather than historical controls) in order to ensure comparability between the intervention and control groups.
- Prospective (rather than retrospective) studies to ensure a more thorough and systematical assessment of factors related to outcomes.
- Larger sample sizes in studies to demonstrate both statistically significant as well as clinically significant outcomes that can be extrapolated to the Medicare population. Sample size should be large enough to make chance an unlikely explanation for what was found.

- Masking (blinding) to ensure patients and investigators do not know to which group patients were assigned (intervention or control). This is important especially in subjective outcomes, such as pain or quality of life, where enthusiasm and psychological factors may lead to an improved perceived outcome by either the patient or assessor.

Regardless of whether the design of a study is a randomized controlled trial, a non-randomized controlled trial, a cohort study or a case-control study, the primary criterion for methodological strength or quality is the extent to which differences between intervention and control groups can be attributed to the intervention studied. This is known as internal validity. Various types of bias can undermine internal validity. These include:

- Different characteristics between patients participating and those theoretically eligible for study but not participating (selection bias).
- Co-interventions or provision of care apart from the intervention under evaluation (performance bias).
- Differential assessment of outcome (detection bias).
- Occurrence and reporting of patients who do not complete the study (attrition bias).

In principle, rankings of research design have been based on the ability of each study design category to minimize these biases. A randomized controlled trial minimizes systematic bias (in theory) by selecting a sample of participants from a particular population and allocating them randomly to the intervention and control groups. Thus, in general, randomized controlled studies have been typically assigned the greatest strength, followed by non-randomized clinical trials and controlled observational studies. The design, conduct and analysis of trials are important factors as well. For example, a well designed and conducted observational study with a large sample size may provide stronger evidence than a poorly designed and conducted randomized controlled trial with a small sample size. The following is a representative list of study designs (some of which have alternative names) ranked from most to least methodologically rigorous in their potential ability to minimize systematic bias:

- Randomized controlled trials
- Non-randomized controlled trials
- Prospective cohort studies
- Retrospective case control studies
- Cross-sectional studies
- Surveillance studies (e.g., using registries or surveys)
- Consecutive case series
- Single case reports

When there are merely associations but not causal relationships between a study's variables and outcomes, it is important not to draw causal inferences. Confounding refers to independent variables that systematically vary with the causal variable. This distorts measurement of the outcome of interest because its effect size is mixed with the effects of other extraneous factors. For observational, and in some cases randomized controlled trials, the method in which confounding factors are handled (either through stratification or appropriate statistical modeling) are of particular concern. For example, in order to interpret and generalize conclusions to our population of Medicare patients, it may be necessary for studies to match or stratify their intervention and control groups by patient age or co-morbidities.

Methodological strength is, therefore, a multidimensional concept that relates to the design, implementation and analysis of a clinical study. In addition, thorough documentation of the conduct of the research, particularly study selection criteria, rate of attrition and process for data collection, is essential for CMS to adequately assess and consider the evidence.

2. Generalizability of Clinical Evidence to the Medicare Population

The applicability of the results of a study to other populations, settings, treatment regimens and outcomes assessed is known as external validity. Even well-designed and well-conducted trials may not supply the evidence needed if the results of a study are not applicable to the Medicare population. Evidence that provides accurate information about a population or setting not well represented in the Medicare program would be considered but would suffer from limited generalizability.

The extent to which the results of a trial are applicable to other circumstances is often a matter of judgment that depends on specific study characteristics, primarily the patient population studied (age, sex, severity of disease and presence of co-morbidities) and the care setting (primary to tertiary level of care, as well as the experience and specialization of the care provider). Additional relevant variables are treatment regimens (dosage, timing and route of administration), co-interventions or concomitant therapies and type of outcome and length of follow-up.

The level of care and the experience of the providers in the study are other crucial elements in assessing a study's external validity. Trial participants in an academic medical center may receive more or different attention than is typically available in non-tertiary settings. For example, an investigator's lengthy and detailed explanations of the potential benefits of the intervention and/or the use of new equipment provided to the academic center by the study sponsor may raise doubts about the applicability of study findings to community practice.

Given the evidence available in the research literature, some degree of generalization about an intervention's potential benefits and harms is invariably required in making coverage determinations for the Medicare population. Conditions that assist us in making reasonable generalizations are biologic plausibility, similarities between the populations studied and Medicare patients (age, sex, ethnicity and clinical presentation) and similarities of the intervention studied to those that would be routinely available in community practice.

A study's selected outcomes are an important consideration in generalizing available clinical evidence to Medicare coverage determinations. The goal of our determination process is to assess net health outcomes. These outcomes include resultant risks and benefits such as increased or decreased morbidity and mortality. In order to make this determination, it is often necessary to evaluate whether the strength of the evidence is adequate to draw conclusions about the direction and magnitude of each individual outcome relevant to the intervention under study. In addition, it is important that an intervention's benefits are clinically significant and durable, rather than marginal or short-lived.

If key health outcomes have not been studied or the direction of clinical effect is inconclusive, we may also evaluate the strength and adequacy of indirect evidence linking intermediate or surrogate outcomes to our outcomes of interest.

3. Assessing the Relative Magnitude of Risks and Benefits

An intervention is not reasonable and necessary if its risks outweigh its benefits. Among other things, CMS evaluates whether reported benefits translate into improved net health outcomes.

The direction, magnitude and consistency of the risks and benefits across studies are important considerations. Based on the analysis of the strength of the evidence, CMS assesses whether an intervention or technology's benefits to Medicare beneficiaries outweigh its harms.

Appendix IV

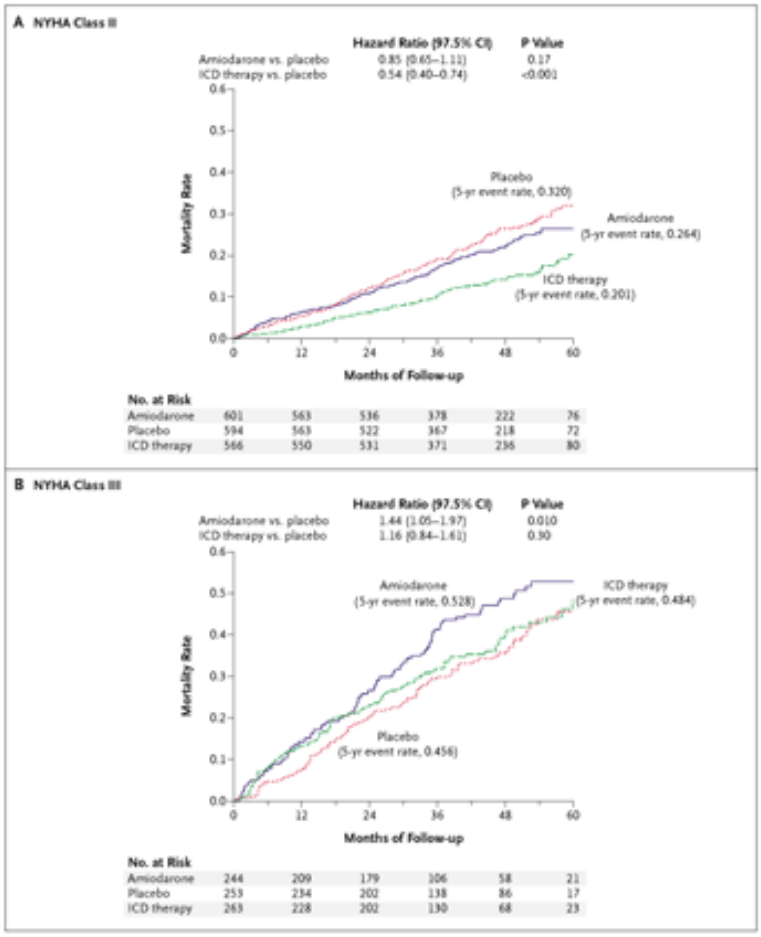

Figure 3. Kaplan–Meier Estimates of Death from Any Cause for the Prespecified Subgroups of NYHA Class II (Panel A) and Class III (Panel B). CI denotes confidence interval.

Reprinted from Bardy GH, Lee KL, Mark DB, et al. Amiodarone or an implantable cardioverter-defibrillator for congestive heart failure. N Engl J Med 2005;352:225-237. (http://content.nejm.org/cgi/content/full/352/3/225/F3)

Appendix V

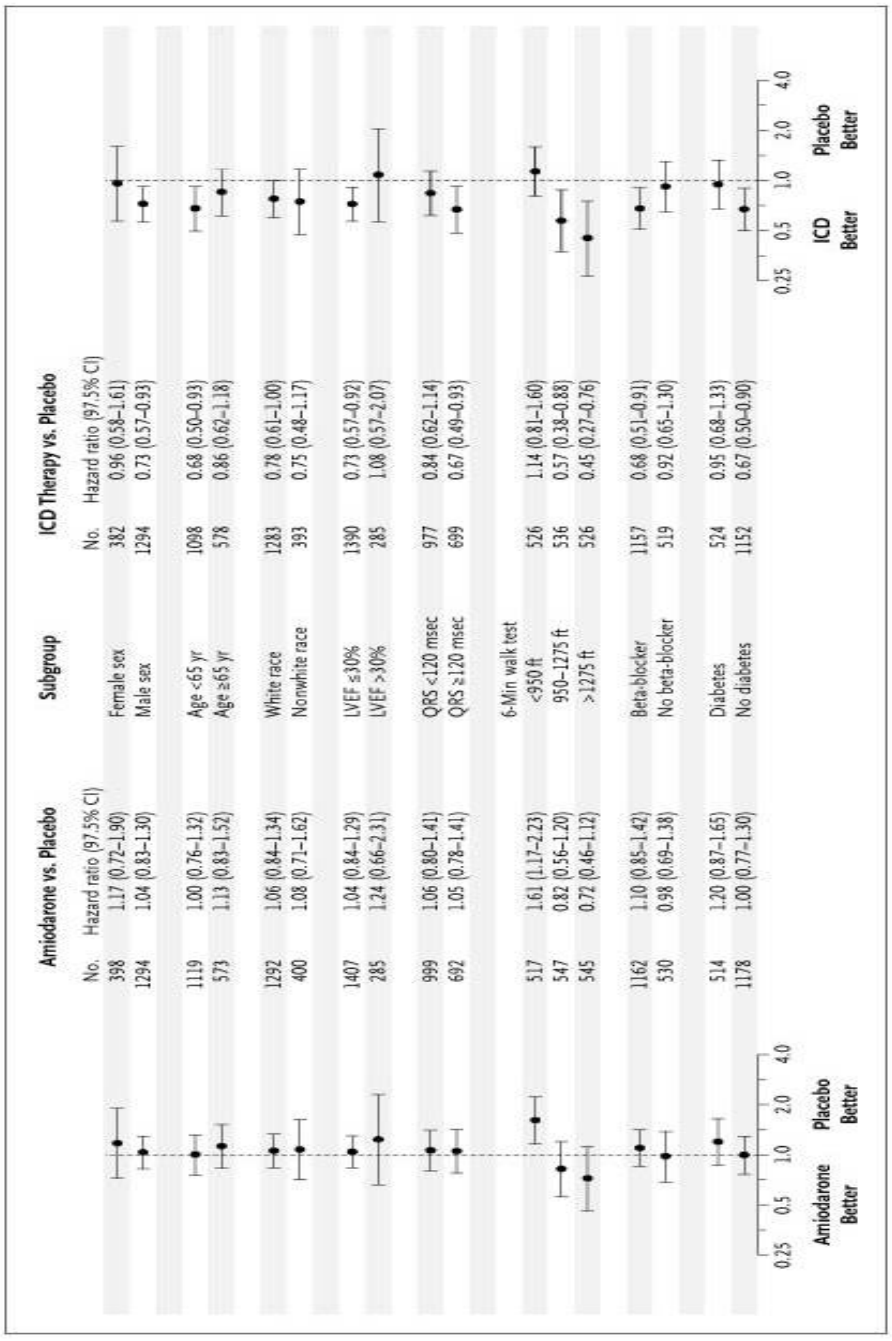

Figure 4. Hazard Ratios for the Comparison of Amiodarone and ICD Therapy with Placebo in Various Subgroups of Interest. CI denotes confidence interval.

Reprinted from Bardy GH, Lee KL, Mark DB, et al. Amiodarone or an implantable cardioverter-defibrillator for congestive heart failure. N Engl J Med 2005;352:225-237. (http://content.nejm.org/cgi/content/full/352/3/225/F4)

Appendix VI

ICD Data Elements

PATIENT IDENTIFYING INFORMATION
Enter the Patient's HIC
Enter Date of Implant
Enter Date of Birth
Gender
Enter Race / Ethnic Group

HISTORY and CLINICAL CHARACTERISTICS
Does the patient have history of any of the following?
- Angina pectoris
- Atrial fibrillation
- CABG surgery
- Cancer
- Congestive heart failure
- Coronary artery disease
- Diabetes
- Hypertension
- Myocardial infarction
- Pacemaker
- PTCA
- Sudden cardiac arrest
- Syncope
- Ventricular arrhythmias
- Cigarette smoker

Enter Left ventricular ejection fraction (%)
Test used to measure LVEF
Enter heart rate (beats/min)
Enter blood pressure (mm HG)
Enter QRS interval (msec)
Is there a left bundle branch block?
Is there a right bundle branch block?
NYHA (current status)
Enter duration of heart failure (months)
Is there ischemic cardiomyopathy?
Is there nonischemic cardiomyopathy?

MEDICATIONS on ADMISSION
Is the patient on the following medications?
- ACE inhibitor
- Adenosine
- Amiodarone
- Angiotensin receptor blocker (ARB)
- Antiarrhythmic Other
- Beta Blocker
- Coumadin
- Digoxin
- Diuretic
- Dofetilide
- Isuprel
- Procainamide
- Propafenone
- Sotalol

FACILITY INFORMATION
Enter Hospital Medicare Provider #
Was the procedure performed in a:

PROVIDER INFORMATION
Physician Medicare Provider #
Physician Specialty

ICD INDICATIONS
IDCM, documented prior MI and LVEF ≤ 30%
NIDCM > 9 months and LVEF ≤ 30%
IDCM, documented prior MI, NYHA II-III, LVEF > 30% and ≤ 35%
NIDCM > 3 months, NYHA II-III, LVEF ≤ 35%
CRT-D implantation and NYHA IV
Familial or inherited condition with a high risk of life-threatening VT

DEVICE INFORMATION
What type of device was implanted?
ICD manufacturer
Enter the ICD model number

IN-HOSPITAL COMPLICATIONS
- Cardiac arrest
- Cardiac perforation
- Cardiac valve injury
- Coronary venous dissection
- Death
- Drug reaction
- Erosion of ICD pocket
- Hemothorax
- Infection related to device
- Lead dislodgement
- Myocardial infarction
- Pericardial tamponade
- Pneumothorax
- Pocket hematoma
- Programming problems
- Stroke
- TIA