Multicenter Automatic Defibrillator Implantation Trial–Cardiac Resynchronization Therapy (MADIT-CRT): Design and Clinical Protocol

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The planned MADIT-CRT trial is designed to determine if CRT-D will reduce the risk of mortality and HF events by approximately 25% in subjects with ischemic (NYHA class I-II) and non-ischemic (NYHA class II) cardiomyopathy, left ventricular dysfunction (EF $\leq$ 0.30), and prolonged intraventricular conduction (QRS duration $\geq$ 130 ms).

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MADIT; cardiac resynchronization therapy; heart failure

Heart failure (HF) with its associated morbidity and mortality remains a major unresolved public health problem in the United States and throughout the world. It is estimated that HF affects nearly 5 million people in the United States alone and claims more that 300,000 lives annually.[1] The MADIT-II trial demonstrated improvement in overall survival with an implantable cardioverter defibrillator (ICD) in high-risk subjects with prior myocardial infarction and advanced left ventricular dysfunction (ejection fraction $\leq$0.30) despite the occurrence of HF in this population.[2] Similar results were found in the recently published SCD-HeFT and DEFINITE trials.[3,4] Cardiac resynchronization therapy (CRT) with biventricular pacing is effective as adjunctive therapy to pharmacologic management of patients with severe HF and intraventricular conduction delay, with improvement in ventricular function, exercise capacity, and quality of life.[5–7]

Published results of CRT and combined CRT with ICD (CRT-D) have been obtained primarily from subjects with NYHA Class III/IV heart failure, and FDA indications for CRT devices are currently restricted to this population. There have been two randomized studies of CRT-D in subjects with NYHA Class I/II heart failure published thus far, encompassing over 450 subjects between them. The largest randomized study to date of NYHA Class I/II subjects were enrolled in the VENTAK CHF/CONTAK CD Study, with 263 subjects followed for 6 months.[8] Significant reductions in LV dimensions as measured with echocardiography were reported. However, no improvement in symptoms or exercise tolerance was found. A slightly smaller randomized study of 186 NYHA Class II

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subjects enrolled in the MIRACLE ICD II study with 6-month follow-up also found a significant reduction in LV dimensions and improvement in left ventricular ejection fraction, but no improvement in 6-minute walk or quality of life.[9] Neither study was designed to evaluate the effects of CRT-D on all-cause mortality and hospitalization in these populations. In the COMPANION trial, CRT-D improved survival and reduced hospitalization for heart failure in both ischemic and nonischemic cardiomyopathy subjects who were in NYHA functional class III and IV.[10]

Whereas the goal of resynchronization therapy in patients with moderate-to-severe heart failure is one of treatment, the goal in patients with mild heart failure may be one of prevention, with resynchronization inhibiting or slowing the dysfunctional remodeling process. This conclusion is consistent with the report of a panel of heart failure experts who met at a symposium sponsored by the Heart Failure Society of America in February 2003. This group recommended that future studies of patients with mild heart failure should be directed to slowing the progression of the disease.[11]

The planned MADIT-CRT trial is designed to determine if CRT-D will reduce the risk of mortality and HF events by approximately 25% in subjects with ischemic (NYHA class I–II) and nonischemic (NYHA class II) cardiomyopathy, left ventricular dysfunction (EF $\leq$ 0.30), and prolonged intraventricular conduction (QRS duration $\geq$130 ms).

OBJECTIVES

1. The primary objective of this trial is to determine whether CRT-D in high-risk, relatively asymptomatic subjects with ischemic and nonischemic cardiomyopathy will significantly reduce the combined endpoint of all-cause mortality or HF events, whichever comes first, when compared to ICD-only therapy.
2. The three secondary objectives of this trial, in prioritized order, together with the hypothesized outcomes, are:
   - Evaluate the effects of CRT-D, relative to ICD-only, on the changes from baseline to 1 year in ECHO-determined left ventricular internal volume at end systole (LVESV) with CRT-D therapy turned off during the 1-year echocardiogram. It is hypothesized that the CRT-D group will have, on average, a decrease in LVESV, significantly exceeding the corresponding average change in the ICD-only group.
   - Evaluate the effects of CRT-D, relative to ICD-only, on the changes from baseline to 1 year in ECHO-determined left ventricular internal volume at end diastole (LVEDV) with CRT-D therapy turned off during the 1-year echocardiogram. It is hypothesized that the CRT-D group will have, on average, a decrease in LVEDV, significantly exceeding the corresponding average change in the ICD-only group.
   - Evaluate the effects of CRT-D, relative to ICD-only, on the subject-specific rates of multiple HF events over the full study period. It is hypothesized that the CRT-D group will have, on average, lower rates of multiple HF events.
3. The tertiary objectives of this trial are to:
   - Evaluate the effects of CRT-D on all-cause mortality.
   - Evaluate the effects of CRT-D on appropriate ICD therapy for ventricular tachycardia (VT) and ventricular fibrillation (VF).
   - Evaluate the effects of CRT-D, relative to ICD-only, on the changes from baseline to 1 year in NYHA functional class. It is hypothesized that, at 1 year, the average NYHA class for the CRT-D group will be lower than that for the ICD-only group, after adjusting for any differences in baseline values.
   - Evaluate the effects of CRT-D, relative to ICD-only, on the accumulated changes in quality of life within the full study period. It is hypothesized that the assessed quality of life in the CRT-D group will, on average, exceed that in the ICD-only group.
   - Evaluate by echocardiographic/Doppler technique at the 12-month follow-up whether CRT-D when compared to subjects receiving ICD-only reduces the degree of mitral regurgitation.
   - Evaluate whether functional capacity (as measured by distance achieved during a 6-minute hall walk) at the 12-month follow-up is greater in subjects receiving CRT-D than in those receiving ICD-only.
   - Evaluate the association between the level of brain natriuretic peptide (BNP) at baseline and outcome in subjects randomized to CRT-D.
   - Evaluate whether the level of brain natriuretic peptide (BNP) at the 12-month

follow-up visit is lower in the CRT-D group than the ICD-only group.
- Evaluate whether Holter-recorded noninvasive electrocardiologic parameters can identify subjects with increased hemodynamic benefit in CRT group.

DESIGN

General

In this study, subjects with ischemic (NYHA class I or II) and nonischemic (NYHA class II) cardiomyopathy, left ventricular dysfunction (EF $\leq$ 0.30), and prolonged intraventricular conduction (QRS duration > 130 ms) will be randomized to CRT-D or ICD-only. Randomization will be stratified by clinical center and cardiomyopathy type. Approximately 60% of the subjects will be randomly assigned to receive a CRT-D with biventricular pacing, and 40% will receive ICD-only. Optimal pharmacological therapy for the underlying heart disease will be required in both treatment arms. Length of follow-up for each subject will depend on the date of entry into the study, since all subjects will be followed to a common study termination date.

Sample Size and Group Sequential Design

The primary end point is heart failure or death, whichever comes first. The cumulative 2-year end point in the group receiving ICD-only is estimated at 30%. In the trial, we estimate that CRT-D will result in an approximate 25% reduction in the 2-year cumulative end point when compared with ICD-only, i.e., from 30% to 22.6% with an estimated CRT-D:ICD-only hazard ratio of 0.75. The significance level (α) has been set at 0.05, with the hypothesis being two-sided. The power ($1 - \beta$), the probability of finding a difference given that a specified difference actually exists, has been set at 0.95. The "crossover" rates before the primary endpoint occurs are assumed to be a 10% dropout from CRT-D to ICD-only and a 2% drop-in from ICD-only to CRT-D.

A Wang–Tsiatis group-sequential design with $\Delta = 0.1$ and up to 20 analyses will be utilized in this trial[12,13] (Fig. 1). This design will permit early termination of the trial if (1) CRT-D efficacy is meaningfully greater than that hypothesized for ICD-only; or (2) if ICD-only efficacy is meaningfully greater

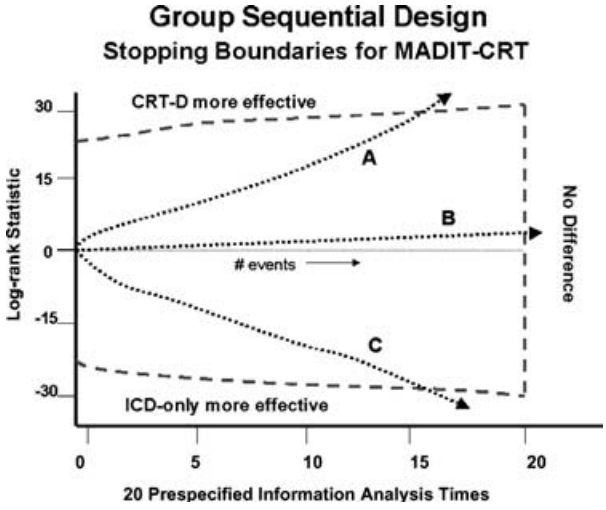

Figure 1. Schematic presentation of the group-sequential design and the associated stopping boundaries (dashed lines). The vertical axis is a measure of the observed treatment differences (efficacy). The horizontal axis is a measure of information collection (mortality or heart failure events, whichever comes first). Stopping boundaries are prespecified for benefit of CRT-D or ICD-only, or no difference. Examples of possible outcomes are provided by the three arrows: A = early termination for CRT-D benefit; B = termination for no difference between the two treatments; C = early termination for ICD-only benefit. Reaching the upper (lower, respectively) boundary will result in an estimated hazard ratio of <0.85 (>1.18, respectively); an estimated hazard ratio between 0.85 and 1.18(1/0.85) is consistent with a "no difference" conclusion. The 20 prespecified analyses are scheduled at approximately equal information times.

than that hypothesized for CRT-D. This trial design allows for the possibility of a delayed effect of treatment, for the "no difference" conclusion is allowed only at the maximal duration of the trial.

With these assumptions, the plan is to randomize 1820 patients in a 3:2 CRT-D:ICD-only ratio (1092 patients in the CRT-D arm and 728 patients in the ICD-only arm) to provide for a slightly larger group in the CRT-D arm, thereby permitting greater efficacy for subgroup analyses in this arm, with little effect on primary analysis. With up to 125 participating centers at an overall enrollment rate of 70 subjects per month, enrollment is expected to require a period of approximately 26 months. In such a scenario, the follow-up would average 33 months per subject with a trial duration of 45 months, if there is truly no difference between the treatments; the follow-up would average 20 months with a trial

duration of 33 months if the event rates are as hypothesized with a true hazard ratio of 0.75. Any slower rate of recruitment will prolong the duration of the trial, about one additional month for each 2-month delay in reaching target enrollment. A faster enrollment rate will shorten the duration of the trial. A greater or lesser event rate than that projected will shorten or lengthen the trial duration, respectively.

Eligibility

Patients eligible for this study include males and females more than 21 years of age (no upper age cutoff) with either ischemic heart disease in NYHA class I or II for the past 90 days prior to and at the time of enrollment, or nonischemic heart disease in NYHA class II for the past 90 days prior to and at the time of enrollment.

Ischemic heart disease is defined by a documented (Q-wave or enzyme-positive) prior myocardial infarction more than 90 days before enrollment, and/or one or more prior coronary artery bypass graft surgeries or percutaneous coronary interventions (balloon and/or stent angioplasty) more than 90 days before enrollment.

Nonischemic heart disease is defined by an abnormality of the myocardium capable of producing heart failure. Diseases that conform to this definition either directly affect, infiltrate between, or replace myocardial cells and excludes subjects with primary valvular disease. Nonischemic cardiomyopathies can be classified as dilated, hypertrophic, and restrictive types. Dilated cardiomyopathy has a low ejection fraction and increased ventricular volume, with ventricular compliance that is normal or increased, and it is this type of nonischemic cardiomyopathy that is eligible for MADIT-CRT. The relatively common causes of nonischemic cardiomyopathy of the dilated type include idiopathic cardiomyopathy, inflammatory myocarditis, familial cardiomyopathy, alcoholic heart disease, and Chagas' disease. For the most part, the clinical course of subjects with nonischemic cardiomyopathy is progressive deterioration, but reversibility can occur in acute viral myocarditis and with discontinuation of alcohol in alcoholic heart disease.

For both types of heart disease, eligibility requires (1) stable optimal pharmacologic therapy for the underlying cardiac disorder; (2) an ejection fraction $\leq$0.30 by angiographic, radionuclide, or echocardiographic methods within 90 days prior to enrollment; (3) QRS duration $\geq$130 ms on printout of a current ECG using a market-approved electrocardiographic recorder; and (4) sinus rhythm by ECG.

Exclusions

Eligible subjects will be excluded from enrollment if any of the following conditions apply:

- Existing indication for CRT therapy;
- Implanted pacemaker;
- Implanted ICD or CRT device;
- NYHA Class I with nonischemic cardiomyopathy;
- NYHA Class III or IV in the past 90 days prior to or at the time of enrollment;
- Coronary artery bypass graft surgery or percutaneous coronary intervention (balloon and/or stent angioplasty) within the past 90 days prior to enrollment;
- Enzyme-positive myocardial infarction within the past 90 days prior to enrollment;
- Angiographic evidence of coronary disease sufficient to be a candidate for coronary revascularization and likely to undergo coronary artery bypass graft surgery or percutaneous coronary intervention in the foreseeable future;
- Second- or third-degree heart block;
- Irreversible brain damage from preexisting cerebral disease;
- Women who are pregnant or plan to become pregnant during the course of the trial (women of child-bearing potential must have a negative pregnancy test within 7 days of enrollment);
- Reversible nonischemic cardiomyopathy such as acute viral myocarditis or discontinuation of alcohol in alcohol-induced heart disease;
- Chronic atrial fibrillation;
- Presence of any disease, other than the subject's cardiac disease, associated with a reduced likelihood of survival for the duration of the trial, e.g., cancer, uremia (BUN $>$ 70 mg/dl or creatinine $>$3.0 mg/dl), liver failure, etc.;
- Participation in any other clinical trial;
- Subjects unwilling or unable to cooperate with the protocol;
- Subjects who live at such a distance from the clinic that travel for follow-up visits would be unusually difficult;
- Subjects who do not anticipate being a resident of the area for the scheduled duration of the trial; or
- Subjects unwilling to sign the consent for participation.

Recruitment

Recruitment will occur in up to 125 hospital centers in the United States (≤100) and in Europe (≤25). Screening for enrollment will be performed in compliance with HIPPA requirements. Patients who meet the eligibility criteria and do not have any exclusions will be recruited by the clinical cardiology groups associated with each enrolling center. Logs will be kept at each center of all identified patients who meet the clinical eligibility criteria. For eligible patients who are not enrolled, the reason for nonenrollment (exclusion) will be recorded. A flow diagram of enrollment is presented in Figure 2.

Consent

The study with its possible benefits and risk will be discussed with the patient's primary care physician and with the patient. A brochure containing such information will be available. Prior to the baseline reference examination, the patient will be required to sign a consent for participation in MADIT-CRT.

Baseline Evaluation

After the patient signs the consent, a baseline reference examination will be performed including a clinical history, physical exam, 12-lead ECG, and echocardiogram.

Randomization

The random assignment to one of the two study groups will be made by the Coordination and Data Center (CDC) and transmitted to the enrolling clinical center by logging on to a Web-based automated program or by telephone with hard copy to follow. Randomization will be made only after

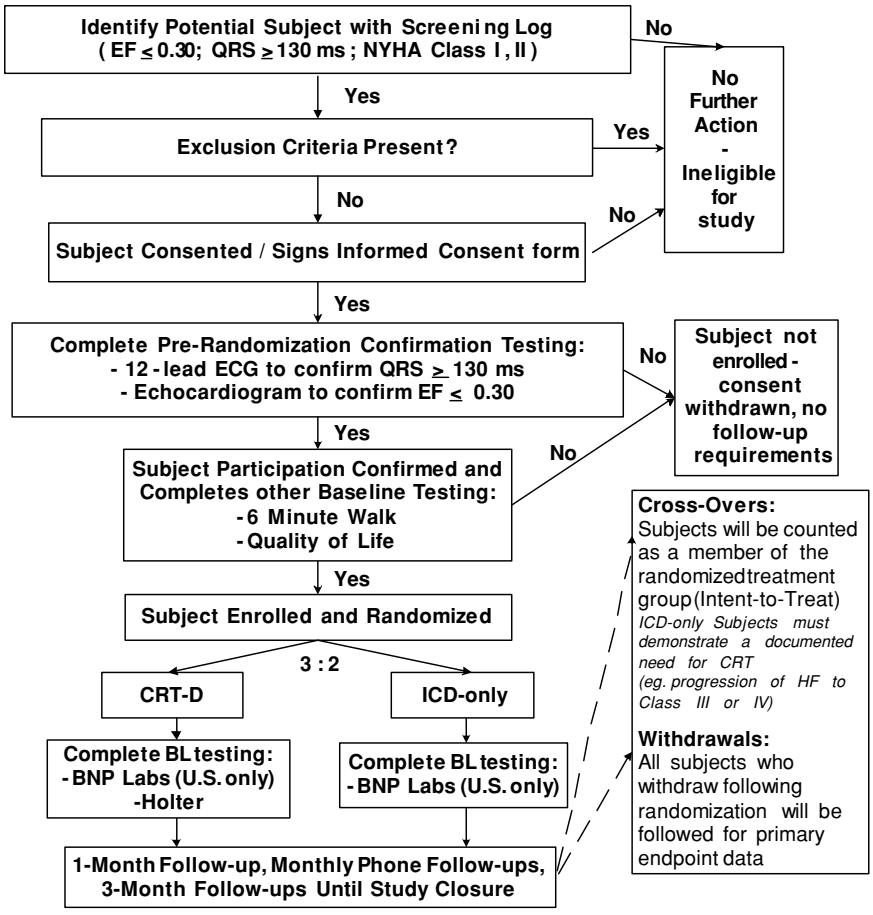

Figure 2. Flow diagram of enrollment cascade.

verification that the steps mentioned above have been completed. Baseline testing will then be completed, including (1) quality-of-life assessment prior to informing subject of treatment assignment; (2) 6-minute walk; (3) blood sample for BNP analysis (U.S. only); and (4) 24-hour Holter recording (CRT-D subjects only). The date of randomization serves as the subject's date of entry, or enrollment date, into the clinical trial. Each randomized subject will remain counted as a member of the assigned treatment group to which he or she was assigned (intention-to-treat) regardless of subsequent protocol adherence. For the purpose of analysis, subjects will not be censored at withdrawal, and every effort will be made to ascertain the occurrences or nonoccurrence of the primary endpoints.

Optimal Pharmacologic Therapy

All subjects who participate in the study are required to receive optimal pharmacologic therapy for their heart disease as defined below:

- *Beta-Blockers*: All subjects must have a beta-blocker prescribed to a therapeutic dose for the last 3 months, and stable for at least 1 month prior to enrollment, and if not, the reason that the physician did not prescribe a beta-blocker must be documented on a study case report form. The choice of selective or nonselective beta-blocker use is left to the investigator's discretion.
- *Angiotensin-converting enzyme (ACE) Inhibitors*: All subjects must have ACE inhibitor therapy prescribed to a therapeutic dose and stable for at least 1 month prior to enrollment, and if not, the reason that the physician did not prescribe ACE inhibitor therapy must be documented on a study case report form.
- *Angiotensin receptor blockers (ARBs)/Angiotensin II inhibitors*: Angiotensin receptor blockers may be prescribed in place of ACE inhibitors in those subjects who have previously failed or are contraindicated for ACE inhibitors.
- *Statins (lipid-lowering agents)*: All ischemic patients should have a statin prescribed, and if not, the reason that the physician did not prescribe a statin must be documented on a study case report form.

The use of antiarrhythmic medications is discouraged in this study. If the subject is receiving an antiarrhythmic medication, the medication and the reason for its prescription must be documented on a study case report form. Digoxin, beta blockers (except Sotalol) and calcium channel blockers should not be recorded as antiarrhythmic medications.

Implant of CRT-D or ICD-only

Subjects randomized to either the CRT-D or ICD-only arm of the trial will have a Guidant, commercially available device implanted by a qualified physician. All devices in the MADIT-CRT trial are market-released products and should be implanted according to the physician and/or center standard operating procedure.

Device Programming

CDT-D Brady Programming

The goals are to maximize biventricular pacing and maximize tracking of intrinsic sinus rhythm, if possible.

CRT-D Settings

- Programmed mode must be DDD with a lower rate of 40 bpm and hysteresis off;
- Pacing output in each chamber should be at least twice the voltage threshold (unless this would exceed the maximal output of the device). The minimum output should be 2.5 V and 0.5 msec;
- AV delay should be programmed using latest approved optimization techniques;
- LV and RV timing should be simultaneous;
- The lower rate should not be increased or rate-responsive mode utilized unless the patient is experiencing both: (a) pacing at the lower rate limit for >60% of the total time between scheduled or unscheduled ICD visits on different days separated by 7 or more days; and (b) complaining of moderate or severe fatigue or shortness of breath. If patients with sinus bradycardia do not improve with a trial of rate-responsive pacing, consideration should be given to resuming DDD 40.

ICD-only Brady Programming

The goal is to minimize ventricular (and atrial if applicable) pacing unless the patient develops significant symptomatic bradycardia, i.e., an indication for anti-bradycardia pacing.

Single-Chamber ICD

- Pacing mode must be VVI with a lower rate of 40 bpm and hysteresis off;

- Pacing output should be at least twice the voltage threshold (unless this would exceed the maximal output of the device). The minimum output should be 2.5 V and 0.5 msec;

Dual-Chamber ICD

- Pacing mode must be DDI with a lower rate of 40 bpm and hysteresis off;
- Pacing output in each chamber should be at least twice the voltage threshold (unless this would exceed the maximal output of the device). The minimum output should be 2.5 V and 0.5 msec;
- AV delay should be programmed to 280 msec.
- The pacing mode should not be converted to a tracking mode (DDD, VDD, DDDR or VDDR), the lower rate should not be increased, and rate-responsive mode should not be utilized unless the patient is experiencing both (1) pacing at the lower rate limit for >60% of the total time between scheduled or unscheduled ICD visits on different days; and (2) complaining of moderate or severe fatigue or shortness of breath. If patients with bradycardia do not improve with a trial of rate-responsive pacing, or patients with intermittent symptomatic AV block do not improve with atrial tracking mode, consideration should be given to resuming VVI 40 (single) or DDI 40 (dual).

CRT-D and ICD-Only Ventricular Tachycardia and Fibrillation Therapy

- Programmed mode monitor + therapy;
- Sensitivity should be programmed according to physician discretion;
- Two-zone configuration:
  - VT zone set at 180 bpm,
  - VF zone set at 210 bpm;
- SVT discrimination algorithms should be programmed with nominal settings for the VT zone;
- Detection should be 2.5 seconds for the VT zone, and 1.0 seconds for the VF zone;
- VT zone first therapy should be burst-type antitachycardia pacing with 8 pulses at 88% of the measured cycle length with a 10 msec decrement between bursts, then shock therapy;
- Second therapy should be shock at DFT plus at least 10 J (if possible). The remaining therapies should be maximal energy shocks. All shocks should be biphasic. Nominal or reversed polarity should be used, if necessary, based on DFT testing.

Reprogramming should not be performed to diverge from the above recommendations unless inappropriate therapy has occurred.

Follow-up

All follow-up visits will use the randomization date as the starting point for determining the timing of all follow-up visits. A follow-up schedule that identifies the date intervals during which a subject should be contacted by phone or be seen at a visit (delineated on the schedule) will be provided to the enrolling center for each enrolled subject following randomization. Every effort will be made to ensure compliance with this schedule.

Phone contact will be made monthly (those months when a follow-up is not scheduled) with each enrolled subject in order to closely track heart failure events and/or mortality occurrence, to identify occurrence of any adverse events, and to facilitate prompt collection of complete source documentation for each event. Subjects will be seen in the follow-up clinic at 1 month after randomization, and then at 3-month intervals until the termination of the study. At each clinic visit, a standard clinical evaluation will be carried out. In addition, all devices will undergo device testing according to agreed-upon guidelines. If a visit is missed for any reason, data on endpoints and adverse events will be collected at the subsequent visit.

End Points

Ascertainment of end points, death, and heart failure events, will be carried out by each local center. All deaths will be reported immediately to the Coordination and Data Center. Deaths will also be reported immediately to Guidant for required transmission to the Food and Drug Administration.

The Heart Failure and Mortality Committees will review all primary end points that occur in the MADIT-CRT study. Each committee's decisions are based on independent physician review of the data. Two end point subcommittees blinded to treatment group have been established to independently review information on end point events:

- **Heart Failure Committee:** HF Events will be documented by clinical data from the hospital or outpatient subject record in English, the official language of the study. The defining clinical criteria will be distributed to the enrolling center personnel prior to study initiation. Classification of

cause and circumstances surrounding the heart failure event will occur upon agreement of the reviewers.

In MADIT-CRT, we will categorize a subject as having a "heart failure event" when the subject has symptoms and/or signs consistent with congestive heart failure and (1) receives intravenous decongestive therapy greater than 2 hours (IV diuretics, IV neseritide, IV inotropes), that does not involve formal inpatient hospital admission, regardless of the setting (i.e. in an emergency room setting, in the physician's office, etc.), or (2) receives an augmented heart failure regimen with oral or intravenous medications during an in-hospital stay (formal hospital admission is defined as admission to hospital that includes a calendar date change).

- **Mortality Committee:** Every effort will be made to classify all deaths as to cause; cardiac deaths will be classified in terms of suddenness and arrhythmic mechanism by prespecified Hinkle–Thaler criteria.[14] Operative deaths associated with the implantation of the CRT-D and ICD-only devices will be counted as cardiac deaths. Terminal events will be documented by clinical data from the hospital or outpatient subject record in English, the official language of the study.

Protection of Human Subjects

At each clinical center, the routine follow-up interval history, physical examination, and device interrogation will be used to identify possible adverse reactions to the device. The clinical center's MADIT-CRT physicians are responsible for insuring that the therapies rendered are consistent with the well-being of the patients. If a situation arises where it is in the best interest of the patient that the device be removed or changed, then the procedure will be carried out while alerting the Coordination and Data Center.

All information and data collected for MADIT-CRT concerning subjects or their participation in this investigation will be considered confidential by Guidant and by all parties involved in the trial. HIPAA confidential guidelines will be followed.

Data Monitoring and Quality Control

Study data will be monitored closely by the Coordination and Data Center. Monthly reports will be generated on data completion and error rates for each clinical center. An automatic forms accounting and monitoring system will be initiated for each participant at the time of randomization. This system provides the capability to monitor the status, volume, and disposition of data as well as to identify data due, overdue, and backlogged. In addition, all study data will undergo an extensive computer edit, and this information will be provided to the clinical centers to help improve and maintain data quality control procedures designed to detect inaccuracies and inconsistencies. This information will be used to make decisions about relevant adjustment procedures in the study procedures.

To ensure protocol compliance at all participating investigational sites, Guidant or a Guidant representative will conduct monitoring visits. All participating sites will be monitored during the course of the study with visits occurring as frequently as deemed necessary to ascertain adherence to the protocol procedures, as well as maintenance of the highest-quality data.

The morbidity and mortality endpoint data and reported adverse events will be continuously monitored by the Data Safety and Monitoring Board. All data are managed and maintained by the CDC, and the data will be maintained at the CDC throughout the course of the trial. Any information categorized by treatment arm will be excluded from progress reports sent to Guidant and the Investigational Centers. The Mortality and Heart Failure Committees whose role is to make a final assessment on the primary endpoints will be blinded to randomized treatment arms.

Core Laboratories

Several core laboratories have been established, and these include: (1) The Electrogram Analysis Core Lab; (2) Echocardiogram Core Lab; (3) Noninvasive Electrocardiology Core Lab; (4) Brain Natriuretic Core Lab; and (5) Quality-of-life Core Lab.

Data Analysis

Statistical tests of the difference in the first occurrence of the primary end point (rate of combined all-cause mortality or HF event, whichever comes first) between the randomized CRT-D and ICD-only groups will be computed at periodic intervals during the trial by the Data Safety Monitoring Board as part of the sequential design, and at the conclusion of the study. Primary analysis will be based on statistical evaluation comparing the life-table event-free survival time graphs for CRT-D and ICD-only

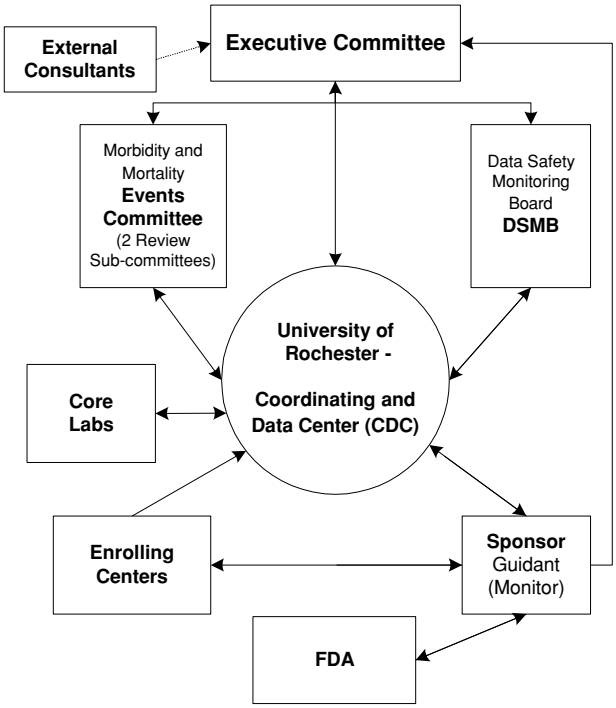

Figure 3. MACIT-CRT organizational chart.

arms of the trial, the graphs being constructed by the method of Kaplan and Meier.[15] The stratified log-rank test[16,17] (stratified by enrollment center and ischemia status) will be used to evaluate statistical significance, adjusted for the group-sequential stopping rule of the trial with maximum-likelihood ordering;[13] late-reported data will be appropriately incorporated.[18] The hazard ratio for CRT-D relative to ICD-only, based on proportional hazards modeling, will similarly be estimated, and 95% confidence limits determined, each adjusted for the sequential design. Analyses of the possible interaction effect with a treatment arm for each of a prespecified list of risk factors will be performed using the Cox proportional-hazards regression model,[19] adjusted to the group-sequential design.[20] All analyses will be carried out according to the intention-to-treat principle.

Prespecified secondary analyses and tertiary studies will be carried out. Some of the secondary and tertiary studies require continued monitoring of subjects after an initial nonfatal heart failure event. Hence, all subjects will be followed, including the identification of recurring heart failure events until study completion. Some substudies will be carried out concurrently, including cost-effective (confined to the U.S. centers) and tissue-Doppler evaluations.

Organizational Structure

The organizational structure for MADIT-CRT is presented in Figure 3. Guidant Corporation will provide the funding for MADIT-CRT through a research grant to the University of Rochester School of Medicine and Dentistry.

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