CLINICAL STUDY PROTOCOL

Study Title:	Junctional AV Ablation in CRT-D Patients with Atrial Fibrillation (JAVA-CRT Trial)
Sponsor:	University of Rochester
Clinical Trials.gov:	NCT02946853
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Indication:	Patients with atrial fibrillation eligible for CRT-D
Intervention:	Ablation of AV junction
Study Type:	Randomized clinical trial
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CONTENTS

1. PURPOSE OF THE STUDY AND BACKGROUND

1.1. Background

Cardiac resynchronization therapy (CRT) is a demonstrably effective device intervention for patients with broad QRS and ventricular dysfunction and is a class I indication for patients in sinus rhythm, LBBB and EF ≤ 30-35%. However, many patients with heart failure (HF) are unable to maintain sinus rhythm and approximately 30-36% of CRT patients are in atrial fibrillation (AF). Unfortunately, there is lack of evidence for the benefits of CRT in the absence of sinus rhythm. The recent RAFT study in patients with less advanced HF found no benefit at all for CRT for permanent AF patients although most patients did not achieve sufficient biventricular pacing.

Approximately 100,000 CRT implants were performed in the US in 2011 at a cost of approximately $1.8 billion. The absence of CRT benefit in the high-risk subset of AF patients who undergo CRT would generate substantial utilization of health care resources in the form of hospitalization and re-hospitalization, urgent care for HF decompensation, and intensified frequent outpatient management.

There is retrospective and observational data that suggest that only CRT patients with AF who undergo atrioventricular junctional (AVJ) ablation can respond as well as patients in sinus rhythm. AVJ ablation regularizes rhythm, eliminates tachycardia, and forces 100% biventricular pacing without fusion or pseudofusion. In the absence of a randomized clinical trial, however, there are concerns regarding making a significant proportion of CRT patients pacemaker dependent. It is believed that AVJ ablation is performed in only small numbers of patients at the present time.

We propose a randomized controlled clinical trial in 40 subjects with permanent AF who are eligible for cardiac resynchronization therapy with defibrillator (CRT-D) to test the benefit of AVJ ablation on clinical outcome.

1.2. Purpose of the study

The primary aim of the study is:

- To determine if patients with permanent AF who meet conventional criteria for CRT-D and undergo AVJ ablation have improved left ventricular remodeling as assessed by left ventricular end-systolic volume reduction ≥ 15% from baseline to 6 months.

The secondary aims of this study are:

- To determine if subjects with permanent AF who meet conventional criteria for CRT-D and undergo AVJ ablation, relative to subjects without AVJ ablation, have:
  1. Improved left ventricular ejection fraction
  2. Diminished left ventricular end-diastolic volume
  3. Lower risk of heart failure requiring augmented oral or IV treatment regimen during an in-hospital stay or IV decongestive therapy outside of a formal inpatient hospital admission
  4. Lower likelihood of experiencing inappropriate implantable cardioverter-defibrillator (ICD) therapy
  5. Lower risk of ventricular tachycardia (VT) or ventricular fibrillation (VF) requiring appropriate ICD therapy
  6. Higher percentage of biventricular pacing
  7. Improved quality of life
  8. Acceptable safety and complication rate in this high-risk heart failure population

2. STUDY DESIGN

2.1. Overview

JAVA-CRT trial is proposed as an unblinded randomized controlled longitudinal trial. At randomization subjects receiving CRT-D implantation for standard clinical indications will be randomized 1:1 to undergo AVJ ablation or to be treated conventionally without AVJ ablation. Subjects will be required to be on optimal medical therapy including maximally tolerated doses of beta-blockers, ACE-inhibitors or ARBs, aldosterone antagonists, and statins, digoxin, and aspirin as recommended by current guidelines. Warfarin or a novel oral anticoagulant will be used for stroke prevention. Beta-blockers and digoxin will be used for rate control of ventricular response. AVJ ablation will be performed at the time of CRT-D implantation. Programming of implantable devices will be by protocol and will intend to provide maximal CRT pacing with attention to rate cutoffs and enhanced features. Subjects will be excluded from the trial if ventricular rates at rest are > 90 bpm despite optimal medical therapy or < 50 bpm, or if they have heart block or symptomatic bradycardia that necessitates permanent pacing.

It will not be possible to perform this trial in feasible and efficient manner as double-blinded. The primary endpoint of left ventricular volume on echocardiogram will be analyzed with the echo core lab blinded to subject treatment assignment. We acknowledge the potential for unblinding if the rhythm recorded on the echocardiogram suggests intact atrioventricular nodal conduction, but this is unavoidable in the pilot study and mitigated by the quantitative analysis of the primary endpoint and efforts at using only recordings with paced beats. The adjudication of secondary heart failure hospitalization endpoints will be done by review of medical records that have had data redacted or removed so that committee members will perform their duties without risk of bias.

2.2. Rationale for Study Design

The main innovation in the trial relates to the concept of the study. As described above, there are no data from a randomized clinical trial establishing evidence for clinical benefit of CRT in AF patients. We realize that this proposal is not designed to assess clinical benefit measured by endpoints of heart failure hospitalization or death, but obtaining proof of concept by demonstrating significant reduction in left ventricular volume will be essential to pursue a more definitive study. Testing the hypothesis that AVJ ablation will result in much more effective CRT pacing is very much needed in light of widespread use of CRT in AF patients without sufficient scientific proof. Knowing that 36% of CRT-D patients present in AF, the economic impact of treatment optimized by adding AVJ ablation will be very significant for health care (assuming the trial proves the hypothesis). Furthermore, since a prior study suggests that even a high percentage of biventricular pacing in the absence of AVJ ablation may not provide for the best possible outcomes from CRT, the proposed study is not only scientifically appropriate but also ethically sound.

3. CHARACTERISTICS OF THE RESEARCH POPULATION

3.1. Subject Characteristics

a) **Number of Subjects**
   This trial will enroll 40 subjects at 20-40 enrolling sites who meet study inclusion and exclusion criteria as described in Section 3.2.

b) **Gender and Age of Subjects:** Male of female subjects aged 21 years or older. We expect to enroll 25% women.

c) **Racial and Ethnic Origin:** There are no restrictions on race or ethnicity in this study. We expect to enroll 25% minority subjects.

3.2. **Inclusion and Exclusion Criteria**

3.2.1. **Inclusion Criteria**

- Age > = 21 years on date of consent
- Optimal pharmacologic therapy is defined by published guidelines from the American Heart Association and the American College of Cardiology
- Existing indication for CRT device with initial implant scheduled within 1 calendar month on or from date of randomization
- Ischemic or nonischemic cardiomyopathy
- LVEF ≤ 35% within 12 calendar months prior to or on consent date by angiographic, radionuclide, or echocardiographic methods
- NYHA class II-IV (ambulatory) on consent date
- QRS ≥ 120 ms for LBBB and ≥ 150 ms for non-LBBB patients within 1 calendar year prior to or on consent date
- Continuous AF > 3 calendar months when no further efforts to restore sinus rhythm are feasible or pursued**

  ***ECG evidence of AF will be required at enrollment and at 2 additional time points, one within 3calendar months and one ≥ 3 calendar months prior to enrollment, with no intervening ECGs revealing sinus rhythm and/or no successful effort to restore sinus rhythm for > 24 hours*

OR

- Active CRT-D device implanted within the last calendar year with <15% improvement in LVSEV from pre-implant cardiac imaging. The evaluation of LVSEV post implant must be within the last three calendar months.

- Continuous AF > 3 calendar months when no further efforts to restore sinus rhythm are feasible or pursued (see defininition above)

3.2.2. **Exclusion Criteria**

- Ventricular rate > 90 bpm at rest despite maximal medical therapy evidenced on 12-lead ECG within 1 calendar year prior to or on consent date
- Ventricular rate < 50 bpm at rest evidenced on 12-lead ECG within 1 calendar year prior to or on consent date
- Heart block/symptomatic bradycardia that necessitates permanent pacing
- Acute coronary syndrome or coronary artery bypass surgery or percutaneous coronary intervention (balloon and/or stent angioplasty) within 3 calendar months prior to consent date
- Enzyme-positive myocardial infarction within the past 3 calendar months prior to consent
- Severe aortic or mitral valvular heart disease eligible for percutaneous or surgical repair/replacement procedures
- Angiographic evidence of coronary disease that requires coronary revascularization and with likelihood of undergoing a CABG or PCI in the next 3 calendar months following consent date
- Prior AVJ ablation any time in the past
- Any medical condition likely to limit survival to < 1 year
- Presence of ACC/AHA Stage D refractory Class IV symptoms listed for transplant or requiring inotropic support at time of consent.
- Contraindication to systematic anticoagulation
- Renal failure requiring dialysis at time of consent.
- AF due to reversible cause e.g. hyperthyroid state

- Women who are pregnant or plan to become pregnant during the course of the trial** Note: Women of childbearing potential must have a negative pregnancy test within 7 days prior to randomization.
- Participation in other clinical trials that will affect the objectives of this study
- History of non-compliance to medical therapy
- Participation in other clinical trials (observational/lead registries are allowed) with approval from the CDC
- Inability or unwillingness to provide informed consent
- Resides at such a distance from the enrolling site so travel to follow-up visits would be unusually difficult
- Does not anticipate residing in the vicinity of the enrolling site for the duration of the trial
- Short-lived AF or in sinus rhythm

** Women will be allowed to enter this study if surgically sterile, postmenopausal (at least 1 year without periods), or willing to use a medically acceptable method of birth control prior to study entry and while participating in the study.

4. SUBJECT IDENTIFICATION, RECRUITMENT AND CONSENT

4.1. **Method Of Subject Identification And Recruitment**

Subjects will be recruited from ongoing local referrals of patients indicated for cardiac resynchronization therapy with defibrillator (CRT-D) devices or from patients being medically monitored for an implanted CRT-D device. As indicated above, verification of permanent atrial fibrillation will be required when considering eligible potential subjects.

4.2. **Process of Consent**

The site investigator and/or study coordinator will consent subjects in this study. The consent document will be used as a guide for the verbal explanation of the study and will be the basis for a meaningful exchange between the investigator and the potential subject. The subject's signature provides documentation of agreement to participate in a study, but is only one part of the consent process. The consent document will not serve as a substitute for discussion and the potential subject will be invited to ask any questions or concerns that will be answered by the study team members. Once a participant indicates that he or she does not want to take part in the research study, this process stops. The potential subject will be given sufficient opportunity to consider whether or not to participate. Refusal to take part or withdraw from the study at any time will not interfere with the future medical treatment.

5. METHODS AND STUDY PROCEDURES

5.1. **Study Procedures**

This study is designed as a 2-arm unblinded randomized clinical trial. A total of 40 subjects receiving or with CRT-D devices for standard clinical indications will be randomized 1:1 to the atrioventricular junctional (AVJ) ablation or to a control arm without ablation, stratified by enrolling site. All subjects will be followed for 6 months. The study procedures to be conducted for each subject enrolled in the study are presented in tabular form (Schedule of Activities) below and described in the text that follows:

Table 1. Schedule of Activities

PROCEDURES	Screening Visit	Randomization - Baseline – Procedure Visits		Follow-up Visits		
	Visit 1	**Visit 2**	**Visit 3**	**Visit 4**	**Visit 5**	**Visit 6**
	Consent within 1 calendar month prior to randomization	Day 1	Within 1 calendar month after randomization date	1 calendar month ± 7 days	3 calendar months ± 14 days	6 calendar months ± 14 days
	Screening	**Randomization-Baseline**	**Ablation +/- CRT-D**	**1 month post random-ization**	**3 months post randomi-zation**	**6 months post randomi-zation**
Informed Consent	✓					
Pregnancy test when applicable (within 7 days prior to randomization date)	✓					
Eligibility Confirmation	✓					
Randomization		✓				
Demographics /Medical History		✓				
Physical Exam (Limited)		✓		✓	✓	✓
CV Medication Prescribed		✓			✓	✓
Symptom Assessment		✓		✓	✓	✓
Quality of Life		✓**				✓
12-leadECG		✓*		✓*	✓*	✓*
Echocardiogram		✓*				✓
CRT-D Implantation†			✓*			
CRT-D Programming /Episode Reports			✓*	✓*	✓*	✓*
AVJ ablation			✓*			
Adverse Event			✓	✓	✓	✓
Heart Failure Event				✓	✓	✓
Protocol Deviations		✓	✓	✓	✓	✓
Subject Status			✓	✓	✓	✓

* standard of care procedures

** obtain quality of life questionnaire prior to informing subject of treatment assignment

† Ablation only for active CRT-D devices

CRT-D Implantation and Programming: For subjects having an index device procedure, the CRT-D will be implanted following clinically approved indications using standard techniques and leads will be placed in the right ventricle (RV) and the coronary sinus for biventricular (BiV) pacing. In case left ventricular (LV) lead cannot be positioned in the coronary sinus, direct epicardial techniques are permitted

For primary prevention subjects (indicated for ICD without prior cardiac arrest or hemodynamically compromising VT/VF), ICD programming should follow parameters shown in Table 2 below. These programming recommendations have been shown to reduce the risk of inappropriate and appropriate ICD therapies and increase survival. For secondary prevention subjects (indicated for ICD due to prior cardiac arrest or hemodynamically compromising VT/VF), the ventricular tachycardia zone should be programmed at a rate commensurate with the subject's documented clinical arrhythmia; however, the ventricular fibrillation zone should remain at 200 bpm or greater (Table 3).

Table 2. CRT-D Programming Recommendations - Primary Prevention

Rate in Single VT Zone	At least 185-200 bpm
Delay	At least 6-12 secs or 30 intervals
ATP Therapy	On for all zones (at least 1 attempt, 8 stimuli, 84-88% of TCL, burst)
Shock Energy	Maximum for all shocks
Discrimination Algorithms	On for rhythms > 200-230 bpm
Discriminator Time-out	Off
Lead Failure Alerts	On
Noise Detection and T-wave Oversensing	On
VT Monitoring Zone	On

Table 3. CRT-D Programming Recommendations - Secondary Prevention

Rates for Single/Dual Zones	(1) 10-20 bpm below clinical VT rate, if known; (2) For 2nd zone if desired, at least 185-200 bpm
Delay	At least 6-12 secs or 30 intervals
ATP Therapy	On for all zones (at least 1 attempt, 8 stimuli, 84-88% of TCL, burst)
Shock Energy	Maximum for all shocks
Discrimination Algorithms	On
Discriminator Time-out	Off
Lead Failure Alerts	On
Noise Detection and T-wave Oversensing	On
Additional VT Monitoring Zone	Optional

All subjects should maintain rate-responsive BiV VVIR pacing throughout the study. In all patients, the pacemaker should be programmed to a VVIR mode with a lower rate of 80 bpm for the first calendar month after implant to mitigate the risk of polymorphic ventricular tachycardia for those patients undergoing AV junction ablation. Following that the rate can be decreased to 60 ppm during routine clinical care. The pacemaker should be programmed in a VVIR mode with a lower rate of 60 bpm and an upper sensor rate set at 80% of age-corrected maximum heart rate. The upper sensor rate should remain unchanged throughout the study. Device algorithms designed to promote fusion and increased pacing during atrial fibrillation (e.g. ventricular sensed response, trigger pacing, ventricular rate regularization) should remain programmed ON throughout the study. Patients randomized to either arm of the study are programmed in a similar fashion, as they are both in permanent AF. Should sinus rhythm spontaneously develop, or as a result of shock in response to VT, the device may need to be reprogrammed to a dual chamber mode.

AV Junction Ablation Procedure: At the discretion of the investigator, ablation of the AVJ should be performed within 2 days of implantation of a market-released CRT defibrillator (CRT-D) device (unless active CRT-D device has been implanted), although specific institutional or subject circumstances may necessitate a delay of up to 7 days. For subjects with a previously implanted CRT-D device, ablation must take place within 30 days of randomization. Ablation of the AV junction is a relatively simple procedure. Ablation is usually targeted at the atrial side of the tricuspid valve annulus in the region of the compact AV node. A deflectable ablation catheter is placed on the annulus where it records a large His-bundle electrogram. The catheter is then withdrawn until it records a large atrial electrogram and small His-bundle electrogram. It is at this site that radiofrequency at 30-50W is delivered for up to 60 secs; if complete heart block does not ensue, the ablation catheter is repositioned and the process repeated. A prior study has demonstrated that the procedure can be successfully performed in >99% of patients. For rare subjects for whom there is difficulty, ablation can also be performed successfully at the left intraventricular septum using a retro-aortic approach. If conduction recovers, which is rare, the ablation will be repeated. There conceivably may be a very rare subject who fails both approaches, and these subjects will be followed in their assigned arm and treated with medical therapy for rate control, i.e. intent to treat. The cardiac rhythm will be observed for at least 30 minutes following ablation to ensure the persistence of complete heart block with either ventricular asystole or a stable and regular escape rhythm. Additional AVJ ablation procedures may be performed if the first procedure is not successful. AVJ ablation is routinely performed in clinical practice and is routinely reimbursed. However, despite these practices there is no evidence from randomized clinical trials regarding clinical benefit of this procedure in those undergoing CRT-D implantation.

Randomization as a method of experimental control has been extensively used in human clinical trials. It prevents the selection bias and insures against accidental bias. It produces the comparable groups and eliminates the source of imbalance after treatment assignment. Finally, it permits the use of probability theory to express the likelihood of chance as a source for the difference of the final outcome. Randomization in this study will occur at visit 2. It should be noted that that visit 2 could take place on the same day as visit 1 and visit 3.

1. CRT-D device implantation or
2. CRT-D device implantation and AVJ ablation procedure

For subjects with an existing CRT-D device

1. Ablation
2. Medical management

Subjects will be notified that randomization is part of this study during the consent process. Subject will be informed which randomized arm they have received after completing the quality of life questionnaire. Subject will be notified that either treatment arm may be less or more effective, or may have more or less side effects.

Randomization will be stratified by enrolling site and generated per the scheme described in Section 11. The randomization strings for treatment assignment will be provided to the database programmer at the coordination site by chief statistician Derick Peterson and uploaded in the electronic data capture system with appropriate testing and validation that the system is working correctly prior to the beginning of subject

randomization. The enrolling site has full responsibility for completion of the CRFs required for subject randomization. The enrolling site may contact the data center project manager and will notify about randomization results only if the enrolling site has no internet access or the web base program will automatically assign the randomization treatment assignment and subject ID based on the randomization strings provided by the biostatistician. The randomization result is viewed by the enrolling site in the eDC system following randomization or documented on the paper CRF which is returned to the enrolling site if randomization cannot be done through the eDC system. All eligibility criteria will be confirmed prior to providing the randomization treatment assignment/subject ID to the enrolling site.

5.2. **Subject Consent**

Each potential subject will have the protocol described to them by one of the physicians or research coordinators at the enrolling sites. Potential subjects will sit down with the coordinator or physician and have the opportunity to ask questions. Those who meet inclusion/exclusion criteria will then be asked to sign consent for study participation. At this time they will sign an "informed consent" form that is fully approved by the local IRB following local IRB consent administration regulations. It is the responsibility of the investigator to ensure that subjects are eligible to participate in the study prior to enrollment and throughout the study. Once informed consent has been obtained, all screening tests and procedures have been assessed and study eligibility has been confirmed, subjects will be randomized and assigned a unique subject identification number. The enrolling site will enter data in the web base system and the system will assign the subject ID after study eligibility criteria are met. The scheme for assigning subject ID is as follow: first 2 numbers are assigned for enrolling site and will not change for duration of the study. Next two numbers are specific to a randomized subject in the enrolling site.

The principal investigator ensures that informed consent from each potential research participant will be obtained by an IRB approved consent designee and documented. The following person may obtain consent: the principal investigator, sub-investigators, or study team members listed on the IRB application form as a consent designee. Each individual who will interact with potential research participants to obtain consent will submit evidence of human subject compliance training per local IRB regulations.

5.3. **Visit 1: Screening**

- Potential subjects will be screened to determine eligibility for participation in the study per medical record review. Potential subjects will be identified based on planned CRT-D implant or existing active CRT-D device. Those who fulfill the study eligibility criteria and current indication for CRT-D implantation or existing active CRT-D device can be approached for inform consent, but additionally ECG evidence of AF will be required at consent and meet study criteria prior to patient randomization. The screening visit might occur on the same day as the Baseline and procedure visit described below.

5.4. **Visit 2: Randomization and Baseline Assessment**

The following tasks will be performed and documented at the Visit 2 (Visit 2 could take place on the same day as Visit 1 and Visit 3) following informed consent:

- Reconfirm inclusion and exclusion criteria prior to randomization. Presence of AF in potential subjects who qualify for CRT-D implantation or existing CRT-D device will be confirmed as follows: AF present at screening visit and at 2 additional time points, one within 3 months and one ≥ 3 months prior to enrollment, with no intervening ECGs revealing sinus rhythm and/or no successful effort to restore sinus rhythm for > 24 hours.
- Subjects will undergo an echocardiogram at Baseline Visit prior to CRT-D implantation if no echocardiogram was performed within the past calendar year prior to randomization to qualify patient for CRT-D implant per current medical guidelines. For subjects with an existing CRT-D device, an echocardiogram demonstrating <15% change in LVSEV in comparison to pre-implant cardiac imaging must be within three calendar months prior to consent.

- Perform randomization to AVJ ablation or conventional treatment without ablation if potential subject meets as study eligibility criteria via the electronic data capture system or manually if internet access is not possible.

Note: Some of the following data will be required to confirm study eligibility criteria and recorded at time of screening confirmation and randomization. If not required to confirm study eligibility, this data will be recorded after randomization occurs.

- Perform clinical assessment and collect data on current prescribed CV medications
- Complete limited physical examination including vital signs, body weight, and height
- Perform symptom assessment
- Obtain a copy of standard 12-lead ECG used to confirm study eligibility
- Obtain most recent echocardiogram images obtained within 1 calendar year prior to or on randomization date used to determine study eligibility and prior to CRT-D implant
- Quality of Life assessment (prior to providing randomized treatment assignment to subject)

5.5. **Visit 3: Procedure Day(s)**

CRT-D implantation (unless subject has an existing, active CRT-D device) and AVJ ablation (in subjects randomized to AVJ ablation arm) are expected to be performed during this visit which must occur within on or within 1 calendar month after randomization date. These procedures could be performed on the same day as Baseline Visit 1 that will reflect usual clinical practice. Both procedures usually are performed on the same day while the subject is in electrophysiology lab for CRT-D implantation. However, the timing of the AVJ ablation is left to the discretion of physician. It is recommended that AVJ ablation be performed within 2 days of CRT-D implantation. Programing of CRT-D should need to be adjusted at the time of AVJ ablation as described above.

5.6. **Visit 4: Follow-up at 1 calendar month after Randomization** (1 calendar month $\pm$ 7 days)

During this follow-up visit investigators/coordinators should:

- Perform limited clinical assessment, collect vital signs Obtain a copy of standard 12-lead ECG
- Assess CRT-D implant status
- Perform CRT-D interrogation and reprogramming as needed
- Obtain information regarding adverse events and congestive heart failure

5.7. **Visit 5: Follow-up at 3 calendar months after Randomization** (3 calendar months $\pm$ 14 days)

During this follow-up visit investigators/coordinators should:

- Perform limited clinical assessment, collect vital signs and collect data on current prescribed CV medications
- Obtain a copy of standard 12-lead ECG
- Perform CRT-D interrogation and reprogramming as needed
- Obtain information regarding adverse events and congestive heart

5.8. **Visit 6: Follow-up at calendar 6 months after Randomization** (6 calendar months $\pm$ 14 days)

During this follow-up visit investigators/coordinators should:

- Perform limited clinical assessment, collect vital signs and collect data on current prescribed CV medications
- Obtain a copy of standard 12-lead ECG
- Perform Echocardiogram per study echo acquisition manual
- Perform CRT-D interrogation and reprogramming as needed
- Obtain information regarding adverse events and congestive heart
- Quality of Life assessment
- Document closeout of subject participation in the study

5.9. **Costs to the Subject**

All treatments and tests are considered standard of care and as such will be billed using the patient's medical insurance coverage with the exception of the 6 month echocardiogram. There will be no charges for research activities to the subject. AVJ ablation is routinely performed in clinical practice and is routinely reimbursed. However, despite these practices there is no evidence from randomized clinical trials regarding clinical benefit of this procedure in those undergoing CRT-D implantation.

5.10. **Payment for Participation**

Subjects will not receive payment for participating in this research study.

5.11. **Return of Individual Research Results**

No research results will be provided to the subject other than the standard of care discussion of clinical outcomes.

5.12. **Concomitant CV Medications**

Optimal pharmacological treatment of heart failure is expected in enrolled subjects as defined by published guidelines from the American Heart Association and the American College of Cardiology.

5.13. **Subject Withdrawals**

Subjects will be advised in the written informed consent forms that they have the right to withdraw from the study at any time without prejudice. Subjects may be withdrawn as lost to follow-up by the investigator if they do not return for follow-up after 2 documented attempts to contact the subject. These subjects will not undergo any additional study activities prior to withdrawal.

6. ASSESSMENT OF STUDY ENDPOINTS

6.1. **Echocardiogram (ECHO)**

Echocardiographically quantified left ventricular systolic volume is the primary endpoint of this study. Subjects will undergo an ECHO at Baseline Visit prior to CRT-D implantation if no echocardiogram was performed within the past calendar year prior to randomization and at a 6-month follow-up visit after CRT-D implantation. The 6 month ECHO is expected to be paid for by the study and baseline echo is a standard-of care procedure normally performed before a CRT-D implantation. ECHO image acquisition performed after study consent must follow a standardized protocol; images will be digitized and sent to central ECHO Core Lab for blind assessment if possible. ECHO image acquisition that was performed to confirm eligibility prior to study consent will need to be sent to ECHO Core Lab at the Washington University in St. Louis for approval regarding correct images and quality after the subject signs the approved study consent. Sites will be supplied with training materials that will describe in detail the methodology for obtaining JAVA-CRT echocardiograms. Training sessions will be conducted and documented for all participating sites.

The ECHO will be sent to Dr. John Gorcsan, Professor of Medicine/Cardiology at the Washington University in St. Louis Medical Center. Dr. Gorcsan is respected leader in the field with vast experience as clinician and echocardiography expert. He has served as Director of ECHO Core Lab for numerous clinical trials including recent ECHO-CRT trial. He and his team will perform centralized blinded Echo reading. The ECHO will be used to also assess left ventricular diastolic volumes, left atrial volume, left ventricular function, and left ventricular dyssynchrony. We will request that echo data will be de-identified when sent from enrolling site to the ECHO Core Lab but just in case of identification still present the core lab will have "honest broker" who is a third party (an echo technician) who will receive the echos and de-identify them. The de-identified echos will then be analyzed by ECHO Core Lab.

6.2. **Electrocardiogram (ECG)**

Standard 12-lead ECGs are expected to be standard of care following CRT-D implant and/or AVJ ablation and will be obtained to document rhythm and presence of atrial fibrillation as well as to assess and document CRT-D paced QRS morphology.

6.3. **CRT-D Interrogation**

An interrogation of implanted CRT-D will be performed at each follow-up visit to document percentage of biventricular pacing and to document burden of appropriate and inappropriate ICD therapies. Assessment of CRT-D implant status and LV lead status will also be performed in addition to assessment of device programming.

6.4. **Clinical Assessment**

A clinical assessment will be performed to include functional status (NYHA class), interim hospitalizations, comorbidities, medications and heart failure event status. Vital signs and weight/height will be collected at baseline and at all study visits. Vital signs include blood pressure, and heart rate.

6.5. **Quality of Life Assessment**

Quality of life data will be acquired at baseline prior to the subject being informed of the randomized treatment assignment and at 6-month follow-up visit using the Kansas City Cardiomyopathy Questionnaire (KCCQ) administered to the subject.

6.6. **Congestive Heart Failure**

Subjects will be categorized as having a "heart failure event" when the subject has symptoms and/or signs consistent with heart failure and:

1. receives intravenous decongestive therapy (IV diuretics, IV neseritide, IV inotropes), that does not involve formal in-patient 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).

Source documentation must be submitted to the CDC along with the completed CRF. Additional documentation will be requested from the enrolling center as needed. Initially, required documentation will only require a comprehensive discharge summary enabling the endpoint reviewer to determine the heart failure classification. If the discharge summary is not sufficient to determine a classification or additional information is needed to complete the heart failure adjudication data requirements then documentation will be requested from the enrolling center that may include some or all of the following, if available:

- History and physical, or admit note, or ER note
- Test results
- Chest X-ray, lab work, echo, ultrasound, other test results as appropriate
- Consults
- Operative reports
- Progress notes from the chart

The collection of heart failure events will stop at the point the trial is terminated, enrollment has been stopped, and the subject has had their last clinic follow-up visit.

7. SAFETY AND REPORTABLE EVENTS

7.1. **Adverse Event Definition**

An adverse event is any symptom, sign, illness, or experience that develops or worsens during the course of the study. Any adverse event related to the AVJ ablation should be reported regardless of whether it met the definition of a serious adverse event as described in Section 7.2. All serious cardiovascular adverse events

(including stroke) must be reported per definition in Section 7.2.

7.2. **Serious Adverse Event Definition**

A serious adverse event is defined as any adverse medical experience that results in any of the following outcomes:

- death;
- is life-threatening;
- requires inpatient hospitalization or prolongation of existing hospitalization;
- results in permanent impairment of a body structure or a body function;
- requires medical or surgical intervention to prevent permanent impairment or damage.
- lead to fetal distress, fetal death or a congenital abnormality or birth defect.

7.3. **Recording Adverse Events Per Definition in Section 7.1**

At each subject visit the site study staff will assess adverse events per definition in Section 7.1 by recording all voluntary complaints of the subject and by assessment of clinical and laboratory features. At each study visit, the subject should be questioned directly regarding the occurrence of any adverse experience since his/her last visit.

All adverse events, whether observed by the Investigator, elicited from or volunteered by the subject, should be documented on or following randomization date and within 10 calendar days of date reported to the enrolling site. Ventricular tachyarrhythmias will be documented in the ICD interrogations unless reported as an adverse event related to the AVJ ablation per the definition in Section 7.1. Each adverse event will include a brief description of the experience, the date reported to the enrolling site, the date of onset, the date of resolution, the duration and type of experience, the severity, relationship to subject condition, procedure, drug or device, contributing factors, and any action taken. Event status if not resolved will be tracked at each follow-up with final status indicated at the conclusion of study participation e.g., resolved, ongoing, unresolved.

7.4. **Responsibilities for Reporting Adverse Events**

The Investigator will record all adverse events per Section 7.1 definition that occur during the study period in the appropriate source documents and/or AE case report form with 10 calendar days of the date reported to the enrolling site. The study period for reporting adverse events (e.g., from the time of randomization to final study visit) will be 6 months, the local IRB will be notified by the enrolling site per local IRB regulations. The Investigator will comply with local regulations regarding the reporting of adverse events. Adverse events reported by enrolling sites will be promptly reported to Data Coordinating Center Institutional Review Board, NIH, and FDA per local regulations. Similar to other clinical trials conducted by University of Rochester investigators, adverse events will be immediately reported to the Coordination and Data Center (CDC) via dedicated web-based case report forms to the PI (Dr. Steinberg) and Co-PI (Dr. Zareba). The CDC will be forwarding relevant documents to the Chair of DSMB for review and Chair will determine whether individual case will require immediate assessment by full DSMB committee or it could be assessed during electively scheduled DSMB meeting. The main point of assessment by DSMB will be to judge whether given adverse event could be related to AV junctional ablation.

8. **RISK/BENEFIT ASSESSMENT**

8.1. **Potential Risks**

Early risk to patients: The ablation catheter needs to be introduced through the femoral veins. This can result in either bleeding (hematoma) or thrombosis. The former was reported in 1 of 252 subjects (0.4%) in one study; the latter was reported in 1 of 156 subjects (0.6%) in another study. When the ablation is performed after implantation of the CRT device, it is possible to dislodge one of the implanted leads with the ablation catheter;

this was observed in 2 of 156 subjects (1.2%) in a prior study. This complication would require repositioning of the lead(s) that dislodged.

Late complications: There are 2 feared late complications of AV junction ablation. The first is that dislodgement of the ventricular lead in a pacemaker dependent subject could be fatal. However, a stable underlying escape rhythm is present in 67% of subjects following ablation. In addition, each subject in this trial will be undergoing biventricular pacing. It would be distinctly unusual for both the right and left ventricular leads to dislodge at the same time. Dislodgement of one ventricular lead would lead to loss of biventricular pacing but would still allow the other ventricular lead to pace the heart. In addition, contemporary left ventricular leads are multipolar, providing additional pacing redundancy.

The second feared complication is polymorphic ventricular tachycardia. In early trials of AV junction ablation, sudden cardiac death was observed in ~5% of patients. It was subsequently recognized that this was due to bradycardia-dependent polymorphic tachycardia. This adverse event can be eliminated by gradually reducing the lower pacing rate after initial programming is set at a higher than usual lower rate cutoff (as has been designed in this trial). Arrhythmic mortality was observed in only 2 of 252 subjects (0.8%) when such a protocol was routinely employed in a post-AV junction trial of pacemaker patients. In our study, all subjects will have an implantable defibrillator; thus, in the extremely rare event that a subject develops post-ablation polymorphic ventricular tachycardia, the defibrillator would be able to resuscitate the subject.

8.2. **Protection Against Risks**

All subjects that are treated for AF and heart failure with CRT are observed and treated in an optimal fashion as dictated by clinical standards to minimize any adverse events and to maximize the likelihood for clinical success. If the subject experiences any adverse event during the study, they will be treated in a manner consistent with clinical standards and the subject will be responsible for the costs of treatment.

8.3. **Potential Benefits to Subjects**

There is no guarantee of benefit from the AVJ ablation procedure. The study can provide better understanding of how to manage AF in the setting of HF in patients who will receive CRT. It is expected that the patient's heart failure status including symptoms and function, quality of life, and need for hospitalization could possibly improve.

8.4. **Alternatives to Participation**

Alternatives to participation are not to participate in the study and receive the same care outside of the formal study.

9. DATA AND SAFETY MONITORING PLAN

A data and safety monitoring board (DSMB) will be convened to independently monitor the conduct and the outcomes of the trial. The DSMB will be responsible for monitoring the safety and well-being of the subjects participating in this study and ensuring the ethical conduct of the trial. Since this study is a pilot project enrolling only 40 subjects and since the primary endpoint consists of echo-derived measures of LV function, the main focus of DSMB activity will be to monitor clinical adverse events that could be attributed to the procedure of ablation. Data on clinical events including procedural complications, HF events, ventricular tachyarrhythmias requiring ICD therapy, and death will also be collected by the study and provided to DSMB for evaluation of risks associated with AVJ ablation treatment in CRT patients. In the above capacities, the DSMB will be advisory to the Steering Committee responsible for overseeing the design, conduct, and data collection/analysis of the trial. The board will be comprised of 4 independent members: (1) a statistician with experience in clinical trials; (2) 2 cardiologists with expertise in HF clinical trials; and (3) 1 electrophysiologist with expertise in device implantation and experience with AVJ ablation. All cardiologists and the statistician selected for the DSMB must come from institutions not participating in the trial and have no personal or professional relationship with any participating investigator. The DSMB will meet before trial commencement and 4 times after each group of 20

subjects is enrolled. It is anticipated that these meetings will take place via conference call. One of the clinical cardiologists will be selected to chair the committee and will serve as the principal representative of the group.

10. CONFIDENTIALITY OF DATA AND INFORMATION STORAGE

Efforts will be made to maintain confidentiality of study data. All study data will be coded with an unidentifiable study code. The study coordinator for each enrolling site will locally maintain a key linking the subject's name with study data which will not be shared outside of the enrolling site. Subjects' personal information will be kept confidential and will not be released without his/her written permission, except as described in this section or as required by local law. Subject's personal information may be shared, to the extent necessary, among the research staff, with the Institutional Review Board and for research oversight as dictated by local regulations.

All information and data collected concerning subjects or their participation in this investigation will be considered confidential by the CDC. No social security numbers or direct identifiers will be collected by the CDC. Study data collected during this investigation may be used by the CDC for the purposes of this investigation, publication, to support future research and/or other business purposes. HIPAA authorization will be obtained from each subject by every enrolling site per local regulations and enrolling sites are expected to follow all local regulations related to data collection.

All data will be submitted using a password protected electronic data capture system with access limited to only those authorized by the Principal Investigator at each enrolling site per an electronic access request document with delegation made by the Principal Investigator. All study data will be coded with a study subject number that is assigned at the time of treatment randomization and cannot be linked to the patient's identify except at the individual enrolling sites. Source document records to support event adjudication or core laboratory analysis will be redacted of all PHI before being sent to the coordinating center and only the subject ID will be recorded to link the subject to this data. The electronic data will be directly extracted from web system for data collection.

11. STATISTICAL METHODS AND POWER CONSIDERATIONS

Overall Study Design and Primary Endpoint: This study is designed as a 2-arm unblinded randomized clinical trial. A total of 40 subjects receiving CRT-D will be randomized 1:1 to AVJ ablation or control arm (without AVJ ablation), stratified by enrolling site. The primary endpoint is the binary response defined as ≥ 15% reduction in LVESV from baseline to 6 months.

Randomization Scheme: Enrolled subjects will be 1:1 randomized to AVJ ablation (with CRT-D) or control (CRT-D only). The randomization sequence will consist of a string of random 4- and 6-blocks. That is, there will be a 50% chance that the first block will consist of 4 subjects (2 AVJ ablation + 2 control, in random order), and a 50% chance that it will contain 6 subjects (3 AVJ ablation + 3 control, in random order). Each subsequent block will similarly be of random size. This procedure makes it very difficult for anyone to predict whether the next treatment assignment will be AVJ ablation (or control), helping to ensure integrity of the study. In contrast, if each block were of size 4, then it would be trivial to perfectly predict every 4^{th} treatment assignment as well as the 3^{rd}, if the first two were both AVJ ablation or both control, which would be undesirable. Randomization will be stratified by enrolling site. The randomization scheme will be generated by chief statistician Derick Peterson and provided to the CDC per Section 5.

Endpoint: The primary endpoint is the binary response defined as ≥ 15% reduction in LVESV from baseline to 6 months.

Power and Sample Size: Randomizing 20 subjects per arm (for a total of 40 subjects), and allowing for up to 10% drop-out due to withdrawal, death, or inadequate imaging, we expect at least n=18 evaluable subjects per arm. This sample size will provide 80% power to detect an absolute change of 50% in response rates, using a 0.05 level 2-sided Fisher exact test, assuming the actual response rate in the AVJ ablation arm is 80-85%, as in

Gasparini 2006 (1) and Ferreira 2008 (6), where the empirical change in response rates was Δ = 49% and 33%, respectively.

Crossovers: We anticipate that virtually no subjects will cross over from the AVJ ablation arm to the control arm. We expect at most 2-5% crossovers from control to the AVJ ablation arm, but we will work with investigators to consider these crossovers ideally only after trial completion so that they would have no effect on the primary endpoint. In any case, since the primary analyses will be conducted on an intention to treat (ITT) basis, crossovers will not affect the primary analysis. Furthermore, the stated response rates pertain to the planned ITT analyses, so they and the associated power computations already implicitly account for the small expected effect of the limited crossovers we anticipate for this study.

Statistical Methods: The primary analysis will be an intention-to-treat (ITT) analysis based on Fisher's exact test of the null hypothesis that the response rates are identical for both arms, conditional on the total number of responders. Response rates for each arm will be estimated by the empirical proportions (maximum likelihood estimates), along with associated Clopper-Pearson exact 95% confidence intervals (CI). Maximum likelihood estimates and associated 95% CI for the odds ratio (OR), relative risk (RR), and the absolute change in proportions will be used to summarize the treatment effect.

Secondary Analyses: Secondary endpoints include: a) change in LVEF from baseline to 6 months; b) LV end diastolic volume and change from baseline to 6 months; c) HF event including repeated HF events; d) all-cause mortality; e) VT/VF arrhythmic events requiring ICD therapy; f) inappropriate ICD therapy; g) percentage BiV pacing; h) quality of life; and i) complications related to AVJ ablation procedure. Since power for analyzing most secondary endpoints will be limited, secondary analyses will be mainly descriptive in nature. However, to the extent feasible, statistical analysis will be performed, as described briefly below.

Continuous secondary endpoints (a), (b), and (h) will be compared across arms using Wilcoxon and t-tests and summarized via means, medians, and standard deviations. Linear models will also be employed to adjust for potential effects of baseline values and demographic characteristics. Power for some of these particular comparisons is expected to be relatively high, given that mean changes on the order of 0.75 SD (0.50-1.00 SD) can be detected with 88-91% (55-99%) power, using a 0.05 level t-test with 36-40 evaluable subjects per arm.

Censored time-to-first-event endpoints (c) and (d) will be modeled using Cox models, although power is expected to be very low for these secondary endpoints. Secondary endpoint (c) also includes repeated heart failure hospitalizations. A cause-specific Anderson-Gill regression model (a generalization of the Cox model for a first event) treating death as a competing risk will be used to assess any difference in ongoing risk of repeated therapy in the two arms of the trial. Inference (p-values and confidence intervals) will be based on the robust grouped jackknife covariance estimator to account for potential dependencies between times to repeated heart failure hospitalizations. Secondary endpoint (f) concerns inappropriate ICD shocks. A cause-specific Cox model will be used to model time to first inappropriate shock, while repeated shock episodes will be modeled using a cause-specific Anderson-Gill model, with inference based on the robust grouped jackknife covariance estimator. Each of these will treat death as a competing risk.

Secondary endpoint (e) is about repeated appropriate ICD therapies; for it, a robustified Anderson-Gill model will be carried out to assess any difference in ongoing risk of repeated therapy in the two arms of the trial.

Safety endpoints of ablation (i) will include perforation/tamponade, cardiac arrest during procedure, groin hematoma requiring evacuation, other vascular interventions, need for transfusion, failure to achieve heart block, and need for repeat ablation procedure. Counts and proportions will be used to summarize the distributions of these discrete safety endpoints.

12. ORGANIZATION OF THE STUDY

The organization structure of this small pilot trial is based on collaboration between Dr. Jonathan Steinberg serving as overall PI being in charge of site and subject recruitment with Drs. Wojciech Zareba as Co-PI, who will ensure coordination of the trial utilizing infrastructure successfully developed at the Heart Research Follow-up Program at University of Rochester Medical Center, Rochester, NY. Serving as the CDC the University of Rochester will be responsible for overall study management, data management, data reporting and center communications for the study. The University of Rochester will also be responsible for other project management tasks.

The University of Rochester Heart Research directed by Dr. Wojciech Zareba and his team has developed a limited access electronic data capture (EDC) web-based management system for several past and ongoing studies located on a production server hosted by the University of Rochester. The system integrates subject enrollment from enrolling sites, randomization, follow-up, invoicing, and core lab and endpoint adjudication committees with confidentiality as described in Section 10. Manual and/or automatic queries will be created in the EDC system and will be issued to the site for appropriate response. Enrolling site staff will be responsible for resolving all queries in the database, in a timely manner. The enrolling site principal investigator (PI) provides his/her electronic signature on the appropriate electronic case report forms (eCRFs) in compliance with local regulations. Changes to data previously submitted to the sponsor require a new electronic signature by the PI acknowledging and approving the changes. Database backups are performed regularly.

The Principal Investigator of an Enrolling site is responsible for ensuring that the study is conducted in accordance with the protocol and ethical principles that have their origins in the Declaration of Helsinki, any conditions of approval imposed by the reviewing IRB/EC, and prevailing local laws and/or regulations, whichever affords the greater protection to the subject.

The Principal Investigator's responsibilities include, but are not limited to, the following:

• Prior to beginning the study, sign the Clinical Study Agreement documenting his/her agreement to conduct the study in accordance with the protocol.
• Provide his/her qualifications and experience to assume responsibility for the proper conduct of the study and that of key members of the center team through up-to-date curriculum vitae or other relevant documentation and disclose potential conflicts of interest, including financial, that may interfere with the conduct of the clinical study or interpretation of results.
• Make no changes in or deviate from this protocol, except to protect the life and physical well-being of a subject in an emergency; document and explain any deviation from the approved protocol that occurred during the course of the study.
• Create and maintain source documents throughout the clinical study and ensure their availability with direct access during monitoring visits or audits; ensure that all clinical-investigation-related records are retained per requirements.
• Ensure the accuracy, completeness, legibility, and timeliness of the data reported to the CDC in the CRFs and in all required reports including query resolution and event source documentation. At completion of the study the Principal Investigator will be responsible for approval of the data collected via electronic signature of all CRFs.
• Record, report, and assess (seriousness and relationship to the subject condition/device/procedure) every adverse event per the protocol definition to the CDC and local reporting requirements as well as supply the CDC/IRB with any additional requested information related to the safety reporting of a particular event
• Allow and support regulatory authorities and the IRB/EC when performing auditing activities if needed.
• Ensure that informed consent is obtained in accordance with applicable laws, this protocol and local IRB/EC requirements.
• Make all reasonable efforts to avoid subject withdrawal prior to 6 months and ascertain the reason(s) for a subject's premature withdrawal from clinical investigation while fully respecting the subject's rights.

• Ensure that an adequate investigation site team and facilities exist and are maintained and documented during the clinical investigation.
• Ensure appropriate training requirements are met and adequate supervision of those to whom tasks are delegated. The investigator is accountable for regulatory violations resulting from failure to adequately supervise the conduct of the clinical study.
• Prior to gaining Approval-to-Enroll status, PI will provide to the CDC documentation verifying that their IRB/EC is registered or that registration has been submitted to the appropriate agency, as applicable according to national/regulatory requirements. A copy of the written IRB/EC approval and approved Informed Consent Form must be received by the CDC before recruitment of subjects into the study. Prior approval must also be obtained for other materials related to subject recruitment or which will be provided to the subject.
• Obtain Annual IRB/EC approval and renewals throughout the duration of the study as required by local IRB/EC requirements. Copies of the IRB/EC continuance of approval must be provided to the CDC.

13. HEART FAILURE EVENTS ADJUDICATION COMMITTEE PROCESS

A secondary endpoint in JAVA-CRT is occurrence of heart failure events. Hospitalization for heart failure has been used as a heart failure event in several prior drug and device trials, but not all subjects who require treatment for severe heart failure are admitted to the hospital. Symptoms and signs of heart failure such as fatigue, exertional dyspnea, orthopnea, paroxysmal nocturnal dyspnea, edema, rales, and pulmonary congestion are the cardinal findings of congestive heart failure. These signs and symptoms may be quite variable in presentation and severity, and the diagnosis of heart failure has both objective and subjective components. In addition, some of the symptoms and signs of heart failure can mimic or co-exist with unrelated conditions such as bronchitis, asthma, and pneumonia.

The physician who makes a diagnosis of heart failure in a given subject utilizes information from the medical history, physical exam, and relevant laboratory data before initiating or augmenting decongestive therapy.

Decongestive therapy can involve:
1. more rigorous dietary salt restriction, reduction in physical activity, or elevating the head with pillows for sleep at night;
2. initiation or augmentation of appropriate oral drugs such as diuretics, vasodilators, angiotensin converting enzyme inhibitors, angiotensin receptor blockers, aldosterone receptor blockers, or cardiac glycosides;
3. initiation of intravenous medication including diuretics, neseritide (intravenous BNP), inotropes (phosphodiesterase inhibitors, or adrenergic/dopaminergic agonists); and/or
4. ventilatory support.

Many asymptomatic subjects with ejection fractions <0.35 are on a spectrum of oral drugs to prevent or inhibit the development of heart failure. The development of heart failure usually manifests by new symptoms and signs of the disorder that represent a change from the baseline state. Therapy for heart failure encompasses a wide range of interventions. Initiation of intravenous decongestive therapy, whether in the clinic, the emergency ward, or in an in-hospital setting, involves clinical judgment by the attending physician with integration of a host of clinical and laboratory findings before the therapy is started. Intravenous decongestive therapy is an excellent marker of a severe heart failure event.

In JAVA-CRT, subjects will be categorized 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(IV diuretics, IV neseritide, IV inotropes)**, that does not involve formal in-patient 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).

Heart Failure Event Endpoint Committee Adjudication Process

Composition and Duties

The JAVA-CRT Heart Failure Event Endpoint Committee will consist of, at a minimum, three non-participating cardiologists. One of the cardiologists specializes in heart failure, while the other two are an electrophysiologist and a non-invasive, general cardiologist. The committee will be responsible for the adjudication of the occurrence of heart failure events in the JAVA-CRT clinical trial and will meet quarterly at a minimum. The purpose of this process is to provide maximum uniformity and continuity in the review and categorization of heart failure events, while still maintaining latitude for professional judgment by the investigators and committee members.

The Committee will receive information regarding all heart failure events from the enrolling sites. This information will be first sent to the Coordination and Data Center (CDC) where the supporting documentation will be reviewed for completeness and then forwarded to the committee. The committee then reviews and adjudicates the events within 1 calendar month of report of the event to the CDC provided that sufficient supporting documentation has been received from the enrolling site. If the supporting documentation is not sufficient or non-existent within a reasonable period of time, the enrolling site coordinator is contacted and the required documents are requested. As with all data, sometimes the enrolling site coordinator is unable to retrieve sufficient source documentation on the heart failure event. If there is sufficient evidence in the form of notes from the PI or enrolling site that the requested supporting documentation is not available despite numerous attempts and these requests have been diligent, the case is sent to the Endpoint Committee for adjudication.

Two broad categories of heart failure events have been established to review. They are events that occur in 1) hospitalized; and 2) ambulatory, out-of hospital settings. The Committee will review and adjudicate all heart failure events. The Committee will classify each event as **a heart failure event**, **not a heart failure event,** or *needing additional information.*

Review of CHF Case Report Forms

Each study data form will be systematically reviewed and validated by the Heart Failure Committee. For this purpose, JAVA-CRT data forms have been created. These forms are endpoint-specific. The committee members will initially review each study data form submitted in advance of the scheduled committee meeting and will independently document the results of their review on CHF Event Classification Forms developed by the committee.

Reporting of Classification

The Committee will complete a CHF Event Adjudication Data Form to the CDC that will be included in the JAVA-CRT database with a confirmation report document forwarded to the DSMB by the CDC following data entry. A copy of each confirmation document will be archived by the committee and the event review will be considered closed.

14. Key References

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