MULTICENTER AUTOMATIC DEFIBRILLATOR IMPLANTATION TRIAL – CHEMOTHERAPY-INDUCED CARDIOMYOPATHY

(MADIT-CHIC)

CLINICAL PROTOCOL

Version 3.0 (February 23, 2018)

Funding Provided By:

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Other Institutions	A list of other institutions involved in the trial is maintained and provided in the Manual Of Operations.

Current Version 3.0: Revision History

Revision Number	Release Date	Section	Change	Reason for Change
3.0	February 23, 2018	Protocol cover page, Contact Information, Section 28.1 and Appendix A	Remove Dr. Moss as PI	Passing of PI
3.0	February 23, 2018	Protocol cover page, Contact Information, Section 28.1 and Appendix A	Add Dr. Valentina Kutyifa as new PI	Passing of PI
3.0	February 23, 2018	Section 17.5 and Appendix A	Remove references to Dr. Sanjeev Francis	Dr. Francis is no longer at MGH and not involved in the study

Version 2.0 Revision History

Revision Number	Release Date	Section	Change	Reason for Change
2.0	Jan 27, 2015		Added exclusion criteria	Increase number of eligible subjects and clarification
2.0	Jan 27, 2015		Added inclusion criteria	Clarification on etiology of chemotherapy-induced heart disease and time frame for enrollment
2.0	Jan 27, 2015		Added verbiage with time frame to include months	Oversight page 15 section 4, paragraph 1
2.0	Jan 27, 2015		Revised power calculation	Decrease number of required enrolled subjects
2.0	Jan 27, 2015		Changed programming definition	Clarification
2.0	Jan 27, 2015		Changed to Boston Scientific generator versus device system and components	Allow more flexible FDA-approved lead component use by site
2.0	Jan 27, 2015		Added Device Deficiency reporting requirements	Oversight

2. Protocol Synopsis

MULTICENTER AUTOMATIC DEFIBRILLATOR IMPLANTATION TRIAL – CHEMOTHERAPY-INDUCED CARDIOMYOPATHY (MADIT-CHIC)	
Objective(s)	The primary objective of this trial is to determine if CRT-D in high-risk patients with chemotherapy-induced cardiomyopathy will significantly improve the left ventricular ejection fraction (LVEF) by echocardiography within 6 months of initiating CRT without adversely affecting mortality. The secondary objectives are to: 1) determine the effects of CRT on all-cause mortality; 2) determine by echocardiographic evaluation at 6 months if CRT therapy improves left ventricular volume at end systole (LVESV) and end diastole (LVEDV). The tertiary objectives are to evaluate CRT therapy at 6 months on: 1) NYHA functional class when compared to baseline; and 2) change in atrial size. In addition, during the 6-month clinical course, the effects of CRT on the frequency of heart failure with the end point as inpatient hospitalization for heart failure will be evaluated in the study population.
Indication(s) for Use	Boston Scientific CRT-D devices are intended to provide resynchronization therapy for patients with overt or subclinical heart failure and compromised LV function.
Device	Subjects registered in this trial must be implanted with a Boston Scientific commercially available CRT-D generator, with the device implant procedure performed by a qualified physician per standard of care and indication guidelines. All device components used in the MADIT-CHIC trial must be market-released products and be implanted using standard operating procedures.
Study Design	The study is a non-randomized, prospective observational study in 30 subjects with chemotherapy-induced cardiomyopathy who meet guideline-based indications for CRT-D. Subjects will be followed for 6 months post-implant, and clinical data related to their functional status and echocardiographic measures of reverse remodeling will be collected at the 6-month follow-up visit. Day zero is date of implant. After the 6-month visit, each registered subject will then have clinical CRT-D and cardiac follow-up per device standard of care guidelines, but will no longer be registered in the research study and require study data collection.

MULTICENTER AUTOMATIC DEFIBRILLATOR IMPLANTATION TRIAL – CHEMOTHERAPY-INDUCED CARDIOMYOPATHY (MADIT-CHIC)	
Planned Number of Subjects	30 registered subjects
Planned Number of Centers / Countries	The study will be initially conducted at approximately 10-15 US centers. If necessary, more sites may be invited to participate to meet the 30 subject registration goal.
Primary Endpoint	Significant improvement in echo-determined LVEF between baseline and 6 months in high-risk cardiac patients with chemotherapy-induced cardiomyopathy.
Method of Assigning Subjects to Treatment	Study enrollment and registration using the electronic data capture system that is available 24/7 to all designated enrolling center personnel.
Follow-up Schedule	Following registration, subjects will have scheduled visit follow-ups at 3 (phone) and 6-month (clinic) intervals following device implant. Relevant event history, cardiac medications, physical assessment, device event and programming status, and adverse events will be collected at each clinic follow-up visit. Events will be collected at the 3-month phone follow-up. At the 6-month visit, a repeat echocardiogram will be obtained. Subjects will be followed through the 6 month visit. The study will end when the last registered subject reaches the 6 month visit. Once the study is finished, subjects will continue to be followed per local CRT-D standard of care guidelines.
Study Duration	The estimated duration of the trial is 2.25 years, and that includes 6 months for start-up to get the enrolling centers on board, 12 months for subject registration, 6 months for follow-up of last registered subject, and 3 months for close-out and data analyses.
Required Medication Therapy	All study subjects will need to be on guideline-directed stable optimal pharmacologic therapy for the cardiac condition, consisting of loop diuretics, aldosterone antagonists, beta blockers and/or ACE/ARB as tolerated, unless contraindicated, with stable doses for one month prior to study registration. Medications may be prescribed and adjusted as required for cardiac condition.

MULTICENTER AUTOMATIC DEFIBRILLATOR IMPLANTATION TRIAL – CHEMOTHERAPY-INDUCED CARDIOMYOPATHY (MADIT-CHIC)	
Key Inclusion Criteria	• Subject is age 18 (or of legal age to give informed consent specific to state and national law) up to 80 years of age • Male or female • Subject who was without clinical heart failure at initiation of chemotherapy/radiation-induced treatment for an underlying malignancy, but developed clinical heart failure (cardiomyopathy: reduced LVEF with a LBBB-type of conduction disturbance; see next inclusion item) 6 months or more after initiation of the chemotherapy without other evident cause of the cardiomyopathy. • Subject eligible for implantation of a CRT-D device according to one of the following options in currently available guidelines: *Class 1:* o *LVEF ≤ 35% AND* o *Sinus rhythm AND* o *LBBB with a QRS duration ≥150 ms AND* o *NYHA class II, III or ambulatory IV symptoms on guideline-directed medical therapy* *Class 2a1:* o *LVEF ≤ 35% AND* o *Sinus rhythm AND* o *LBBB with a QRS duration 120-149ms AND* o *NYHA class II, III or ambulatory IV symptoms on guideline-directed medical therapy* *Class 2a2:* o *LVEF ≤ 35% AND* o *Sinus rhythm AND* o *Non- LBBB with a QRS duration ≥150 ms AND* o *NYHA III or ambulatory IV symptoms on guideline-directed medical therapy* • Subject on stable* optimal pharmacologic therapy for the cardiac condition that is guideline-based and may include one or more of the following medications: Loop diuretics (e.g., furosemide, bumetanide, torsemide) unless the subject is not indicated, is contraindicated, or is intolerant of loop diuretics; Angiotensin converting enzyme (ACE) inhibitors and/or angiotensin receptor blocker (ARB) unless the subject failed, is not indicated, or is contraindicated for these therapies; Aldosterone antagonists unless the subject is not indicated, or is intolerant of aldosterone antagonists; Beta-blockers unless the subject is not indicated, contraindicated, or is intolerant of beta-blockers. The choice of selective or non-selective beta-blockers use is left to the Investigator's discretion * For purposes of the study, "stable" is defined as subject prescribed

MULTICENTER AUTOMATIC DEFIBRILLATOR IMPLANTATION TRIAL – CHEMOTHERAPY-INDUCED CARDIOMYOPATHY (MADIT-CHIC)	
Key Inclusion Criteria *(Continued)*	set medication doses for at least one month prior to study registration, unless contraindicated or not tolerated. Medications may be prescribed and adjusted as required for cardiac condition during the study.

Key Exclusion Criteria at Time of Consent	• Subject with a currently implanted pacemaker or ICD device • Previous implant with a CRT/CRT-D device • Subject cardiac condition not presumed to be caused by chemotherapy • Documented symptomatic or hemodynamically unstable ventricular tachyarrhythmia • Subjects on active chemotherapy (must be at least 6 calendar months after last chemotherapy treatment) • Subject with permanent or chronic AF, or cardioversion for AF within the past 3 calendar months before consent date • Subject with structural heart disease such as congenital heart disease, valvular heart disease, e.g., rheumatic valvular heart disease, amyloid heart disease, etc. • Subject with coronary artery bypass graft surgery or percutaneous coronary intervention within the past 3 calendar months before consent date • Subject with enzyme positive myocardial infarction within the past 3 calendar months prior to consent date • Unstable angina requiring hospitalization, with diagnostic work up and intervention within the past 3 months prior to consent date • Subject with angiographic evidence of coronary disease who are candidates for coronary revascularization and are likely to undergo coronary artery bypass graft surgery or percutaneous coronary intervention in the foreseeable future • Subject in Class IV and expected to undergo transplant within study duration • Current or past history of drug addiction or abuse that caused cardiomyopathy • Subject who is pregnant or plans 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 consent date • Subject with recent CVA or TIA within the previous 3 months prior to consent date.

MULTICENTER AUTOMATIC DEFIBRILLATOR IMPLANTATION TRIAL – CHEMOTHERAPY-INDUCED CARDIOMYOPATHY (MADIT-CHIC)	
Key Exclusion Criteria at Time of Consent *(Continued)*	• Subject with presence of any disease, other than the subject's cardiac or cancer disease, associated with a reduced likelihood of survival for the duration of the trial, e.g., uremia, liver failure, active malignant disease, etc. • Subject participating in any other clinical trial • Subject unwilling or unable to cooperate with the protocol • Subject who lives at such a distance from the clinic that travel for follow-up visits would be unusually difficult • Subject who does not anticipate being a resident of the area for the scheduled duration of the trial • Subject unwilling to sign the consent for participation • Subject whose physician does not allow participation

Statistical Methods	
Primary Statistical Hypothesis	CRT-D is associated with a mean improvement in LVEF from baseline to six months.
Statistical Test Method and Sample Size Parameters	Per description in Section 12.2

3. Table of Contents

2.1. *Table of Figures*

2.2. *Table of Tables*

4. Introduction

With the advent of new therapies and an increasing number of long-term cancer survivors, the incidence and consequently the interest in chemotherapy-induced cardiomyopathy (CHIC) have been increasing. CHIC is a dose-dependent cardiomyopathy and presents as congestive heart failure several months to years after the administration of chemotherapy.[1] Among the several chemotherapeutic agents that cause cardiomyopathy, the most frequently incriminated in the pathogenesis of CHIC are anthracyclines.

Greater than one-half of the patients exposed to just this class of drugs will show evidence of cardiac dysfunction, with 5% presenting with overt symptomatic heart failure. The overall incidence of CHIC is significantly underestimated as within the US alone, greater than 60,000 patients receive just anthracyclines every year.[2] Despite this, there is little data on their response to conventional heart failure therapy. There is some preliminary evidence from two small, retrospective case-series suggesting that patients with CHIC and evidence of conduction tissue disease (i.e. a wide QRS duration) may significantly benefit from cardiac resynchronization therapy (CRT).[3,4]

Our hypothesis is based on the assumption that CHIC is pathophysiologically similar to other forms of non-ischemic cardiomyopathy and CRT may serve to positively alter the natural history and improve the clinical trajectory and outcome in this cohort of patients as it has done in other forms of cardiomyopathy.[5] Our study aims to assess the impact of cardiac resynchronization therapy on clinical response and left ventricular reverse remodeling in patients with chemotherapy-induced cardiomyopathy.

5. Device Description

Subjects registered in this trial will be implanted with a Boston Scientific commercially available CRT-D generator within the specific countries where enrolling centers are located, with the device implant procedure performed by a qualified physician per local standard of care guidelines. All device components used in the MADIT-CHIC trial must be market-released products and must be implanted using standard operating procedures.

6. Objectives

The primary objective of this trial is to determine if CRT-D in high-risk patients with chemotherapy-induced cardiomyopathy will significantly improve the left ventricular ejection fraction (LVEF) by echocardiography within 6 months of initiating CRT without adversely affecting mortality. The study population will consist of patients with approved guideline-based indication for CRT-D. All subjects will receive CRT-D device with resynchronization therapy and potential for defibrillation as required.

The secondary objectives are to: 1) determine the effects of CRT on all-cause mortality; 2) determine by echocardiographic evaluation at 6 months if CRT therapy improves left ventricular volume at end systole (LVESV) and end diastole (LVEDV).

The tertiary objectives are to evaluate CRT therapy at 6 months on: 1) NYHA functional class when compared to baseline; and 2) change in atrial size. In addition, during the 6-

month clinical course, the effects of CRT on the frequency of heart failure with the end point an inpatient hospitalization with augmented treatment for heart failure will be evaluated in the study population.

7. Endpoints

7.1 *Echocardiography Endpoints*

Echocardiograms will be performed by the enrolling sites at baseline before implant and 6 months following device implant. All images will be analysed centrally by an echocardiography core lab. The core lab will measure the left ventricular ejection fraction (LVEF), which is the primary endpoint of the trial, as well as the atrial size and the left ventricular volumes (LVESV and LVEDV), which are part of the secondary objectives. For more detail on the core lab, please refer to section 13.3.1.

7.2 *Recurrent Heart Failure*

Heart failure events will be documented by clinical data from the investigative center record in English, the official language of the study. These events will be documented in the electronic case report form as adverse events. A heart failure event will be defined as when the subject has an inpatient admission for congestive heart failure.

7.3 *Subject Death*

The mortality event case report form will be completed in the electronic data capture system when reporting a subject death. Mortality events will be documented by clinical data from the investigative center record in English, the official language of the study. Collected death information includes details about cause of death, device functioning, and other relevant details. The device must be interrogated (if possible) and the case report form listed above must be completed and transferred to the electronic data capture website as soon as possible after notification to the center. Every attempt must be made to return all Boston Scientific CRM system components to sponsor.

A subject death during the study must be reported to the CDC as soon as possible and in conjunction with adverse event reporting requirements. The center's IRB/ERC must be notified of any deaths in accordance with that center's IRB/ERC policies and procedures, even if supporting documents are not yet available. Documentation of endpoints will utilize appropriate sources of information.

Notification of death shall include a detailed narrative of the pertinent events in addition to the required device status forms. The death narrative must be submitted to the CDC as soon as possible and must include all of the following, if available:

- Date and time of death
- Rhythm at the time of death, if known (include any available documentation)
- Whether or not the death was witnessed
- Any other circumstances surrounding the death

- Whether the death was device or procedure related
- Approximate time interval from the initiating event to death
- Place death occurred
- Device status/activity at the time of death
- Immediate cause of death

If any of the above information is not available, this must be stated in the death narrative. A copy of the death records and an autopsy report (if performed) must also be sent to the CDC as soon as possible with English translation provided as required by a certified language translator. The pulse generator must be interrogated, all data saved to the subject data disk, and the device returned to BSC if possible. An Out-of-Service data form must be submitted for all out-of-service devices. If spontaneous events have occurred and been recorded by the device since the last follow-up, an additional follow-up form must be completed with this additional data. In the event that the device is not explanted, the same procedure must be followed to retrieve the data and turn off the device.

8. Design

This is a prospective, non-randomized, multicenter investigation conducted at US centers.

8.1. *Scale and Duration*

The plan is to register approximately 30 subjects in approximately 10-15 enrolling centers in one year. We anticipate a registration rate averaging 0.21 subjects/center/month achieving 30 registered subjects in 12 months (0.21 x 12cntrs x 12mo = 30). Device implantation will be carried out within 14 days of registration. The ongoing recruitment rate will be closely monitored. If the monthly recruitment rate is meaningfully less than the projected average of 0.21 subjects/center/month, then new centers may be added to enhance registration upon MADIT-CHIC Executive Committee approval.

The estimated duration of the trial is 2.25 years, and that includes 6 months for start-up to get the enrolling centers on board, 12 months for subject registration, 6 months for follow-up of last registered subject, and 3 months for close-out and data analyses.

Consented (enrolled) subjects will be registered formally in the study using an electronic system and undergo CRT-D device implant. Following device implant, registered subjects will have scheduled clinical follow-ups at 3 (phone) and 6 (in-clinic) months. After the 6-month visit, each registered subject will then have clinical CRT-D and cardiac follow-up per device standard of care guidelines, but will no longer participate in the research study and require study data collection. The subject must not be withdrawn after reprogramming or device explant or device inactivation and must be followed per protocol through the 6 month protocol-required clinic visit unless withdrawal requested by the physician or subject.

8.2. *Treatment Assignment*

There is no treatment assignment since all registered subjects will be implanted with a CRT-D device.

8.2.1. Treatment and Control

All registered subjects will be implanted with a Boston Scientific CRT-D generator that is commercially available (current or future generations) within the US.

8.3. *Justification for the Study Design*

The study design is a classical, non-randomized trial that minimizes bias, and this design is optimal for this trial.

9. Subject Selection

9.1. *Study Population and Eligibility*

Enrollment
Prior to formal registration into the trial as a study participant, the subject's most recent ejection fraction, and the current 12-lead ECG will be examined if possible to determine if the subject initially meets the study inclusion/exclusion criteria. Subjects who meet all available entry criteria and agree to participate in the study will be asked to sign a written informed consent that has been approved by the investigational center's Institutional Review Board (IRB) /Ethics Review Committee (ERC). All subjects who give written informed consent are considered enrolled in the study.

9.2. *Inclusion Criteria*

Subjects who meet all of the following criteria (see Table 9.2-1) will be given consideration for inclusion in this clinical investigation, provided no exclusion criterion (see Table 9.3-1) is met.

Table 9.2-1: Inclusion Criteria

Clinical Inclusion Criteria	• Subject is age 18 (or of legal age to give informed consent specific to state and national law) up to 80 years of age • Male or female • Subject who was without clinical heart failure at initiation of chemotherapy/radiation-induced treatment for an underlying malignancy, but developed clinical heart failure (cardiomyopathy: reduced LVEF with a LBBB-type of conduction disturbance; see next inclusion item) 6 months or more after initiation of the chemotherapy without other evident cause of the cardiomyopathy. • Subject eligible for implantation of a CRT-D device according to one of the following options in currently available guidelines: *Class 1:* o *LVEF ≤ 35% AND* o *Sinus rhythm AND* o *LBBB with a QRS duration ≥150 ms AND* o *NYHA class II, III or ambulatory IV symptoms on guideline-directed medical therapy* *Class 2a1:* o *LVEF ≤ 35% AND* o *Sinus rhythm AND* o *LBBB with a QRS duration 120-149ms AND* o *NYHA class II, III or ambulatory IV symptoms on guideline-directed medical therapy* *Class 2a2:* o *LVEF ≤ 35% AND* o *Sinus rhythm AND* o *Non- LBBB with a QRS duration ≥150 ms AND* o *NYHA III or ambulatory IV symptoms on guideline-directed medical therapy* • Subject on stable* optimal pharmacologic therapy for the cardiac condition that is guideline-based and may include one or more of the following medications: Loop diuretics (e.g., furosemide, bumetanide, torsemide) unless the subject is not indicated, is contraindicated, or is intolerant of loop diuretics; Angiotensin converting enzyme (ACE) inhibitors and/or angiotensin receptor blocker (ARB) unless the subject failed, is not indicated, or is contraindicated for these therapies; Aldosterone antagonists unless the subject is not indicated, or is intolerant of aldosterone antagonists; Beta-blockers unless the subject is not indicated, contraindicated, or is intolerant of beta-blockers. The choice of selective or non-selective beta-blockers use is left to the Investigator's discretion * For purposes of the study, "stable" is defined as subject prescribed set medication doses for at least one month prior to study registration, unless contraindicated or not tolerated. Medications may be prescribed and adjusted as required for cardiac condition during the study.

9.3. *Exclusion Criteria*

Subjects who meet any one of the following criteria (Table 9-3.1) will be excluded from this clinical study.

Table 9-3.1: Exclusion Criteria

Clinical Exclusion Criteria	• Subject with a currently implanted pacemaker or ICD device • Previous implant with a CRT/CRT-D device • Subject cardiac condition not presumed to be caused by chemotherapy • Documented symptomatic or hemodynamically unstable ventricular tachyarrhythmia • Subjects on active chemotherapy (must be at least 6 calendar months after last chemotherapy treatment) . • Subject with permanent or chronic AF, or cardioversion for AF within the past 3 calendar months before consent date • Subject with structural heart disease such as congenital heart disease, valvular heart disease, e.g., rheumatic valvular heart disease, amyloid heart disease, etc. • Subject with coronary artery bypass graft surgery or percutaneous coronary intervention within the past 3 calendar months before consent date • Subject with enzyme positive myocardial infarction within the past 3 calendar months prior to consent date • Unstable angina requiring hospitalization, with diagnostic work up and intervention within the past 3 months prior to consent date • Subject with angiographic evidence of coronary disease who are candidates for coronary revascularization and are likely to undergo coronary artery bypass graft surgery or percutaneous coronary intervention in the foreseeable future • Subject in Class IV and expected to undergo transplant within study duration • Current or past history of drug addiction or abuse that caused cardiomyopathy • Subject who is pregnant or plans 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 consent date • Subject with recent CVA or TIA within the previous 3 months prior to consent date. • Subject with presence of any disease, other than the subject's cardiac or cancer disease, associated with a reduced likelihood of survival for the duration of the trial, e.g., uremia, liver failure, active malignant disease, etc. • Subject participating in any other clinical trial • Subject unwilling or unable to cooperate with the protocol • Subject who lives at such a distance from the clinic that travel for follow-up visits would be unusually difficult • Subject who does not anticipate being a resident of the area for the scheduled duration of the trial • Subject unwilling to sign the consent for participation • Subject whose physician does not allow participation

Abbreviations: AF = atrial fibrillation;

10. Subject Accountability

10.1. *Point of Enrollment*

The subject is considered enrolled in the study at the time the consent form is signed. No study related testing, procedures, etc. can take place until the informed consent is signed.

Study personnel must explain to the subject that even if the subject agrees to participate in the study and signed the study ICF, more detailed record review and test results required to determine study eligibility may demonstrate that the subject is not a suitable candidate for the study.

Study eligibility will be confirmed prior to formal study registration when a unique subject registration ID will be assigned to the subject.

10.2. *Withdrawal*

All subjects who sign an informed consent in this clinical study (including those withdrawn from the clinical study or lost to follow-up) shall be accounted for and documented in the specified case report form. If a subject withdraws from the clinical investigation, the reason(s) shall be reported in the specified case report form. Reasons could include but not limited to subject did not meet inclusion/exclusion criteria, consent withdrawal, lost to follow-up or death. Lost to follow-up subjects must have documented attempts to contact them prior to declaration of withdrawal. All open adverse events must be closed or documented as chronic as of the date of subject withdrawal. Data collected up to the point of subject withdrawal may be used in the study analysis. Withdrawn subjects will not be replaced. While study withdrawal is discouraged, subjects may withdraw from the study at any time, with or without reason, without prejudice to further treatment. Subjects will remain with the existing device components implanted at the time of withdrawal.

10.3. *Subject Status and Classification*

All subjects are required to read, sign and date an Informed Consent prior to any study test and implant procedures. All subjects who sign an Informed Consent Document will be considered enrolled in the study. All subjects who are registered will be included in the primary endpoint analysis based on the intention-to-treat principle. A deviation form will be required for all statuses listed below if the subject has been registered except implant and withdrawal. Adverse events will be collected on all consented subjects regardless of registration status up to the time of study withdrawal.

Consent-ineligible refers to a subject who is not registered but who has signed the consent and does not meet study eligibility criteria.

Intent refers to a subject who has signed the consent, is registered, but then does not undergo an implant. The original Informed Consent Document and screening documentation for intent subjects must be maintained in the Center's administrative files. For example, if a subject signs the informed consent form, completes all baseline testing, is registered and then refuses implant, they would be handled as intent.

An *attempt* refers to a subject who has been registered and has had anesthesia administered in preparation for the surgical implant procedure, but does not receive a device. These subjects are followed in accordance with the follow-up schedule. An example of an attempt subject is a subject in whom the physician is unable to place leads and stops the procedure before implanting a device.

An *implant* refers to a subject who is registered and who is successfully implanted or tested with the system per the study protocol. These subjects are followed in accordance with the follow-up schedule and included in all analyses of safety and performance.

A *withdrawal* refers to a subject who has been consented and is determined to be inactive in the study due to physician discretion, subject choice, lost to follow-up, or subject death. Final status information will be included on all registered subjects as available per the Informed Consent document. If a subject is determined to be ineligible or refuses study participation after meeting eligibility criteria and signing consent without undergoing registration, the subject is formally withdrawn from the study. Subjects who have not signed consent do not need to be formally withdrawn.

10.4. *Registration Controls*

There is no pre-specified limit for number of subjects who can be enrolled (consented). The number of registered subjects will be strictly limited to 30 subjects. Enrolling centers will be sent communication when the number of registered subjects reaches 25. When the number of subjects reaches 25, registration will only be carried out manually with direct contact with center and the Coordination and Data Center at the University of Rochester. All processes related to registration control will be communicated clearly to the enrolling centers. There are no pre-specified ratios of male and female registered subjects.

11. Study Methods

11.1. *Screening*

Prior to study registration, the subject's medical record, laboratory results, the ejection fraction, and 12-lead ECG obtained within 1 calendar year prior to screen date will be examined to determine if the subject meets the study inclusion/exclusion criteria.

11.2. *Enrollment/Informed Consent*

Subjects who initially meet all the entry criteria per available standard of care testing and record review and agree to participate in the study will be asked to sign a written informed consent that has been approved by the investigational center's Institutional Review Board (IRB) /Ethics Review Committee (ERC). All subjects who give written informed consent are considered enrolled in the study. No study related testing, procedures, etc. can take place until the informed consent is signed.

If full record review not permitted per local regulations prior to study consent signature, then study consent signature may be obtained from the subject with subsequent complete

review of record and study testing to determine if study eligibility criteria are fully met. Study personnel must explain to the subject that even if the subject agrees to participate in the study and signed the study ICF, test results required to determine study eligibility may demonstrate that the subject is not a suitable candidate for the study.

No post-consent follow-up is required for subjects who do not meet study eligibility criteria for registration. All subjects who sign consent must be withdrawn from the study if subject is not registered.

After initial study eligibility is confirmed using an echo and 12-lead ECG obtained within the past calendar year prior to screening date, then a post-consent standard 12 lead ECG and echocardiogram obtained using the study instruction manual for echocardiogram acquisition must be done to respectively confirm that the QRS and EF value meet study eligibility criteria and eligibility for a CRT-D implant. These tests are usually done per standard of care at the time of device implant. If the subject meets eligibility criteria and is registered, then these test results must be sent to the appropriate core laboratory following registration.

11.3. *Registration*

Registration assignment will be made by using the electronic data capture system that is available 24/7 to all PI-designated enrolling center personnel. Subjects will be registered within 1 calendar month following consent. Study eligibility and eligibility for a CRT-D implant must be confirmed prior to registration.

11.4. *Implant*

Subjects must have a commercially-available or future generation Boston Scientific CRT-D generator implanted by a qualified physician within 14 days of registration. All devices in MADIT-CHIC must be implanted per physician and/or center standard operating procedure. It is recommended that the left ventricular lead be placed in a lateral or posterolateral coronary vein, but ultimately the choice of left ventricular lead location is left to the discretion of the implanting physician. Following implant, the device must be programmed as pre-specified in Section 11.5. Subjects will be followed in accordance with the follow-up schedule.

11.5. *Device Programming*

Standard atrial synchronized-ventricular paced resynchronization therapy will be utilized. Should the subject develop atrial fibrillation during the course of the study, pharmacologic therapy will be utilized to control the ventricular response rate to achieve $\geq$90% ventricular pacing. On the basis of the recent MADIT-Reduce Inappropriate Therapy (MADIT-RIT) trial findings[6], the CRT-D device will be programmed to deliver ATP/shock therapy at $\geq$200 beats per minute.

General programming features for implanted biventricular devices include:

- ATP values at default (81% coupling interval and 81% cycle length)
- DFT at implanting physician's discretion
- Backup pacing: DDI with 300ms for paced AV

Programming Requirements

Parameters	Programming
Ventricular Tachy Therapy Zones	2
Zone 1 (VT) Rate Cutoff	170 bpm
Zone 1 (VT) Zone Rate Therapy	Monitor Only
Zone 2 (VF) Zone Rate Cutoff	200 bpm
Zone 2 (VF) Zone Duration	2.5 seconds
Zone 2 (VF) Zone Therapy	Shock + Quick Convert ATP

11.6. *Baseline*

11.6.1 Baseline (before implant)

- Demographics
- Cancer treatment medications
- Cardiac medications
- Physical assessment
- Medical and cardiac event history
- Functional Status (NYHA)
- 12-lead ECG (send to core lab)
- Echocardiogram per study protocol (send to core lab)
- Adverse events
- Deviations

11.6.2 Baseline (after implant)

- Device data (implant, device events, programming)
- Adverse events
- Deviations

11.7 *Clinic Follow-up Visits*

All follow-up visits will use the device implant date as the starting point for determining the timing of all follow-up visits. An in-clinic visit is required at the 6 month interval for all registered subjects. A phone visit will be done at 3 months to capture any events.

A follow-up schedule that identifies the date intervals during which a subject must be contacted will be provided to the enrolling center for each subject following study registration and initial device implant. Every effort will be made to ensure compliance with this schedule.

At the clinic visit, a clinical evaluation must be carried out. In addition, all devices will undergo device testing according to agreed-upon guidelines. During all office/clinic visits, the device will be interrogated and the information will be documented on the follow-up form. At each clinical center, the routine follow-up interval history and examination will be used to identify possible adverse reactions to the implanted device. If a visit is missed for any reason, all major events as defined below will be collected at the subsequent visit.

The following data is required at the phone visit:

- Functional Status (NYHA)
- Adverse Events including heart failure events, emergency department visits, hospitalizations, and deaths
- Device events
- Deviations

The following data is required at the office/clinic visit:

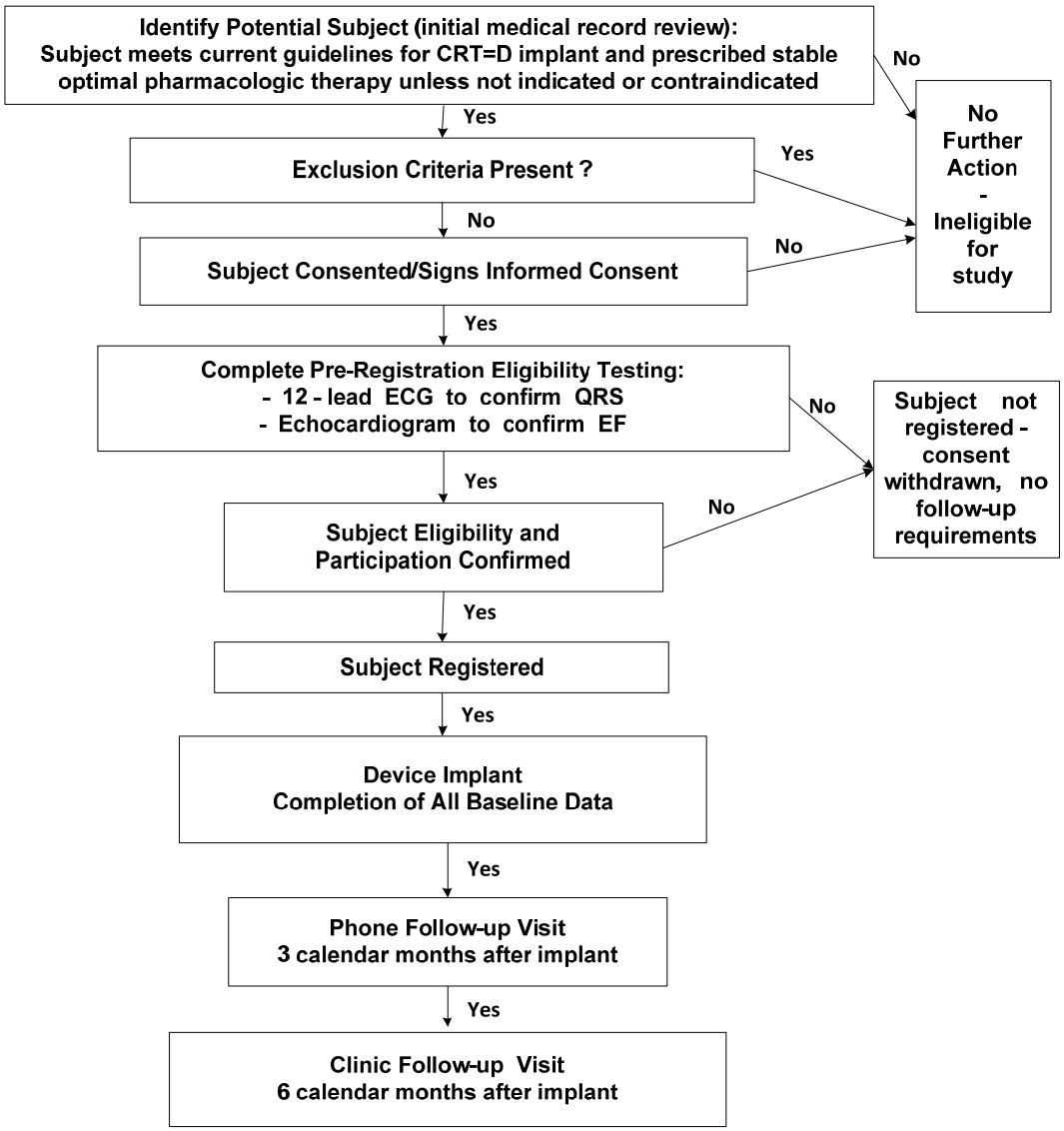
- Physical as directed on the follow-up case report form
- Functional Status (NYHA)
- Adverse Events including heart failure events, emergency department visits, hospitalizations, and deaths
- Echocardiogram
- Cardiac medications
- Device programming
- Changes in any device components such as explant, implant or revisions
- Device events
- Deviations

11.8 *Data Collection*

The figure indicating study data flow is shown in Figure 11.8-1.

The figure indicating data collection is shown in Figure 11.8-2.

Figure 11.8-1: Study Data Flow



The data collection schedule is shown in Table 11.8-1.

Table 11.8-1: Data Collection Schedule

Reportable Data Items	Consent/ Before Registration	Registration and Implant	Phone Visit 3 calendar months after implant date	Clinic Visit 6 calendar months after implant date
Timeframe	Consent obtained. Confirm study eligibility criteria are met before registration including all ECG and Echo eligibility required to confirm CRT-D implant eligibility requirement.	Registration to occur within 1 calendar month after date consent obtained. Implant to occur within 14 days after registration date.	3 months (+/- 30 days)	6 months (+/- 30 days)
Inclusion/Exclusion	√	√ (recheck prior to registration)		
Informed Consent including signature date	√			
ECG (Required)	√			
Echo (Required)	√ (after ECG and all inclusion and exclusion parameters met)			√ (6 month visit only)
Cancer-Treatment Medications		√		
Cardiac Medications	√			√
Demographics including gender, race and ethnicity		√		
Medical History		√		
Cardiac Events and Procedures		√	√	√
Device Implant and Components		√	√	√
Device Programming		√		
Device Interrogation/ Programming Status		√		√
Physical Assessment including weight, height and NYHA class		√	NYHA Class	√
Adverse Events		√	√	√
Protocol Deviations		√	√	√

11.9 *Study Completion*

The DSMB may recommend termination of the study at any time should prospective ethical or safety guidelines not be met. The active trial will be completed after every subject has completed the 6 month visit. All 6 month follow-up data will be collected via an in-clinic visit. No follow-up data will be collected after the subject's 6 month visit.

11.10 *Source Documents*

Data collection requirements are summarized in Table 11.8-1. Printed, optical or electronic document containing source data shall be used. Examples include hospital records, laboratory notes, device accountability records, radiographs, records kept at the investigation site, and at the laboratories involved in the clinical study.

Where copies of the original source document as well as printouts of original electronic source documents are retained, these shall be signed and dated by a member of the investigation center team with a statement that it is a true reproduction of the original source document.

12. Statistical Considerations

12.1 *Endpoints*

12.1.1 Primary Endpoint

The primary endpoint will be the change in left ventricular ejection fraction (LVEF) from baseline to six months.

12.1.1.1 Hypotheses

The primary hypothesis is that CRT-D is associated with a mean improvement in LVEF from baseline to six months.

12.1.1.2 Sample Size

In this clinical trial, 30 registered subjects will receive CRT-D. This sample size should be sufficient for detecting clinically meaningful effects of CRT on LVEF over 6 months, allowing for an anticipated 20% dropout rate during this time period.

12.1.1.3 Statistical Methods

The analysis will focus on the improvement in LVEF from baseline to six months for each patient. This primary outcome variable will be regressed on baseline LVEF, center, and disease etiology using an analysis of covariance (ANCOVA) model. If the baseline LVEF term in the model has a p-value > 0.2, it will be omitted from the model, thereby concluding that the change from baseline is unaffected by the corresponding baseline value.

The underlying assumptions of the ANCOVA model will be thoroughly checked (normality, homogeneity of variances, etc.), and remedial measures (e.g. transformations) will be carried out if serious violations of these assumptions are detected. Data from the MADIT-CRT trial suggest that the model assumptions should be reasonable for the primary outcome variable.

According to similar analyses in 749 MADIT-CRT patients, but comparing one-year LVEF with baseline, the standard deviation (SD) of the improvement in LVEF was approximately 5 percentage points. Using this estimate of SD, the following total sample sizes (N) were obtained based on a 5% two-sided significance level and 80% power to detect various values of mean improvement from baseline to six months in LVEF for CRT using a t-test.

Treatment Effect (mean improvement in LVEF)	N with 10% dropout	N with 20% dropout	N with 30% dropout
1	**222**	**249**	**285**
2	**58**	**65**	**75**
3	**27**	**30**	**35**
5	**12**	**13**	**15**
8	**7**	**8**	**9**

This table shows that 80% power can be attained with 65-75 enrolled patients, assuming a dropout rate of 20-30% (i.e. complete LVEF data on 52 patients), to detect effects as small as 2 percentage points. Effects of 5 or more points can be detected with 80% power using 15 or fewer patients.

The primary analysis will be carried out according to the intention-to-treat principle. All subjects registered in the study with complete data on the primary endpoint will be included in the primary analysis.

12.1.2 Efficacy Endpoints

The secondary and tertiary endpoints include:

1. All-cause mortality.
2. Recurrent heart failure
3. Changes in LVESV and LVEDV between baseline and six months.
4. Change in NYHA functional class between baseline and six months.
5. Change in left atrial size between baseline and six months.

12.1.2.1 Hypotheses

The hypotheses associated with the secondary and tertiary endpoints listed in section 2.1.2 are as follows.

1. CRT-D reduces the risk of all-cause mortality
2. CRT-D reduces the risk of recurrent heart failure events
3. CRT-D is associated with a mean improvement in LVESV and on LVEDV from baseline to six months
4. CRT-D is associated with improvement in NYHA functional class from baseline to six months with change over time in NYHA functional class categorized as *lower*, *same*, or *higher*.
5. CRT-D reduces left atrial size.

12.1.2.2 Sample Size

The sample size for this clinical trial was determined based on the power to detect minimal clinically meaningful effects on LVEF over six months (see section 12.1.1.2).

12.1.2.3 Statistical Methods

Detailed statistical methods for the secondary endpoints will be presented in a Statistical Analysis Plan (SAP) prior to the primary endpoint analysis.

12.2 *General Statistical Methods*

12.2.1 Analysis Sets

All analyses will be carried out according to the intention-to-treat principle. All subjects registered in the study will be included in the analysis.

12.2.2 Control of Systematic Error/Bias

Selection of subjects will be made from the Investigator's usual patient load. All patients meeting the eligibility criteria and having signed the ICF will be eligible for registration in the study.

12.2.3 Number of Subjects per Investigative Site

No minimum or maximum number of subjects per Investigative Site has been established for this trial.

12.2.4 Interim Analyses

No formal interim analyses are planned for the purpose of stopping this study early for declaring effectiveness or for futility. Handling of drop-outs and missing data will depend on their frequency and the nature of the outcome measure. The distribution of prognostic factors between subjects with and without data may be examined. Detailed statistical methods will be presented in the SAP prior to the primary endpoint analysis.

12.2.5 Subgroup Analyses

Interactions between disease etiology and important baseline variables such as sex and race/ethnicity will be investigated by including the appropriate interaction term in the statistical model and testing for its significance. Detailed statistical methods, along with a list of potential subgroups, will be presented in the SAP prior to the primary endpoint analysis.

12.2.6 Justification of Pooling

Tests for interactions will be used to evaluate treatment differences between subgroups. Registration effects for centers will be used to justify pooling data across investigational sites. Detailed statistical methods will be presented in the SAP prior to the primary endpoint analysis.

12.2.7 Multivariable Analyses

Multivariate models will be constructed using the method of best subsets to select important covariates. Specific details will be presented in the SAP prior to the primary endpoint analysis.

12.2.8 Other Analyses

Other analyses will be presented in the SAP prior to the primary endpoint analysis.

12.2.9 Changes to Planned Analyses

Any changes to the planned statistical analyses made prior to the primary endpoint analysis will be documented in an amended SAP approved prior to the primary endpoint analysis. Changes from the planned statistical methods after the primary endpoint analysis will be documented in the statistical files.

13. Data Management

13.1 *Data Collection, Processing, and Review*

Subject data will be recorded in a limited access secure electronic data capture (EDC) system. Consistent terminology per the study protocol will be used in the study Case Report Forms to be completed in the EDC system.

The clinical database will reside on a production server hosted by University of Rochester Coordination and Data Center using the Omnicomm TrialMaster system. All changes made to the clinical data will be captured in an electronic audit trail and available for review by Boston Scientific Corporation (BSC) or its representative. The associated TrialMaster software and database have been designed to meet regulatory compliance for deployment as part of a validated system compliant with laws and regulations applicable to the conduct of clinical studies pertaining to the use of electronic records and signatures. Database backups are performed regularly.

The Investigator provides his/her electronic signature on the appropriate electronic case report forms (eCRFs) in compliance with local regulations. A written signature on printouts of the eCRFs must also be provided if required by local regulation.

Visual and/or electronic data review will be performed to identify possible data discrepancies. Manual and/or automatic queries will be created in the EDC system and will be issued to the site for appropriate response. Site staff will be responsible for resolving all queries in the database.

13.2. *Data Retention*

The Investigator or Investigational site will maintain, at the investigative site, in original format all essential study documents and source documentation that support the data collected on the study subjects in compliance with ICH/GCP guidelines. Documents must be retained for 2 years since the formal discontinuation of the clinical trial. These

documents will be retained for a longer period of time by agreement with the University of Rochester or in compliance with other local regulations. The Investigator will take measures to ensure that these essential documents are not accidentally damaged or destroyed. If for any reason the Investigator withdraws responsibility for maintaining these essential documents, custody must be transferred to an individual who will assume responsibility and University of Rochester must receive written notification of this custodial change.

13.3. *Core Laboratories*

13.3.1 Echocardiogram Core Laboratory

Echocardiograms will be analyzed from baseline and 6 months (6-month study visit) for all registered subjects. A subset of a standard echocardiographic two-dimensional and Doppler examination will be performed at each time point. A detailed echo analysis protocol will be finalized and available to centers prior to the start of the study.

The echocardiograms for the baseline and 6 month evaluations will be sent to the core laboratory for analysis. The site must retain a copy of the study for clinical and back-up purposes. Sites will not be making any measurements. The echo core laboratory will not be reporting any information to sites.

The echo core laboratory (ECL) will prepare a site instruction manual (SIM) and pocket guide designed to provide study sites information regarding:

1. The required echo views
2. Instructions for how to optimize images for obtaining high quality views, to complement sonographer training with (ECL) staff and serve as a real-time reference
3. How to send echo images to the (ECL) for analysis. This will serve as an onsite reference for study sonographers.

Each site will be asked to designate specific sonographer(s) to perform all study echocardiograms per the SIM. Following review of the SIM and any requested training, each site sonographer will be required to submit 1 sample study performed per the SIM. Studies will be scrutinized for adherence to protocol, acquisition of all required views, and image quality. Itemized direct written feedback and suggestions from the (ECL) will be provided. This is intended to address any individual equipment or operator dependent problems that may arise. Sonographers will have the opportunity to re-submit a sample protocol study per the SIM. Following submission of an adequate sample study, site sonographer will be officially certified, with written documentation. Support will also be available to each enrolling site as needed during the study. Centers will be promptly notified if a study is not performed per the SIM.

The following echocardiographic assessments will be performed:

- Left ventricular volumes will be assessed using the modified Simpson's method from the apical 4-chamber and 2-chamber views; LV ejection fraction will be calculated from LVEDV and LVESV

- LV wall thickness, and end-systolic and end-diastolic chamber dimension will be measured from the parasternal long axis view
- LA volumes at mitral valve opening will be measured from the apical four chamber and two-chamber views by means of the biplane area–length method, and corrected for body surface area.
- LA size measured during systole along the parasternal long-axis view
- Mitral inflow velocity profile: E velocity, A velocity, E/A ratio, deceleration time
- Mitral annular tissue Doppler velocity (septal and lateral): E', A', calculated E/E'
- Assessment and grading of mitral regurgitation by color flow Doppler
- Right ventricular function will be assessed as fractional area change (FAC) from end-diastolic and end-systolic areas in the apical 4-chamber view

All echocardiogram analysis data will be recorded at the Coordination and Data Center.

13.3.2 Electrocardiogram Core Laboratory

A copy of a standard 12-lead ECGs will be obtained and transmitted to the ECG core laboratory electronically at baseline. The12-lead ECG will only be identified using the study-assigned subject ID number.

The ECG will be analyzed centrally by the University of Rochester Noninvasive Electrocardiogram Core Lab and entered in the electronic database at the Coordination and Data Center. The 12-lead ECG will also be used to obtain information on the underlying rhythm (sinus, atrial fibrillation, paced rhythm, other), heart rate, QRS and QT duration, ventricular conduction disturbances, atrial and ventricular hypertrophy, and location of myocardial infarction. QRS duration automatic reading will be verified by manual/visual reading. The QT interval will be routinely measured in lead II. The JT interval will be computed by subtracting the QRS from the QT interval. Both QT and JT intervals will be corrected for heart rate using Bazett's formula. The presence of left bundle branch block, right bundle branch block, or indeterminate ventricular conduction disturbances will be identified according to the WHO Task Force criteria.

14. Amendments

If a protocol revision is necessary which affects the rights, safety or welfare of the subject or scientific integrity of the data, an amendment is required. Appropriate approvals (e.g., IRB/EC/FDA/CA) of the revised protocol must be obtained prior to implementation.

15. Deviations

An Investigator must not make any changes or deviate from this protocol, except to protect the life and physical well-being of a subject in an emergency. An investigator shall notify the CDC and the reviewing IRB/EC of any deviation from the investigational plan to protect the life or physical well-being of a subject in an emergency, and those deviations which affect the scientific integrity of the clinical investigation. Such notice shall be given as soon as possible, but no later than 5 working days after the emergency occurred, or per prevailing local requirements, if sooner than 5 working days.

All deviations from the investigational plan, with the reason for the deviation and the date of occurrence, must be documented and reported to the Coordination and Data Center at the University of Rochester using the EDC system. This data will be reported by the Coordination and Data Center to Boston Scientific, the sponsor of the study. Sites may also be required to report deviations to the IRB/EC, per local guidelines and government regulations.

Deviations will be reviewed and evaluated on an ongoing basis and, as necessary, appropriate corrective and preventive actions (including notification, center re-training, or discontinuation) will be put into place by the sponsor.

16. Device/Equipment Accountability

No investigational devices, device components or equipment will be used in this study. However, data regarding model and serial number of each device component as well as implant, explant, revision, and disposal action dates will be recorded in the EDE system for each study subject.

17. Compliance

17.1. *Statement of Compliance*

This study will be conducted in accordance with ethical principles that have their origins in the Declaration of Helsinki (see Appendix B), and pertinent individual country laws and regulations. The study shall not begin until the required approval/favorable opinion from the IRB/EC and/or regulatory authority has been obtained, if appropriate. Any additional requirements imposed by the IRB/EC or regulatory authority shall be followed, if appropriate.

17.2. *Investigator Responsibilities*

The Principal Investigator of an investigational center is responsible for ensuring that the study is conducted in accordance with the Clinical Study Agreement, the investigational plan/protocol, Medical Device Reporting Regulations, 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 Investigator Agreement and Protocol Signature page 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 clinical investigation.
- 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 sponsor in the CRFs and in all required reports.
- Record, report, and assess (seriousness and relationship to the device/procedure) every adverse event and observed device deficiency.
- Report all SAEs and device effects.
- Maintain the device accountability records and control of the device, ensuring that the device is used in accordance with this protocol and instructions/directions for use.
- Allow the sponsor to perform monitoring and auditing activities, and be accessible to the monitor and respond to questions during monitoring visits.
- Allow and support regulatory authorities and the IRB/EC when performing auditing activities.
- Ensure that informed consent is obtained in accordance with this protocol and local IRB/EC requirements.
- Provide adequate medical care to a subject during and after a subject's participation in a clinical study in the case of adverse events, as described in the Informed Consent Form (ICF).
- Inform the subject of the nature and possible cause of any adverse events experienced.
- As applicable, provide the subject with necessary instructions on proper use, handling, storage, and return of the device when it is used/operated by the subject.
- Inform the subject of any new significant findings occurring during the clinical investigation, including the need for additional medical care that may be required.
- Provide the subject with well-defined procedures for possible emergency situations related to the clinical study, and make the necessary arrangements for emergency treatment, as needed.
- Ensure that clinical medical records are clearly marked to indicate that the subject is registered in this clinical study.
- Ensure that, if appropriate, subjects registered in the clinical investigation are provided with some means of showing their participation in the clinical investigation, together with identification and compliance information for concomitant treatment measures (contact address and telephone numbers shall be provided).

- Inform, with the subject's approval or when required by national regulations, the subject's personal physician about the subject's participation in the clinical investigation.
- Make all reasonable efforts to 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 that maintenance and calibration of the equipment relevant for the assessment of the clinical investigation is appropriately performed and documented, where applicable.

17.2.1. Delegation of Responsibility

When specific tasks are delegated by an investigator, including but not limited to conducting the informed consent process, the investigator is responsible for providing appropriate training 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.

17.3. *Institutional Review Board/ Ethics Committee*

Prior to gaining Approval-to-Register status, the investigational center will provide to the sponsor 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 and/or competent authority approval of the protocol (or permission to conduct the study) and Informed Consent Form, must be received by the Coordination and Data Center in Rochester 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 by the Coordination and Data Center.

Annual IRB/EC approval and renewals will be obtained throughout the duration of the study as required by local/country or IRB/EC requirements. Copies of the Investigator's reports and the IRB/EC continuance of approval must be provided to the sponsor.

17.4. *Coordination and Data Center Responsibilities*

Study data will be monitored closely by the CDC. Monthly reports will be generated on data completion and error rates for each clinical site. An automatic forms accounting and monitoring system will be initiated for each participant at the time of enrollment. The 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 which provides information to the clinical centers to help improve and maintain data quality control procedures designed to detect inaccuracies and inconsistencies. This information will be used in making decisions about adjustment procedures, re-reading of electrocardiograms, and functional evaluation of the devices.

All end-point data will be managed by the CDC, and will be maintained at the CDC throughout the course of the trial. End-point data will be excluded from progress reports sent to Boston Scientific CRM and the Investigational Sites.

17.5. *Clinical Center Responsibilities*

Dr. Jagmeet Singh, the Co-Principal Investigator of the Clinical Core, will be overseeing and integrating all scientific and clinical aspects of this clinical trial. He will review all study protocols, operations and CRFs as well as be in charge of developing and implementing subject recruitment including regular contact with enrolling sites, and subsequently overseeing patient enrollment and activities of core labs. .

17.6. *Role of Boston Scientific Representative*

Boston Scientific (BSC) personnel can provide technical support to the investigator and other health care personnel (collectively HCP) as needed during implant, device testing, and follow-ups at the request of the site investigators. Support may include HCP training, addressing HCP questions, or providing clarifications to HCPs concerning the operation of BSC equipment/devices (including programmers, analyzers, and other support equipment) as part of standard BSC device support.

Typical tasks may include the following.

- Interrogating the device or programming device parameters to investigator-requested settings as well as operating investigational equipment
- Performing lead diagnostic testing using a Pacing System Analyzer or programmer to obtain pacing and sensing thresholds and impedance measurements
- Clarifying device behavior, operation or diagnostic output as requested by the investigator or other health care personnel
- Assisting with the collection of study data from Pacing System Analyzers, programmers, and other equipment

Boston Scientific personnel will not do the following.

- Practice medicine
- Provide medical diagnosis or treatment to subjects
- Discuss a subject's condition or treatment with a subject without the approval and presence of the HCP
- Independently collect study data (defined as primary or secondary endpoint data)
- Enter data in electronic data capture systems or on paper case report forms

17.7. *Confidentiality*

All information and data collected for MADIT-CHIC concerning subjects or their participation in this investigation will be considered confidential by Boston Scientific and the CDC. All data will be handled in accordance with applicable local laws. Authorized

regulatory personnel have the right to inspect and copy all records pertinent to this investigation. 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. All data used in the analysis and reporting of this investigation will be without identifiable reference to specific subject name.

The CDC and Boston Scientific will keep subjects' health information confidential in accordance with all applicable laws and regulations. Boston Scientific and the CDC may use subjects' health information to conduct this research, as well as for additional purposes, such as overseeing and improving the performance of its device, new medical research and proposals for developing new medical products or procedures, and other business purposes. Information received during the study will not be used to market to subjects; subject names will not be placed on any mailing lists or sold to anyone for marketing purposes.

18. Monitoring

Monitoring will not be performed routinely during the study to assess continued compliance with the protocol and applicable regulations. If it is determined that the site requires study monitoring the Investigator/institution guarantees direct access to original source documents by BSC or CDC personnel, their designees, and appropriate regulatory authorities.

The study may also be subject to a quality assurance audit by BSC, the CDC, or its designees, as well as inspection by appropriate regulatory authorities. It is important that the Investigator and relevant study personnel are available during on-site monitoring visits or audits and that sufficient time is devoted to the process.

19. Potential Risks and Benefits

19.1. *Anticipated Adverse Device Effects and Anticipated Adverse Events*

Subjects participating in this study are exposed to the same risks shared by all patients who undergo implantation of a conventional CRT-D system. Based on the literature and on pulse generator implant experience, Table 19.1-1 includes an alphabetical list of the possible adverse events and possible adverse device effects associated with implantation of pulse generator and/or lead system.

As the devices used in this study are all approved devices for the treatment of heart failure patients with moderate to severe systolic dysfunction, no new adverse events are anticipated in this subject population.

Table 19.1-1: Potential Adverse Events and Potential Adverse Device Effects for Pulse Generator and/ or Lead System Implants

List of potential adverse events for implantation of a pulse generator and/ or lead system	
Air embolism	Hemothorax
Allergic reaction	Inability to pace
Arterial damage with subsequent stenosis	Inappropriate therapy (e.g., pacing)
Bleeding	Incisional pain
Breakage/ failure of the implant instruments	Infection including endocarditis
Cardiac perforation	Lead dislodgment
Cardiac tamponade	Lead fracture
Chronic nerve damage	Lead insulation breakage or abrasion
Component failure	Lead tip deformation and / or breakage
Conductor coil fracture	Malignancy or skin burn due to fluoroscopic radiation
Death	Myocardial trauma (e.g., tissue damage, valve damage)
Electrolyte imbalance/ dehydration	Myopotential sensing
Elevated thresholds	Oversensing / undersensing
Erosion	Pericardial rub, effusion
Excessive fibrotic tissue growth	Pneumothorax
Extracardiac stimulation (muscle/ nerve stimulation)	Pulse Generator and/or lead migration
Fluid accumulation	Tachyarrhythmias, which include acceleration of arrhythmias, pacemaker mediated tachycardia, and early, recurrent atrial fibrillation
Foreign body rejection phenomena	Thrombus, thromboemboli
Formation of hematomas or seromas	Valve damage
Heart block	Venous occlusion
Hemorrhage	Venous trauma (e.g. perforation, dissection, erosion)

In addition to the implantation of a pulse generator system, potential adverse events associated with implantation of a coronary venous lead system include:

- Allergic reaction to contrast media
- Renal failure from contrast media used to visualize coronary veins

19.2. *Risks Associated with the Study Device(s)*

Subjects implanted in this study will be exposed to similar risks from a standard device procedure when compared to patients previously implanted with a CRT-D. For a detailed listing of the possible physical effects of a CRT-D system implantation, please see the Physician's Manual.

One potential risk is that in a situation where the disease worsens with time, the CRT-D may not be enough to provide adequate treatment. Additionally, it is possible that a situation may arise where the worsening heart function may make subjects' pacemaker therapy dependent. In that case, if for some unforeseen reason the left ventricular lead gets dislodged or is not working there is a risk of considerably reduced heart function and potentially asystole.

19.3. *Risks associated with Participation in the Clinical Study*

Participation in this study requires ECG and echocardiographic measurements. Possible risks associated with these procedures include:

- Allergic skin reaction or trauma to the skin associated with ECG electrode gel
- If injection of contrast media is necessary to visualize the heart during an echo, discomfort, bleeding, and infection at the injection site or allergic reaction to the contrast media may occur

19.4. *Possible Interactions with Concomitant Medical Treatments*

Subjects may experience a reduction in volume overload upon initiation of CRT. Consequently, it may be necessary to reduce the dosage of diuretics post-implant. Failure to reevaluate and adjust diuretic use may result in volume depletion and includes risks such as hypotension, fatigue, and lightheadedness. There are no known interactions with other standard heart failure medications, including beta blockers, ACE/ARB, and aldosterone antagonists.

19.5. *Risk Minimization Actions*

Risks can be minimized through the use of strict aseptic technique, performing procedures in the appropriate hospital environment, compliance with this protocol and technical implant procedures, adherence to the guidelines for subject selection, close monitoring of the subject's physiologic status during implant and follow-up procedures, and by promptly supplying the CDC with all pertinent information required by this protocol.

19.6. *Anticipated Benefits*

In patients with severe and mild left ventricular dysfunction, randomized clinical studies on left ventricular pacing have demonstrated a reduction in all-cause mortality, alone or in combination with heart failure hospitalization, as well as a reduction in symptoms, an improvement of the exercise capacity, and quality of life. Although it is likely that the

subset of patients that are being studied will benefit from CRT, the extent of benefit in patients with chemotherapy-induced cardiomyopathy is unknown.

19.7. *Risk to Benefit Rationale*

The risks associated with CRT-D can typically be resolved non-invasively with reprogramming or with surgery to correct lead issues. Given the potential for reduction in risk of mortality or hospitalization and symptomatic relief, the benefits generally outweigh the risks.

20. Safety Reporting

20.1. *Definitions and Classification*

Adverse events will be reported in accordance with Medical Device Regulations. An adverse event is defined as an event that affects device performance, cardiovascular function and/or study endpoints. Information collected on the adverse event electronic case report form includes the classification of the adverse event and whether the event was patient- or pulse generator-/lead-related and the outcome of the event. All hospitalizations and emergency department visits will be recorded as adverse events; there is no separate case report form for hospitalizations in this investigation.

Adverse event definitions are provided in Table 20.1-1.

Table 20.1-1: Adverse Event Definitions

Term	Definition
Adverse Event (AE)	Any untoward medical occurrence, unintended disease or injury, or any untoward clinical signs (including an abnormal laboratory finding) in subjects, users or other persons, whether or not related to the medical device. NOTE 1: This includes events related to the medical device or component. NOTE 2: This definition includes events related to any study-related procedures involved. NOTE 3: For users or other persons, this definition is restricted to events related to the medical device.
Serious Adverse Event (SAE)	Adverse event that: - Led to death, - Led to serious deterioration in the health of the subject, that either resulted in: o a life-threatening illness or injury, or o a permanent impairment of a body structure or a body function, or o in-patient or prolonged hospitalization of existing hospitalization, or o medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function - Led to fetal distress, fetal death, or a congenital abnormality or birth defect.

Table 20.1-1: Adverse Event Definitions

Term	Definition
	NOTE 1: Planned hospitalization for a pre-existing condition, or a procedure required by the clinical investigational plan, without serious deterioration in health, is not considered a serious adverse event.
Unanticipated Adverse Device Effect (UADE)	Any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan or application (including a supplementary plan or application), or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects.
Device Deficiency	A device deficiency is any inadequacy of a medical device with respect to its identity, quality, durability, reliability, safety or performance. **NOTE 1**: Device deficiencies include malfunctions, misuse or use errors, and inadequate labeling.

Abbreviations: IRB=Institutional Review Board

Underlying diseases are not reported as AEs unless there is an increase in severity or frequency during the course of the investigation. Death must not be recorded as an AE, but must only be reflected as an outcome of a specific SAE (see Table 20.1-1for AE definitions) unless cause of death is truly unknown.

Any AE experienced by the study subject after informed consent, whether during or subsequent to the procedure, must be recorded in the eCRF.

Refer to Section 19 for the known risks associated with the study device(s).

20.2. *Relationship to Study Device(s)*

The Investigator must assess the relationship of the AE to the study device and/or implantation procedure as related or unrelated. See criteria in Table 20.2-1.

Table 20.2-1: Criteria for Assessing Relationship of Study Device to Adverse Event

Classification	Description
Unrelated	The adverse event is determined to be due to a concurrent illness or effect of another device/drug and is not related to a device component or implantation.
Related	• The adverse event is determined to be potentially related to a device component or implantation, and an alternative etiology is equally or less likely compared to the potential relationship to a device component or implantation, or • There is a strong relationship to a device component or implantation, or recurs on re-challenge, and another etiology is unlikely, or • There is no other reasonable medical explanation for the event.

20.3. *Investigator Reporting Requirements*

The communication requirements for reporting to BSC are as shown in Table 20.3-1.

Table 20.3-1: Investigator Reporting Requirements

Event Classification	Communication Method	Communication Timeline
Unanticipated Adverse Device Effect	Complete AE eCRF page with all available new and updated information. Provide all relevant source documentation (de-identified) for reported event on request.	• Within 2 business days of first becoming aware of the event or as per local/regional regulations. • Reporting required through the end of the study
Serious Adverse Event and Death	Complete AE eCRF page with all available new and updated information	• Within 10 business days of first becoming aware of the event or as per local/regional regulations. • Reporting required through the end of the study
	Provide all relevant source documentation (de-identified) for reported event on request	• When documentation is available
Adverse Event	Complete AE eCRF page, which contains such information as date of AE, treatment of AE resolution, assessment of seriousness and relationship to the device	• No later than 10 working days after becoming aware of the information • Reporting required through end of study
Device Deficiency	Complete Device Deficiency eCRF with all available new and updated information	• Within 1 business day of first becoming aware of the event and as per local/regional regulations • Reporting required through the end of the study

Abbreviations: AE=adverse event; CRF=case report form

20.4. *Reporting to Regulatory Authorities / IRBs / ECs / Investigators*

The CDC is responsible for reporting adverse event information to all participating investigators and regulatory authorities, as applicable.

The enrolling center Principal Investigator is responsible for informing the local IRB/EC, and regulatory authorities of SAE as required by local/regional regulations.

21. Informed Consent

Subject participation in this clinical study is voluntary. Informed Consent is required from all subjects or their legally authorized representative. The Investigator is responsible for ensuring that Informed Consent is obtained prior to the use of any devices, study-required procedures and/or testing, or data collection. If a subject agrees to participate in

the study and signs an Informed Consent form, the final medical review, ECG and/or echocardiogram may demonstrate that the subject is not a suitable candidate for the study.

The obtaining and documentation of Informed Consent must be in accordance with the principles of the Declaration of Helsinki, ISO 14155, any applicable national regulations, and local Ethics Committee and/or Regulatory authority body, as applicable. The University of Rochester Coordination Center IRB must approve the prototype ICF prior to distribution to the investigative center. The ICF must be approved by the center's IRB/EC, or central IRB, if applicable.

The CDC will provide a study-specific template of the ICF to investigators participating in this study following approval by the University of Rochester IRB. The ICF template may be modified to meet the requirements of the investigative center's IRB/EC. Any modification requires approval from the CDC prior to use of the form. The ICF must be in a language understandable to the subject and if needed, the CDC will assist the center in obtaining a written consent translation. Translated consent forms must also have IRB/EC approval prior to their use. Privacy language shall be included in the body of the form or as a separate form as applicable.

The process of obtaining Informed Consent shall:

- be conducted by the Principal Investigator or designee authorized to conduct the process,
- include a description of all aspects of the clinical study that are relevant to the subject's decision to participate throughout the clinical study,
- avoid any coercion of or undue influence of subjects to participate,
- not waive or appear to waive subject's legal rights,
- use native language that is non-technical and understandable to the subject or his/her legal representative,
- provide ample time for the subject to consider participation and ask questions if necessary,
- ensure important new information is provided to new and existing subjects throughout the clinical study.

The ICF shall always be signed and personally dated by the subject or legal representative and by the investigator or an authorized designee responsible for conducting the informed consent process. If a legal representative signs, the subject shall be asked to provide informed consent for continued participation as soon as his/her medical condition allows. The original signed ICF will be retained by the center and a copy of the signed and dated document and any other written information must be given to the person signing the form.

Failure to obtain subject consent will be reported by the CDC to the applicable regulatory body according to their requirements (e.g., FDA requirement is within 5 working days of learning of such an event). Any violations of the informed consent process must be reported as deviations to the sponsor and local regulatory authorities (e.g. IRB/EC), as appropriate.

If new information becomes available that can significantly affect a subject's future health and medical care, that information shall be provided to the affected subject(s) in written form via a revised ICF or, in some situations, registered subjects may be requested to sign and date an addendum to the ICF. In addition to new significant information during the course of a study, other situations may necessitate revision of the ICF, such as if there are amendments to the protocol, a change in Principal Investigator, administrative changes, or following annual review by the IRB/EC. The new version of the ICF must be approved by the IRB/EC. CDC approval is required if changes to the revised ICF are requested by the center's IRB/EC. The local IRB/EC will determine the subject population to be re-consented.

22. Committees

22.1. *Safety Monitoring Process*

The University of Rochester Coordination and Data Center will provide a report of safety events to BSC as requested. Success of this program requires dynamic collection of unmonitored data as soon as the event is reported. During regularly scheduled monitoring visits, clinical research monitors will support the dynamic reporting process through their review of source document information.

22.2. *Executive Committee*

The MADIT-CHIC Executive Committee is independent of Boston Scientific CRM and is responsible for the overall guidance of the study. The Executive Committee will review and finalize the protocol and any amendments. The Executive Committee has the authority to appoint an External Advisory Group as deemed necessary to optimize the conduct of the trial.

The Executive Committee is composed of selected study Coordinating Principal Investigator(s) and key management members of the University of Rochester Coordination and Data Center. Responsibilities may include oversight of the overall conduct of the study with regard to protocol development, study progress, subject safety, overall data quality and integrity, as well as disseminating any study results through appropriate scientific sessions and publications. Executive Committee members may participate in the review and approval of all requests for data analysis, abstract and manuscript preparation, and submission. As appropriate, the Executive Committee may request participation of enrolling site Investigators on the Committee. Current Executive Committee members are listed in Appendix A.

22.3. *Data Safety and Monitoring Board Committee*

An Independent Data Safety and Monitoring Board (DSMB) Committee will meet biyearly, or as needed, to review the results of the trial and to evaluate any safety issues that may arise during the course of the study. The DSMB will consist of individuals who are not involved in this study and no affiliation with BSC and have expertise in biostatistics, electrophysiology, and preventive cardiology. The ongoing trial data will be

transmitted to the DSMB on a weekly basis. The DSMB will carry out periodic data review and will inform the study Principal Investigator on any safety concerns. The DSMB may recommend termination of the study at any time should prospective ethical or safety guidelines not be met. The active trial will be completed after every subject has been followed for 6 months. Responsibilities, qualifications, membership, and committee procedures are outlined in the DSMB Charter.

22.4. *Mortality Review Committee*

The Mortality Review Committee will review all deaths that occur during the MADIT-CHIC trial. Their decisions are based on independent physician review of the data from device interrogation, adverse event case report forms, and subject status case report forms. Classification of the cause of death will utilize the Hinkle-Thalercriteria.[8]Responsibilities, qualifications, membership, and committee procedures are outlined in the Mortality Review Committee Charter. A quorum of three physicians is required for the committee to convene.

All mortality analyses reflect the committee's death classifications. Submission of complete information to the committee is essential for accurate conclusions to be drawn and to reduce the need for additional information and multiple reviews. From the data submitted by the center as outlined in this protocol, the Coordination and Data Center at the University of Rochester compiles a summary of events including date of implant, date of death, age at death, immediate cause of death, subject classification (e.g., attempt, intent, implant), Investigator death classifications, implanted system with serial numbers, implanting center, narrative, observations/complications, deviations, device status, autopsy results, gender, and registration assignment (if applicable).

23. Suspension or Termination

23.1. *Premature Termination of the Study*

The CDC and Data Safety Monitoring Board reserves the right to terminate the study at any stage but intends to exercise this right only for valid scientific or administrative reasons and reasons related to protection of subjects. Investigators, associated IRBs/ECs, and regulatory authorities, as applicable, will be notified in writing in the event of study termination.

23.1.1 Criteria for Premature Termination of the Study

Possible reasons for premature study termination include, but are not limited to, the following.

- The occurrence of unanticipated adverse device effects that present a significant or unreasonable risk to subjects registered in the study.
- A registration rate far below expectation that prejudices the conclusion of the study.
- Suspension or discontinuance of the study device.

23.2. *Termination of Study Participation by the Investigator or Withdrawal of IRB/ EC Approval*

Any investigator, or IRB/ EC in the MADIT-CHIC Study may discontinue participation in the study or withdrawal approval of the study, respectively, with suitable written notice to the CDC. Investigators, associated IRBs/ECs, and regulatory authorities, as applicable, will be notified in writing in the event of these occurrences.

23.2. *Requirements for Documentation and Subject Follow-up*

In the event of premature study termination a written statement as to why the premature termination has occurred will be provided to all participating centers by the CDC. The IRB/EC and regulatory authorities, as applicable, will be notified. Detailed information on how registered subjects will be managed thereafter will be provided.

In the event an IRB or EC terminates participation in the study, participating investigators, associated IRBs/ECs, and regulatory authorities, as applicable, will be notified in writing. Detailed information on how study subjects will be managed thereafter will be provided by the CDC.

In the event an investigator terminates participation in the study, study responsibility will be transferred to a co-investigator, if possible. In the event there are no opportunities to transfer investigator responsibility; detailed information on how registered subjects will be managed thereafter will be provided by the CDC.

23.4 *Criteria for Suspending/Terminating a Study Center*

The CDC reserves the right to stop the inclusion of subjects at a study center at any time after the study initiation visit if no subjects have been registered for a period beyond 6 months after center initiation, or if the center has multiple or severe protocol violations/noncompliance without justification and/or fails to follow remedial actions.

In the event of termination of investigator participation, all study devices and testing equipment, as applicable, will be returned to the CDC unless this action would jeopardize the rights, safety or well-being of the subjects. The IRB/EC and regulatory authorities, as applicable, must be notified. All subjects in the study at the center will continue to be followed per standard of care guidelines. The Principal Investigator at the center must make provision for these follow-up visits unless the CDC notifies the enrolling center otherwise.

24. Publication Policy

The investigators will adhere to the Contributorship Criteria set forth in the Uniform Requirements of the International Committee of Medical Journal Editors (ICMJE; http://www.icmje.org).

25. Reimbursement for Subjects

25.1. *Subject Reimbursement*

Travel and other expenses incurred by subjects as a result of participation in the study will be reimbursed in accordance with pertinent local laws and regulations and per the study site's policy as appropriate.

26. Bibliography

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27. Abbreviations and Definitions

27.1. *Abbreviations*

Abbreviations are shown in Table 27.1-1.

Table 27.1-1: Abbreviations

Acronym/Abbreviation	Term
ACC	American College of Cardiology
ACE	Angiotensin-Converting-Enzyme
ADE	Adverse Device Effect
AE	Adverse Event
AHA	American Heart Association
ASADE	Anticipated serious adverse device effect
ARB	Angiotensin receptor blocker
bpm	Beats per minute
BSC	Boston Scientific
CDC	Coordination and Data Center
CA	Competent Authority
CEC	Clinical Events Committee
CFR	Code of Federal Regulations
CRT	Cardiac Resynchronization Therapy
CRV	Cardiology, Rhythm and Vascular (a business division of Boston Scientific)
DDD(R)	Rate Adaptive Dual Chamber Mode (Tracking)
EC/ IEC	Ethics Committee/ Institutional Ethics Committee
ECG	Electrocardiogram
CRF	Case Report Form
eCRF	Electronic Case Report Form
EDC	Electronic Data capture
FDA	Food and Drug Administration
FU	Follow-up
GCP	Good Clinical Practice
HF	Heart Failure
HCP	Health Care Professional
HRS	Heart Rhythm Society
ICD	Implantable Cardioverter-Defibrillator
ICF	Informed Consent Form
ICH	International Conference on Harmonization
ICMJE	International Committee of Medical Journal Editors
IPG	Implantable Pulse Generator
IRB	Institutional Review Board
ISO	International Standard Organization
LRL	Lower Rate Limit
LBBB	Left bundle branch block
LVEF	Left ventricular ejection fraction
MV	Minute Ventilation
NM	Neuro-mediated syndromes
NYHA	New York Heart Association
PM	Pacemaker
PRM	Programmer/ Recorder/ Monitor
PSA	Pacing System Analyzer
RV	Right ventricle/ ventricular
SADE	Serious Adverse Device Effect
SAE	Serious Adverse Event
US	United States of America
USB	Universal Serial Bus
USADE	Unanticipated Serious Adverse Device Effect

27.2. *Definitions*

Table 27.2-1: Definitions

Term	Definition
Source Data	All information in original records of clinical findings, observations, or other activities in a clinical investigation, necessary for the reconstruction and evaluation of the clinical study (original records or certified copies).
Source Document	Printed, optical or electronic document containing source data. Examples: Hospital records, laboratory notes, device accountability records, radiographs, records kept at the investigation site, and at the laboratories involved in the clinical study.

Abbreviations are defined in Table 27.1-1.

28. Appendices

28.1. *Clinical Trial Organization*

The study will be conducted with the University of Rochester Medical Center (URMC) serving as the Coordination and Data Center (CDC). URMC is located at 265 Crittenden Boulevard, CPU Box 420653, Rochester NY 14620, USA. Multiple individuals will be responsible for duties under the direction of Valentina Kutyifa, MD, PhD, the PI and Mary Brown, RN, MS who is the Program Manager. Other responsibilities are identified in Sections 17. and 22.

APPENDIX A: EXECUTIVE COMMITTEE

Valentina Kutyifa, MD, PhD (PI)	University of Rochester Medical Center Rochester, NY
Jagmeet Singh, MD, PhD (Co-PI)	Massachusetts General Hospital Boston, MA
Christopher Beck, PhD	University of Rochester Medical Center Rochester, NY
Mary W. Brown, RN, MS	University of Rochester Medical Center Rochester, NY
Scott D. Solomon, MD	Brigham and Women's Hospital Boston, MA
Wojciech Zareba, MD, PhD	University of Rochester Medical Center Rochester, NY

APPENDIX B: DECLARATION OF HELSINKI

The World Medical Association Declaration of Helsinki

World Medical Association Declaration of Helsinki: Recommendations Guiding Medical Doctors in Biomedical Research Involving Human Subjects

Adopted by the 18th WMA General Assembly, Helsinki, Finland, June 1964, and amended by the 29th WMA General Assembly, Tokyo, Japan, October 1975 35th WMA General Assembly, Venice, Italy, October 1983 41st WMA General Assembly, Hong Kong, September 1989 48th WMA General Assembly, Somerset West, Republic of South Africa, October 1996 and the 52nd WMA General Assembly, Edinburgh, Scotland, October 2000 Note of Clarification on Paragraph 29 added by the WMA General Assembly, Washington 2002.

A. INTRODUCTION

1. The World Medical Association has developed the Declaration of Helsinki as a statement of ethical principles to provide guidance to physicians and other participants in medical research involving human subjects. Medical research involving human subjects includes research on identifiable human material or identifiable data.

2. It is the duty of the physician to promote and safeguard the health of the people. The physician's knowledge and conscience are dedicated to the fulfillment of this duty.

3. The Declaration of Geneva of the World Medical Association binds the physician with the words, "The health of my patient will be my first consideration," and the International Code of Medical Ethics declares that, "A physician shall act only in the patient's interest when providing medical care which might have the effect of weakening the physical and mental condition of the patient."

4. Medical progress is based on research which ultimately must rest in part on experimentation involving human subjects.

5. In medical research on human subjects, considerations related to the well-being of the human subject should take precedence over the interests of science and society.

6. The primary purpose of medical research involving human subjects is to improve prophylactic, diagnostic and therapeutic procedures and the understanding of the etiology and pathogenesis of disease. Even the best proven prophylactic, diagnostic, and therapeutic methods must continuously be challenged through research for their effectiveness, efficiency, accessibility and quality.

7. In current medical practice and in medical research, most prophylactic, diagnostic and therapeutic procedures involve risks and burdens.

8. Medical research is subject to ethical standards that promote respect for all human beings and protect their health and rights. Some research populations are vulnerable and need special protection. The particular needs of the economically and medically disadvantaged must be recognized. Special attention is also required for those who cannot give or refuse consent for themselves, for those who may be subject to giving consent under duress, for those who will not benefit personally from the research and for those for whom the research is combined with care.
9. Research Investigators should be aware of the ethical, legal and regulatory requirements for research on human subjects in their own countries as well as applicable international requirements. No national ethical, legal or regulatory requirement should be allowed to reduce or eliminate any of the protections for human subjects set forth in this Declaration.

B. BASIC PRINCIPLES FOR ALL MEDICAL RESEARCH

10. It is the duty of the physician in medical research to protect the life, health, privacy, and dignity of the human subject.

11. Medical research involving human subjects must conform to generally accepted scientific principles, be based on a thorough knowledge of the scientific literature, other relevant sources of information, and on adequate laboratory and, where appropriate, animal experimentation.

12. Appropriate caution must be exercised in the conduct of research which may affect the environment, and the welfare of animals used for research must be respected.

13. The design and performance of each experimental procedure involving human subjects should be clearly formulated in an experimental protocol. This protocol should be submitted for consideration, comment, guidance, and where appropriate, approval to a specially appointed ethical review committee, which must be independent of the investigator, the sponsor or any other kind of undue influence. This independent committee should be in conformity with the laws and regulations of the country in which the research experiment is performed. The committee has the right to monitor ongoing trials. The researcher has the obligation to provide monitoring information to the committee, especially any serious adverse events. The researcher should also submit to the committee, for review, information regarding funding, sponsors, institutional affiliations, other potential conflicts of interest and incentives for subjects.

14. The research protocol should always contain a statement of the ethical considerations involved and should indicate that there is compliance with the principles enunciated in this Declaration.

15. Medical research involving human subjects should be conducted only by scientifically qualified persons and under the supervision of a clinically competent medical person. The responsibility for the human subject must always rest with a medically qualified person and never rest on the subject of the research, even though the subject has given consent.

16. Every medical research project involving human subjects should be preceded by careful assessment of predictable risks and burdens in comparison with foreseeable benefits to the subject or to others. This does not preclude the participation of healthy volunteers in medical research. The design of all studies should be publicly available.

17. Physicians should abstain from engaging in research projects involving human subjects unless they are confident that the risks involved have been adequately assessed and can be satisfactorily managed. Physicians should cease any investigation if the risks are found to outweigh the potential benefits or if there is conclusive proof of positive and beneficial results.

18. Medical research involving human subjects should only be conducted if the importance of the objective outweighs the inherent risks and burdens to the subject. This is especially important when the human subjects are healthy volunteers.

19. Medical research is only justified if there is a reasonable likelihood that the populations in which the research is carried out stand to benefit from the results of the research.

20. The subjects must be volunteers and informed participants in the research project.

21. The right of research subjects to safeguard their integrity must always be respected. Every precaution should be taken to respect the privacy of the subject, the confidentiality of the patient's information and to minimize the impact of the study on the subject's physical and mental integrity and on the personality of the subject.

22. In any research on human beings, each potential subject must be adequately informed of the aims, methods, sources of funding, any possible conflicts of interest, institutional affiliations of the researcher, the anticipated benefits and potential risks of the study and the discomfort it may entail. The subject should be informed of the right to abstain from participation in the study or to withdraw consent to participate at any time without reprisal. After ensuring that the subject has understood the information, the physician should then obtain the subject's freely-given informed consent,

preferably in writing. If the consent cannot be obtained in writing, the non-written consent must be formally documented and witnessed.

23. When obtaining informed consent for the research project the physician should be particularly cautious if the subject is in a dependent relationship with the physician or may consent under duress. In that case the informed consent should be obtained by a well-informed physician who is not engaged in the investigation and who is completely independent of this relationship.

24. For a research subject who is legally incompetent, physically or mentally incapable of giving consent or is a legally incompetent minor, the investigator must obtain informed consent from the legally authorized representative in accordance with applicable law. These groups should not be included in research unless the research is necessary to promote the health of the population represented and this research cannot instead be performed on legally competent persons.

25. When a subject deemed legally incompetent, such as a minor child, is able to give assent to decisions about participation in research, the investigator must obtain that assent in addition to the consent of the legally authorized representative.

26. Research on individuals from whom it is not possible to obtain consent, including proxy or advance consent, should be done only if the physical/mental condition that prevents obtaining informed consent is a necessary characteristic of the research population. The specific reasons for involving research subjects with a condition that renders them unable to give informed consent should be stated in the experimental protocol for consideration and approval of the review committee. The protocol should state that consent to remain in the research should be obtained as soon as possible from the individual or a legally authorized surrogate.

27. Both authors and publishers have ethical obligations. In publication of the results of research, the investigators are obliged to preserve the accuracy of the results. Negative as well as positive results should be published or otherwise publicly available. Sources of funding, institutional affiliations and any possible conflicts of interest should be declared in the publication. Reports of experimentation not in accordance with the principles laid down in this Declaration should not be accepted for publication.

C. ADDITIONAL PRINCIPLES FOR MEDICAL RESEARCH COMBINED WITH MEDICAL CARE

28. The physician may combine medical research with medical care, only to the extent that the research is justified by its potential prophylactic, diagnostic or therapeutic value. When medical research is combined with medical care, additional standards apply to protect the patients who are research subjects.
29. The benefits, risks, burdens and effectiveness of a new method should be tested against those of the best current prophylactic, diagnostic, and therapeutic methods. This does not exclude the use of placebo, or no treatment, in studies where no proven prophylactic, diagnostic or therapeutic method exists. See footnote

30. At the conclusion of the study, every patient entered into the study should be assured of access to the best proven prophylactic, diagnostic and therapeutic methods identified by the study.

31. The physician should fully inform the patient which aspects of the care are related to the research. The refusal of a patient to participate in a study must never interfere with the patient-physician relationship.

32. In the treatment of a patient, where proven prophylactic, diagnostic and therapeutic methods do not exist or have been ineffective, the physician, with informed consent from the patient, must be free to use unproven or new prophylactic, diagnostic and therapeutic measures, if in the physician's judgment it offers hope of saving life, re-establishing health or alleviating suffering. Where possible, these measures should be made the object of research, designed to evaluate their safety and efficacy. In all cases, new information should be recorded and, where appropriate, published. The other relevant guidelines of this Declaration should be followed.

Footnote: **Note of clarification on paragraph 29 of the WMA Declaration of Helsinki**

The WMA hereby reaffirms its position that extreme care must be taken in making use of a placebo-controlled trial and that in general this methodology should only be used in the absence of existing proven therapy. However, a placebo-controlled trial may be ethically acceptable, even if proven therapy is available, under the following circumstances:

- Where for compelling and scientifically sound methodological reasons its use is necessary to determine the efficacy or safety of a prophylactic, diagnostic or therapeutic method; or

- Where a prophylactic, diagnostic or therapeutic method is being investigated for a minor condition and the patients who receive placebo will not be subject to any additional risk of serious or irreversible harm.

All other provisions of the Declaration of Helsinki must be adhered to, especially the need for appropriate ethical and scientific review.