Abbott	Clinical Investigation Plan Cover Page

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ADVANCE CRT Registry
ADVANCE Cardiac Resynchronization Therapy Registry
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Sponsor

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ST. JUDE MEDICAL

STUDY PROTOCOL
FOR THE

ADVANCE CRT REGISTRY

December 17, 2015

1.0 Introduction

Therapeutic benefit of cardiac resynchronization therapy (CRT) in patients with advanced heart failure (HF) is well established.[1-3] CRT has been shown to restore the coordination of cardiac contraction and relaxation resulting in improved exercise tolerance, cardiac reverse remodeling, and improved survival in advanced HF patients with interventricular conduction delay. Studies of mechanisms and outcomes suggest that the therapeutic benefit is mediated by device-induced resynchronization, thus leading to continued research focus on identifying patients with underlying mechanical dysynchrony who are most likely to benefit from CRT.[4-9] In spite of these efforts, however, the proportion of patients who fail to respond to CRT remains significant.[10] The mean responder rate from the 15 largest studies is 66.9% based on clinical evaluation methods and even lower, 56.9%, using echocardiographic parameters.[11] Despite this substantial proportion of non-responders, little research has been done to understand how non-responders are identified, treated, and followed in real world clinical practice.

There is no uniform criterion to determine the response to CRT as clinical studies use numerous criteria to define positive response to CRT.[12] Furthermore, the CRT response is very sensitive to the criteria used as the recent article by Fornwalt et al[12] demonstrated that the response rate in sub-group of PROSPET study patients ranged from 32% to 91% based on 15 different response criteria used in many CRT clinical studies. Development of research-based guidance is made more difficult due to the fact that these response criteria are mostly applied in controlled studies. Real-world clinical criteria and their corresponding response rates are still largely unknown.

Furthermore, once patients are determined to be non-responders, the management strategy and the specialty and role of health care providers treating the HF patient is not well understood. A few isolated studies of non-traditional left ventricular (LV) pacing schemes such as cardiac contractility modulation[13], dual or triple site LV pacing[14-16], and endocardial LV pacing[17] led to higher acute hemodynamic improvements or improved clinical outcome. However, the use of these non-conventional LV pacing strategies on non-responders in real world practice is unknown even though the clinical study evaluating the efficacy of dual-site LV pacing is currently being studied[18].

In the recent FREEDOM study, a survey was completed by over 100 investigators to understand the real world practice pattern on patients receiving CRT device.[19] The survey provided valuable insights into the method of device parameter optimization, the method of evaluation of responders and non-responders, the timing of determining the outcome of CRT efficacy, and the device parameter re-optimization pattern difference between responder and non-responder. However, the survey focused mainly on CRT patient managements from the device optimization perspective and the clinical management of non-responders was not investigated.

International registries can provide us a comprehensive understanding regarding the clinical management of CRT-non responders around the world. Such understanding can help us to identify the gaps in knowledge and the area of innovation needed to make CRT a better HF therapy option or provide alternative options to better treat non-responders. The ADVANCE-CRT Registry/Observation study is aimed at elucidating non-responder care in clinical practice settings around the globe. Among the unknowns of interest are the criteria for prescribing CRT for HF management, rate of non-responders, methods of identifying non-responders, treatment options employed by clinicians to improve response, clinicians most involved in deciding each patient's course of care, and healthcare system encounters and utilization.

2.0 Purpose

The intent of this registry/ observational study is to understand comprehensive clinical care strategies for CRT patients especially non-responders in real world clinical practice. The study should provide understanding of the following

- Rate of non-responders to CRT
- Commonly used definitions of response to CRT
- Treatment strategies employed to treat HF in the non-responder population
- Efficacy of treatment strategies used to treat non-responders
- Identification of the decision-making process in the care of non-responders
- Characterization of the management pathway and related therapies following declaration of non-response to CRT
- Role of remote-monitoring in treating and monitoring non-responders

This study may continue up to 4 – 5 years, depending on the rate of enrollment- and follow-up timelines.

3.0 Clinical Protocol

3.1 Study Design and Scope

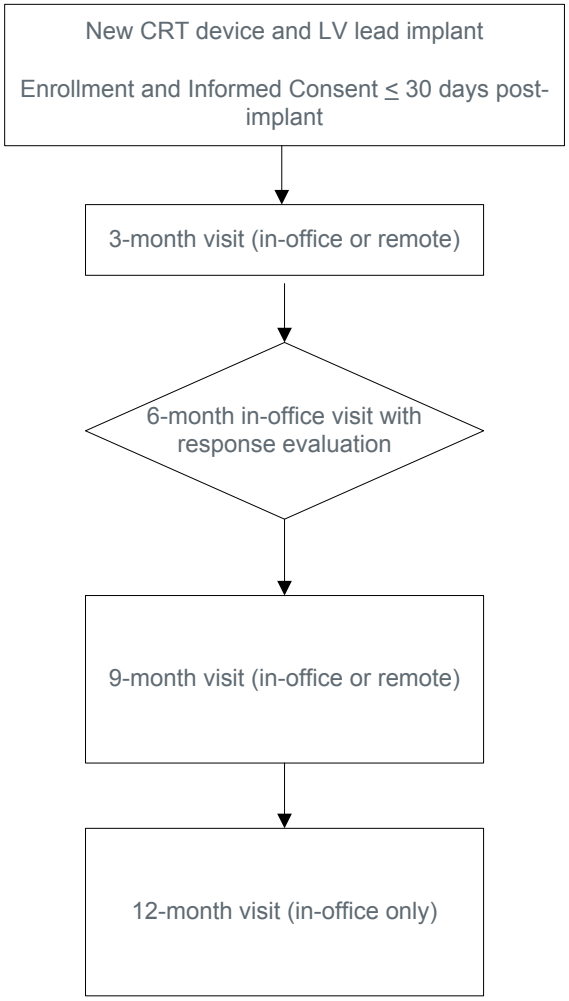
This is a worldwide, multicenter, non-randomized registry/observational study. The study will enroll a minimum of 1500 CRT patients from up to 70 centers worldwide. The goal of the study is to have a maximum of 500 CRT non-responders patients identified and assessed. Hence, the final number of enrolled CRT patients in the study will depend on the number of CRT patients needed to reach a maximum of 500 CRT non-responders. Patients who are successfully implanted with St. Jude Medical CRT-D/P devices will be eligible for enrollment in the study up to 30 days post implant of the device. Once enrolled, all patients will be followed every 3 months for12 months after implant. The responder/non-responder evaluation will occur during the 6 month office visit and criteria used to determine the response to CRT will be captured. All visits except for Enrollment,6-Month, and 12-

Month visits may be performed as in the office or by telephone. Merlin.net remote follow-up is optional but encouraged.

The study will be complete when the last enrolled patient has been followed for 12 months post implant. Arrhythmic episodes and relevant device parameters that can affect CRT outcome such as % biventricular pacing, AT/AF burden, and % PVC will be collected at each in-office device interrogation. All clinical events such as hospitalizations, ER visits, Urgent Care visits, death, etc. will also be collected. Any re-optimization of the device, i.e., AV/VV interval optimization, LV lead repositioning and pacing vector reconfiguration, as well as modified/new clinical therapies administered in attempt to improve the patient's HF condition will be collected. In addition, specialty of clinicians managing and providing care for CRT patients will be noted.

Figure 1. Study Flow Diagram

Study Flow Diagram



3.1.1 Additional Data

- Demographics: gender, age, height, weight, race/ethnicity (if available)
- Medical history
- Implanted devices (model and serial number)
- NYHA class, Patient Global Assessment (PGA)
- Medication
- Echo measurements
- 12 Lead ECG
- Minnesota Living with Heart Failure (MLWHF) and EQ5D quality of life score
- Modified specific activity score (SAS)
- Clinical events and healthcare utilization
- Electrical lead measurements and device diagnostics
- Device session record
- Responder/Non-responder evaluation criteria
- Device re-optimization and clinical therapy modification administered to improve the heart failure condition of patients
- HF management profile for study center

3.2 Sample Size

The study will enroll at least 1500 CRT patients from estimated 70 centers worldwide in order to identify and assess a maximum 500 CRT non-responders.

3.3 Study Duration

The last patient enrolled will be followed for 1 year after implant. patient participation in the study will be completed when the in-office 12 month visit has been completed.

3.4 Patient Selection

The investigational centers will attempt to recruit patients who meet the study inclusion criteria for possible study enrollment.

3.4.1 Inclusion Criteria

Eligible patients will meet **all** of the following:

1. Patient willing and able to sign informed consent
2. Patients implanted with any market-approved St. Jude Medical CRT-D/P device with no prior LV lead placement

3.4.2 Exclusion Criteria

Patients will be excluded if they meet **any** of the following:

1. Are likely to undergo heart transplantation within the next 12 months
2. Are less than 18 years of age
3. Are pregnant or planning to become pregnant during the duration of the study
4. Are currently participating in a clinical investigation that includes an active treatment arm
5. Have a life expectancy of less than 6 months

3.5 Study Procedures

All required study procedures at each specified interval are outlined in the table below.

Upon site activation, CRT patient management strategies will be characterized via a one-time site survey (Practice Characteristics Survey Form). Data collected will request information such as:

- Outpatient practice setting, i.e., university, non-university, teaching
- Presence of and involvement of an HF clinic for HF/CRT management
- Staffing, i.e., number of physicians, HF nurses, electrophysiologists and interventionalists
- Number of HF and CRT patients managed annually
- Presence of any special clinic/protocol in caring for CRT non-responders

Table 1: Data Reporting Schedule

	Enrollment	In-office F/U at 6 months	Other In-office F/Us	Remote F/Us
Medical History	√			
Medications	√	√	√	√
Cardiac Events/Health Care Utilization		√	√	√
12 Lead ECG	√	√‡	√‡	
Lead Electrical Measurements	√	√	√	
Echo Measurements (EF at minimum)	√	√‡	√‡	

Device Diagnostics e.g., AT/AF burden, % biventricular pacing, # of VT/VF episodes, etc.	√	√	√	
Responder/Non-responder evaluation		√	√**	
NYHA	√	√	√	
Patient Global Assessment		√	√*	√*
Modified SAS	√‡	√‡	√‡	
MLWHF and EQ5DQuestionnaires	√‡	√‡	√‡	
Device Re-Optimization (e.g., AV/VV optimization, LV lead revision) intended to improve HF condition		√‡	√‡	
Any new treatment or modification of existing therapy provided to improve HF condition		√‡	√‡	

√: Standard of care, √‡: Report if performed, √*: until the 12 month visit: √**: for 9 mo and 12, mo office visits only

3.5.1 Enrollment (≤ 30 days post device implant)

Obtaining Consent

Patients deemed eligible and willing to participate in the Study must sign a Consent Form prior to study enrollment. A template of the Informed Consent Form is provided in Appendix A. The signed informed consent form must be filed in the hospital/clinic patient medical chart with the study patient's documentation and be available for monitoring and auditing.

Enrollment

A patient is considered enrolled once they have signed an informed consent and have been successfully implanted with an approved St. Jude Medical CRT-D/P device within the last 30 days prior to enrollment. Device implant information will be collected after enrollment and patients may be enrolled in Merlin.net for remote follow-up. The following information should be collected at the Enrollment Visit:

Required Patient Data

- Informed consent
- Demographic information if available

- Pre-Implant NYHA class
- 12 Lead ECG
  - Intrinsic ECG rhythm with QRS width, PR interval, and the morphology, i.e., normal, LBBB, or RBBB conduction pattern. Intrinsic ECG printout should be provided
  - ECG printout with final device programming should be provided if available
- Pre-Implant Echo data including ejection fraction (EF) at minimum
- Medical history, i.e., coronary artery disease (CAD), myocardial infarction (MI), prior cardiac interventions, arrhythmia history, other comorbid conditions, etc.
- If MI is noted, the location of MI should be provided
- Size of scar should be provided if available
- Detailed medication information
- Details of patient HF education if provided

Required Implant/Device Data

- Implanted pulse generator and lead information, i.e., model, serial number, pocket location (pulse generator), lead position
- Final LV lead electrodes locations and reasons for selecting the final pacing location and configuration
- AV/VV interval values and optimization method used, i.e., QuickOpt, echo-guided, ECG, out of box setting, etc.
- Lead electrical measurements, i.e., capture threshold, sensing, impedance
- LV electrical delay (QLV) if available: QLV will be measured from ECG and LV IEGM recordings obtained from the Merlin programmer if done at the Enrollment Visit (data requested if not done as standard of care)
- Device diagnostics such as % BiV pacing, % Atrial pacing, AT/AF burden, VT/VF episodes etc.
- Electronic device session record (uploaded via EDC)

Optional Data (enrollment, 6 month and12 month visit)

- Minnesota Living With Heart questionnaire Failure (MLWHF) and EQ5D
- Modified specific activity score (SAS) evaluation

The following Case Report Forms (CRF) should be completed:

- Enrollment Form
- Medical History Form
- Medication Form
- MLWHF and EQ5D Questionnaires – optional

3.5.2 Follow-Ups:

Recommended follow-up visit schedules are as follows. Patients will have follow-up visits every 3 months for the first 12 months. Patients can be followed in-office or remotely except for the required in-office 6 month and 12 month visit. Follow up visit intervals and windows are calculated based on the CRT system implant date – not the Enrollment Visit date.

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Follow-up visits type	Visit Window
6 Month In-Office Visit	6 month from the implant date ± 60 days
Other Visits (remote or in-office)	Visit Month from the implant date ± 30 days

In this study, each patient's response to CRT will be evaluated at the 6-month in-office visit using two criteria. They are 1) Clinical Composite Score (CCS)[20] and 2) study center-specific criteria. The CCS consists of NYHA assessment, Patient Global Assessment (PGA), HF events, and cardiovascular death. The center-specific criteria are what the center uses for evaluating CRT response in routine HF management. Some commonly used criteria used for determining a response to CRT are left ventricular remodeling parameters from echocardiogram, functional assessments such as 6 minute walk test and NYHA, clinical events or combination of any of those. In this study, the number of non-responders to CRT will be based on the CCS. However, the study center will provide details of their response evaluation as well.

The CCS includes 4 components: NYHA class, Patient Global Assessment (PGA), HF events, and cardiovascular death. The NYHA Class assessment and PGA are determined by an assessor interviewing patients about their symptoms. Specifically, the PGA will be a single interview question that asks the patient to categorize how they feel compared to before they received their CRT implant as either:

- Markedly better
- Moderately better
- Slightly better
- No change
- Slightly worse
- Moderately worse
- Markedly worse

In this study an HF event is defined as any one of the following when the subject has symptoms and/or signs consistent with congestive heart failure:

- Hospitalization for HF ≥ 24 hours
- Hospitalization for HF<24 hours (i.e. outpatient treatment, observational care, ER, Urgent Care, and physician's office visit) requiring administration of IV diuretics, inotropes, and/or vasodilators

Finally, cardiovascular death is defined as sudden cardiac death; heart failure death; myocardial infarction related; or 'other' such as pulmonary embolism, peripheral thromboembolism, stroke, deaths due to vascular procedure, or other major cardiovascular event.

Using the CCS and decision algorithm described in Figure 2, patients are categorized as Improved, Worsened or Unchanged based on the following rules:

"Improved" – patients that demonstrate:

- At least a one-class improvement in NYHA Class OR improvement by PGA ("moderately better" or "markedly better")

AND

- No HF events as described above

AND

- No cardiovascular death

"Worsened" – patients that demonstrate:

- Worsening in NYHA Class OR worsening by PGA ("moderately worse" or "markedly worse")

OR

- Presence of HF events as described above

OR

- Cardiovascular death

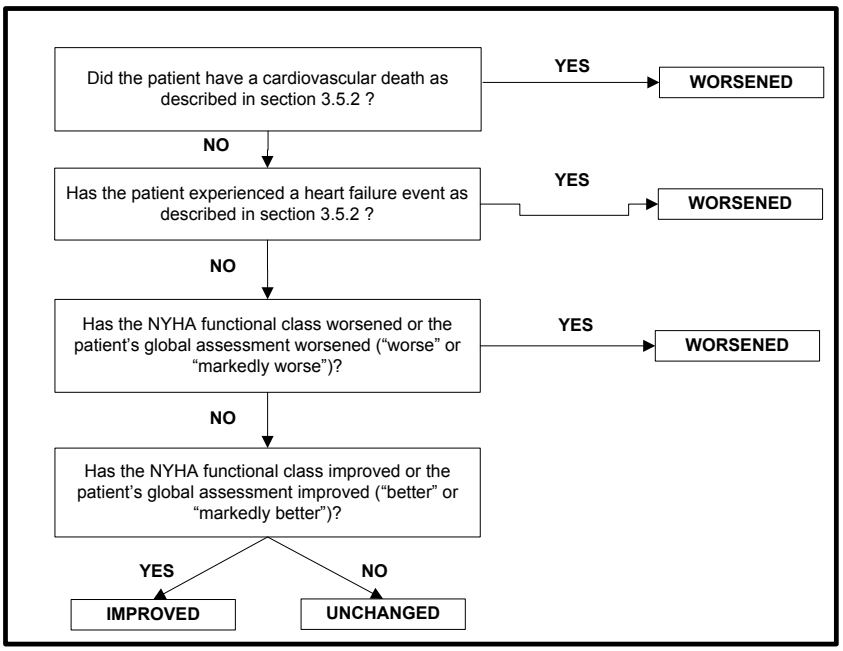
"Unchanged" – patients that are neither "Improved" nor "Worsened".

Patients who are "Improved" using the above definition relative to the Enrollment Visit will be considered as **Responders.** Patients that are "Worsened" or "Unchanged" relative to the Enrollment Visit will be grouped together as **Non-Responders**.

Device settings may be re-optimized, medication may be altered, or patient compliance issues, if any, may be addressed to improve the HF conditions regardless of their responder or non-responder status. If

any measures are taken to improve the HF condition of patients, such information should be provided in follow-up CRFs.

Figure 2. Decision algorithm to classify response to CRT based on CCS



3.5.2.1 6 Month Follow-Up: Required In-Office Visit

The 6 month follow-up should occur at the office of the physician managing the patient.

Required Patient Data

- Detailed medication information
- Cardiac events and health care utilization
- Device diagnostics such as % pacing, AT/AF burden and VT/VF episodes, etc.
- Type of clinicians involved and the treatment provided during the visit. If the patient was seen by other clinicians before the visit and after the previously scheduled visit, type of clinicians involved and the treatment provided should be provided as well
- Patient global assessment (PGA) and NYHA
- Responder/non-responder criteria used which might include:
  - Echo-based: Remodeling assessment such as EF, LVESV, LVEDV
  - Clinical: Functional Assessment such as NYHA, 6MHWT, MLWHF, SAS, time on treadmill
  - Clinical: Symptoms of HF, HF hospitalization, administration of intravenous (IV) inotrope or diuretic therapy, etc.
  - Composite: Any combination of factors

  - Others
- Electronic device session record (uploaded via EDC)

Required Data if Procedures Performed

- 12 Lead ECG with QRS width, PR interval, and the morphology, i.e., normal, LBBB, or RBBB conduction pattern
- 12 Lead ECG printout with final device programming if EP procedures are performed on patients
- Any device re-optimizations or new/modified medical therapies intended to improve the hemodynamics or HF condition of patients. They can be one or more of the following.
  - Device re-optimization
    - Device parameters optimization including AV/VV intervals, lead repositioning, insertion of extra leads, and lead replacement
    - Pacing configuration modifications especially for the Quadripolar lead and reasons for the changes
  - Treatment of an arrhythmia to improve biventricular pacing
    - Treatment of SVT, VT, or frequent PVCs
  - Modification of existing clinical therapy or new therapy attempted to improve HF condition
    - Medication change, e.g. dose adjustments of neurohormonal blockers, beta blockers, loop diuretics, etc.
    - Address compliance issues
      - Medication
      - Salt/water restriction
    - HF education
  - Treatment of other co-morbid conditions
  - Other treatments/device re-optimization used to improve the HF status of patients
- Minnesota Living With Heart questionnaire Failure (MLWHF) and EQ5D
- Modified specific activity score (SAS) evaluation

The following Case Report Forms (CRF) should be completed:

- 6 Month Follow-Up Form
- Medication Form
- Clinical Composite Score Form
- Health Care Utilization Form if applicable
- Adverse Event From if applicable
- Treatment Form if applicable
- System Revision Form if applicable
- MLWHF and EQ5D Questionnaires if applicable

3.5.2.2 3, 9, and12-Month Follow-Ups – In Office

Any follow-up except the 6-month and 12- month follow-up may be done remotely or as an in-office visit. The following information will be reported for a follow-up that is performed in-office.

Required Patient Data

- Detailed medication information
- Cardiac events and health care utilization
- Device diagnostic data
- Type of clinicians involved and the treatment provided during the visit. If the patient was seen by other clinicians before the visit and after the previously scheduled visit, type of clinicians involved and the treatment provided should be provided as well
- NYHA evaluation
- Patient global assessment (PGA) if the follow-up is 12 month or less
- Status of patient's response (responder or non-responder) to CRT based on study center-specific criteria (for 9-month and 12-month, office visits only)
- Echo data including ejection fraction (EF) at minimum*
- Electronic device session record (uploaded via EDC)

*At least 1 per year

Required Data if Procedures Performed

- 12 Lead ECG with QRS width, PR interval, and the morphology, i.e., normal, LBBB, or RBBB conduction pattern
- 12 Lead ECG printout with final device programming if EP procedures are performed on patients
- Any device re-optimizations or new/modified medical therapies intended to improve the hemodynamics or HF condition of patients. They can be one or more of the followings.
  - Device re-optimization
    - Device parameters optimization including AV/VV intervals, lead repositioning, insertion of extra leads, and lead replacement
    - Pacing configuration modifications especially for the Quadripolar lead and reasons for the changes
  - Treatment of an arrhythmia to improve biventricular pacing
    - Treatment of SVT, VT, or frequent PVCs
  - Modification of existing clinical therapy or new therapy attempted to improve HF condition
    - Medication change, e.g. dose adjustments of neurohormonal blockers, beta blockers, loop diuretics, etc.
    - Address compliance issues

        - Medication
        - Salt/water restriction
      - HF education
    - Treatment of other co-morbid conditions
    - Other treatments/device re-optimization used to improve the HF status of patients
- Minnesota Living With Heart questionnaire Failure (MLWHF) and EQ5D
- Modified specific activity score (SAS) evaluation

The following Case Report Forms (CRF) should be completed:
- 3 Month Follow-Up Form for 3 month visit
- Follow-Up Form for other visits
- Medication Form
- Health Care Utilization Form if applicable
- Adverse Event From if applicable
- Treatment Form if applicable
- MLWHF and EQ5D Questionnaires if applicable
- System Revision Form if applicable

3.5.2.3 3 and9 Month Follow-Ups – Remote

Any follow-up except the 6-month follow-up may be done remotely or as an in-office visit. The following information will be reported for a follow-up that is performed remotely.

Required Patient Data
- Detailed medication information
- Cardiac events and health care utilization
- Patient global assessment (PGA) if the follow-up is less than 12 months
- Information regarding the role of remote follow-up in patient management

The following Case Report Forms (CRF) should be completed:
- Follow-up Form
- Medication Form
- Health Care Utilization Form if applicable

3.5.3 Unscheduled Follow-up Visits

A heart failure related clinic visit at any time other than a regularly scheduled visit is considered an unscheduled visit. Follow-up CRF should only be completed via the EDC system. If any device re-optimization or clinical therapy modification was provided to improve the HF condition of patient, Treatment form should be completed.

The following Case Report Forms (CRF) should be completed:

- Follow-up Form
- Treatment Form if applicable
- Adverse Event From if applicable

4.0 Subject Study Completion

Patient participation in the study is complete when each enrolled patient completes the 12 month follow-up visit. Patient participation for patients who have already completed the 12 month visit is considered complete upon the approval of this revised protocol by IRB/EC.

5.0 Protocol Deviations

Investigators are required to adhere to the study protocol, signed Investigator's Agreement, applicable federal (national) or state/local, laws and regulations, and any conditions required by the IRB/Ethics Committee or applicable regulatory authorities.

A protocol deviation is used to describe situations in which the study protocol was not followed. All deviations from the study protocol must be reported to St. Jude Medical. In addition, all deviations must be reported to the reviewing IRB/Ethics Committee and Competent Authorities, if applicable, per their reporting requirements.

The investigator must notify St. Jude Medical and the reviewing IRB/Ethics Committee of any deviation from the study protocol that affects the rights, safety or well-being of the subject or the scientific integrity of the study, including those which occur under emergency circumstances as soon as possible, but not later than 72 hours after the investigator becomes aware of the deviation.

6.0 Adverse Events

6.1 Definitions

6.1.1 Adverse Event (AE)

Any untoward medical occurrence, unintended disease or injury, or untoward clinical signs (including abnormal laboratory findings) in patients, users or other persons, whether or not related to the medical device. Adverse events can be further categorized into procedure or device related in the following definitions.

Procedure Related: The AE is deemed related to the procedure if it occurred during the procedure or if it is directly related to the procedure but was not directly caused by the device

Device Related: The AE is deemed device related if it was directly caused by device

Potential adverse events include:
Allergic reaction to contrast media
AV nodal reentrant tachycardia
Bodily rejection phenomena
Cardiac/coronary sinus dissection
Cardiac/coronary sinus perforation
Cardiac tamponade
Coronary sinus or cardiac vein thrombosis
Endocarditis
Excessive bleeding
Hematoma/seroma
Induced atrial or ventricular arrhythmias
Infection due to procedure or implanted devices
Lead dislodgement
Lead/ Port damage
Local tissue reaction; formation of fibrotic tissue
Loss of pacing and / or sensing due to dislodgement or mechanical malfunction of the pacing lead
Myocardial irritability
Myopotential sensing
Pectoral/diaphragmatic/phrenic nerve stimulation
Pericardial effusion
Pericardial rub
Pnemothorax/hemothorax
Prolonged exposure to fluoroscopic radiation
Pulmonary edema
Renal failure from contrast media used to visualize coronary veins
Rise in threshold and exit block
Thrombolytic or air embolism
Valve damage

6.1.2 Serious Adverse Event (SAE)

An adverse event that:

- Led to death
- Led to a serious deterioration in the health of the subject that either resulted in
  - A life-threatening illness or injury OR

- A permanent impairment to a body structure or a body function OR
- An in-patient or prolonged hospitalization OR
- A medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body OR
- A malignant tumor

- Led to foetal distress, foetal death or a congenital abnormality or birth defect

A planned hospitalization for a pre-existing condition, or a procedure required by the health care professional is not considered a serious adverse event.

6.2 Procedure for assessing, recording and reporting AE and SAE

All SAEs are to be documented and reported to the sponsor within 10 days for US sites and 72 calendar hours for sites outside US after becoming aware of the event or per local regulatory timelines.

All AEs are to be documented and reported no later than 10 working days after becoming aware of the event. Non-Serious Adverse Events documentation and reporting are limited to cardiovascular events.

Should an AE and SAE occur, complete and submit an AE form to St. Jude Medical.

Return any explanted devices or leads to St. Jude Medical for analysis.

Additional information can be requested, if necessary, by the Sponsor for reporting of AEs to regulatory authorities. The investigator must notify the IRB or Ethics Committee, if appropriate, in accordance with national and local laws and regulations.

NOTE: If an adverse event is documented at the patient's last follow up visit, both the notification and follow-up information on the AE CRF are to be provided to the sponsor.

7.0 Other Reported Events

Other Reported Events are any other clinical event that is submitted by the investigator which is not caused by or associated with the study device and/or system component(s) and/or defined as an Adverse Event in section 5.0.

8.0 Health Care Utilization/Hospitalization Visits

For US sites, any clinical event resulting in an inpatient hospital stay, ER visit, observational visit, outpatient visit, or urgent care visit must be reported to St. Jude Medical via the Health Care Utilization Form using the EDC system within 10 working day of the center becoming aware of the patient's admission to the hospital. A planned hospitalization for a pre-existing condition, or a procedure required by the health care professional is not considered a hospitalization.

For all countries except US, any hospitalizations must be reported to St. Jude Medical via the AE form using the EDC system within 72 calendar hours of the center becoming aware of the patient's admission to the hospital.

9.0 Deaths

All patient deaths that occur during this investigation must be reported to St. Jude Medical within 10 days of the center becoming aware of the death for US sites and within 72 calendar hours of the center becoming aware of the death for all sites except US. Adverse Event form should be completed for death for all sites except US. Adverse Event form is not required for death for US sites. Notification of death should include a detailed statement of the pertinent events and be signed by the investigator in addition to the appropriate case report forms (Patient Death form and Patient Withdrawal form). It is the investigator's responsibility to notify the IRB/MEC per the IRB/MEC policy. Details of death and the following information, if available, should be provided in a letter to St. Jude Medical by the investigator summarizing the patient's course since enrollment in the study:

- Date and time of death
- Place death occurred (e.g. hospital, nursing home, patients home)
- If death was witnessed
- Identification of the rhythm at the time of death, if known (include any available documentation)
- Cause of death
- Any other circumstances surrounding the death
- Approximate time interval to death from the initiating event.
- Autopsy report (if performed)
- Whether it was device and/or procedure related
- Whether it was related to the study
- Device configuration at the time of death

Provide clinical notes and witness statements. If possible, interrogate the pulse generator. Retrieve and print all episode diagnostics, IEGMs, and programmed parameters. If applicable, the pulse generator should then be programmed OFF.

Every attempt should be made to explant the pulse generator and/or leads intact. Any explanted devices or leads should be returned to St. Jude Medical for analysis promptly. In the event that the device is not explanted, the above procedure must be followed to retrieve the data. The reason the pulse generator and/or lead(s) are not being returned to St. Jude Medical must be stated clearly on the case report form.

10.0 Withdrawals

Withdrawal is defined as termination of participation of a patient from a clinical trial. All reasonable efforts should be made to retain the subject in the clinical trial until completion of the clinical trial. Reasons for withdrawal include, but are not limited to the following:

- Patient Death
- Patient and/or Family Request
- Patient Participation terminated by Investigator
- Sponsor Request
- System Explant
- Lost to Follow-up: A patient is considered lost to follow up when reasonable efforts to contact the patient have been exhausted and study personnel have abandoned such efforts. Reasonable efforts is defined as a minimum of two documented phone calls made by personnel at the study center to the patient or emergency contact and a certified letter was sent to the last known address

A Withdrawal and other applicable CRFs (e.g. Death or AE) should be completed and sent to St. Jude Medical.

In order to build a comprehensive database for the treatment options and HF progression of CRT non-responders, it is important that patients are retained in the registry for the entire duration of the registry. If there is a potential withdrawal in the registry, please contact a member of the study team to see if there is anything that can be done to keep the patient in the registry.

11.0 Statements of compliance

The study will be performed in accordance with the most current versions of the World Medical Association (WMA) Declaration of Helsinki, ISO 14155 and any regional and/or national regulations and will be compliant to this International Standard and any regional and national regulations, as appropriate.

The investigator shall not start enrolling patients or requesting informed consent prior to obtaining IRB/Ethics Committee approval and Competent Authority approval, if applicable, until receiving authorization from the sponsor in writing for the study.

If additional requirements are imposed by the IRB/Ethics Committee or Competent Authority they shall be followed, if appropriate.

12.0 Risk Analysis

The risks involved with this study are similar to those associated with implantation and follow-up of other commercially available CRT systems. There are no additional risks to the patients enrolled in this study.

13.0 Investigator Information

This clinical study will be conducted by investigators with experience and/or willingness to be trained in the use of the device therapy for the treatment of heart failure patients with CRT devices. A principal investigator should have experience in and/or will be responsible for:

- Conducting the clinical investigation in accordance with the signed agreement with St. Jude Medical, the study plan, GCP guidelines, and any conditions of approval imposed by the IRB/MEC
- Providing signed Investigator/Co-Investigator (s) Agreement
- Providing signed Financial Disclosure Form for Clinical Investigators
- Providing IRB/MEC Approved Informed Consent
- Collection and archiving of data obtained pursuant to the requirements of the investigational plan during the course of the study and after the study has been completed
- Screening and selecting appropriate patients

It is acceptable for the principal investigator to delegate one or more of the above functions to an associate or co-investigator, however, the principal investigator remains responsible for the proper conduct of the clinical investigation, complying with the investigational plan and collecting all required data. In clinical investigations involving active implantation of an investigational product, the investigation is not transferable to other implant centers attended by the investigator unless prior approval is obtained from St. Jude Medical.

14.0 Consent Materials

Failure to obtain informed consent from a patient prior to study enrollment should be reported to St. Jude Medical within 5 working days and to the reviewing IRB consistent with the IRB's reporting requirements.

15.0 IRB Information

IRB/MEC approval for the study and informed consent will be required prior to beginning the study. A copy of the IRB/MEC approval and corresponding informed consent must be forwarded to St. Jude Medical prior to authorization of the institution to begin the study. Any withdrawal of IRB approval should be reported to St. Jude Medical within 5 working days of the withdrawal of approval.

Institutional Review Board (IRB/MEC) for participating Institutions
A list of IRBs for Institutions participating in the study will be provided upon request.

16.0 Other Institutions

The name and address of each institution or investigator, at which a part of the investigation may be conducted, that has not been identified under IRB information, will be provided upon request.

17.0 Records and Reports

The principal investigator (PI) shall maintain all essential study documents from prior, during and (as specified) after the study on file at the site for a minimum of 15 years after the termination of this study, or longer as per local laws, whichever is later.

The PI must contact the sponsor prior to destroying or archiving off-site any records and reports pertaining to this study to ensure that they no longer need to be retained on-site.

All original patient files must be stored for the longest possible time permitted by the regulations at the hospital, research institute, or practice in question. If archiving can no longer be maintained at the site, the investigator will notify the sponsor.

All data and documents shall be made available on request of the relevant authorities in case of an audit.

The sponsor will archive and retain all essential study documents from prior, during and (as specified) after the study as per requirements.

18.0 Publication

This study will be posted on ClinicalTrials.gov and results will be posted on ClinicalTrials.gov as required.

19.0 References

Reference List

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Appendix A

Informed Consent for ADVANCE-CRT Registry

Introduction

You are being asked to take part in this research study because your doctor has determined that you may qualify to take part in the ADVANCE CRT Registry/Observational study. This form explains why this research is being done and what your role will be if you decide to participate. This form also talks about the possible risks that may happen if you take part in this study. This study is sponsored by St. Jude Medical.

Please read this form, and ask your study doctor any questions about the study so that you can have your questions answered before you decide if you want to take part in the study. Please take your time and talk about this information with your family, friend, or family doctor.

This consent form may contain some words that you do not understand. Please ask the study doctor or the study staff to explain any words or information that you do not understand.

If you agree to be in the study, you will need to sign this form. Taking part in this study is entirely voluntary. You may decide not to participate without penalty or loss of benefits to which you are otherwise entitled. This is not a consent form for the CRT system implantation.

Background

In heart failure, the heart cannot pump enough blood to the body. The basic function of the heart is to deliver oxygen-rich blood to the body. When the heart is unable to deliver enough oxygen-rich blood, it results in heart failure. The implanted device has the ability to pace both the right and left side of your heart to improve your heart's ability to pump. Pacing both sides of your heart may help your heart to beat more effectively which may improve your heart failure symptoms. This type of therapy is called **C**ardiac **R**esynchronization **T**herapy (CRT).

A CRT system has three (3) wires (also known as leads or electrodes). The leads are inserted through your veins, positioned in your heart and after testing, connected to the device. These wires allow information to travel between your heart and the device, and help the device to monitor your heart. The study doctor will use x-rays to be sure that the wires are positioned correctly. Your CRT can be a CRT-P (Pacemaker) or CRT-D (Defibrillator). After testing is finished, a pocket for the device will be made under the skin in the left or right upper chest near the shoulder and the incision will be closed.

Cardiac resynchronization therapy (CRT) has proven to be beneficial in advanced heart failure (HF) patients. However, there is a sub-set of patients who do not respond optimally to CRT therapy (non-responders) and little attention has been paid to understanding how non-responders are identified, treated and followed-up, especially in real world practice.

Purpose

The purpose of this registry is to understand comprehensive clinical care strategies for CRT patients, especially non-responders in real-world clinical practice. The registry aims to provide an understanding of the rate of non-responders to CRT, treatment strategies used to treat the non-responders and the role of remote-monitoring in the continued care of non-responders.

Visit Schedule and Procedures

If you are implanted with a market approved St. Jude Medical CRT system you will be eligible for enrollment in the registry within 30 days post-implant of the device. Once enrolled, you will be followed every 3 months until 12 months post- implant. The responder/non-responder evaluation will occur during **the 6 month office visit** and criteria used for determining the response to CRT will be recorded.

Enrollment (≤ 30 days post device implant)

After you have voluntarily signed the informed consent form the following evaluations will be obtained:

- Medical History – pertinent cardiac and health information including NYHA Classification (your current heart failure status assessed by your study physician)
- Medications - your current medications
- ECG – check your heart rhythm
- Echocardiogram – Pre-implant imaging to determine how your heart is pumping
- Device Session Record- device check of your CRT System

Month 6 In-office Visit

The following evaluations will be done:

- Current health status regarding your heart
- Medications – collect information regarding your current medications
- Device Session Record – device check of your CRT System
- Patient Global Assessment (PGA) – a single interview question to see how you are feeling as compared to pre-implant.
- NYHA Classification – assessed by qualified study personnel
- Responder/Non-Responder Evaluation – determined by your study physician
- EKG and Echocardiogram –if requested by your study doctor per standard of care
- Any reprogramming of your device or any new treatment or modification of your current treatment will be collected

Month 3, 9, and 12Follow-Up Visits
3 and 9 month visits may be done in your doctor's office or remotely via Merlin home transmitter system and a phone call follow-up. 12 month visit is required to be done in your doctor's office.
The following evaluations will be done:

- Current health status regarding your heart
- Medications – collect information regarding your current medications
- Device Session Record – device check of your CRT System
- Patient Global Assessment (PGA) – a single interview question to see how you are feeling as compared to pre-implant. *Done up through Month 12 Visit.
- EKG and Echocardiogram – collected if requested by your study doctor per standard of care
- Any reprogramming of your device or any new treatment or modification of your current treatment will be collected
- NYHA Classification- assessed by qualified study personnel at all office visits
- For office visits done at 9 and 1236 month visits, status of your response to CRT will be evaluated by your study physician (or "study provider").

Optional

The following questionnaires can be administered at Enrollment, 6 and 12 month visits

- Modified Specific Activity Scale (SAS) Questionnaire- contains questions about your activity level to help assess your heart failure
- Minnesota Living With Heart Failure (MLWHF) Questionnaire – contains questions about the effects of heart failure and treatments for heart failure on your quality of life
- EQ5D Questionnaire – contains health related questions to assess a quality of life score

There may be a representative of the sponsor at your study visits and the representative may carry out some of the study procedures. The study doctor may direct a representative from the sponsor to collect the signal information. At the study doctor's direction, the sponsor representative may also program your device or run tests to see if your device is working as expected. The sponsor's representative will work under the direction of your study doctor or other care provider.

Duration

The registry will enroll at least 1500 CRT patients from estimated 70 centers worldwide in order to identify and assess a maximum 500 patients who are identified as CRT non-responders. Patient participation in the study is completed upon completion of the 12 month follow-up visit.

Risks

You are not undergoing any experimental techniques or procedures. Your doctor will review the risks related to a standard CRT System implantation in a separate consent form. The St. Jude Medical CRT System has been previously approved by the FDA or by or similar government agencies in other countries. If you are pregnant or planning to become pregnant, you should discuss your participation with your study doctor. Patients who become pregnant while taking part in the study should contact the study doctor right away.

There may be other risks to you that are not known at this time.

Benefits

You may or may not benefit directly from participating in this study. However, the information gathered in this study will add to the understanding of treatment options for patients with heart failure.

Alternatives

Your doctor will discuss other options available to you. Your decision to be in this registry is voluntary. You do not have to be in the registry if you do not want to, and you can change your mind at any time. There will be no penalty to you, and you will not lose any benefits. Your regular medical care at this registry center will not change if you decide not to participate.

Your doctor or sponsor can withdraw you from the registry at any time, even if you want to continue to be in the registry. This could happen if:

- Your doctor believes it is best for you to stop being in the registry.
- You do not follow directions about the registry.
- The sponsor stops the registry for any reason.

If you decide to discontinue participation in this study, tell your doctor or study staff. If you stop being in the registry early, your doctor or study staff may ask you some questions about being in the registry. They may also ask to have additional information collected to help your withdrawal from the study happen safely.

Confidentiality

If you decide to take part in this study, your medical records and personal information will be kept private to the extent allowed by federal, state, and local law. No personal information about you, your illness, or your treatment will be made public.

Information (data) collected from the study will be sent to St. Jude Medical. A special code (letter and number combination) will be used to identify your personal information.

The data may be given to governmental agencies, for example: the Food and Drug Administration (FDA) or similar government agencies in other countries. St. Jude Medical may export data to countries where different data protection laws apply.
Only information about your medical condition as it relates to the CRT System will be provided to St. Jude Medical. In order to verify study data, monitors from governmental agencies (for example: FDA), St. Jude Medical, Contract Research Organizations hired by St. Jude Medical and the Institutional Review Board (IRB)/Ethics Committee (EC) will also have the right to review your medical records as they relate to this study. Data collected during the study may be used for publication(s) but the publications will not include your name or any information that can identify you. In addition, data collected during this study may be used for future research, but your name and information that can readily identify you will not be used.

A description of this clinical trial will be available at **http://www.ClinicalTrials.gov**, as required by U.S. Law. This web site will not include information that can identify you. At most, the web site will include a summary of the results. You can search this web site at any time.

If you receive medical care from a doctor other than your study doctor while taking part in this study, you agree that your medical records will be made available for the collection of data related to this study. To help our study center obtain those medical records, you give permission to provide access to your medical records that may include device records, office visits, laboratory results, surgical/operative reports, medication reports, autopsy report and death certificate.

Costs

You, your insurance company or government health care is responsible for the costs of all tests, procedures and devices that are standard medical treatment for your condition. This is care that would be performed whether or not you participated in this study. There is no guarantee that your insurance company will cover 100% of these costs. You should check with your insurance company to verify coverage or payments of these procedures.

The sponsor of this study is paying for cost of data capture and items that are not deemed standard of care/routine care in the study to the study center.

Compensation

No payment will be made to you for taking part in this study.

What if you are injured because of the study?

If you are injured as a direct result of taking part in this study, medical treatment will be available to you. You, or your insurance company, will be responsible for all costs incurred as a result of that treatment. No other arrangement has been made for financial payments or other forms of compensation (such as lost wages, lost time or discomfort) with respect to such injuries. You do not waive any legal rights by signing this consent form.

During the study, if you experience any medical problems or illnesses from taking part in this study, please contact Dr. _____ at ___-___-_____.

What are your rights if you decide to take part in this study?

Your signature on this consent form means that you have received information about this research study and that you agree to be a part of the study.

You may stop taking part in the study at any time without giving any explanation, and there will be no penalty or loss of benefits to which you are otherwise entitled. If you wish to stop taking part in this research study for any reason, you should contact Dr. _____ at -___-___-_____. A decision to withdraw or to not take part in the study will not affect the quality of medical care that you receive. Your decision will not result in any penalty or loss of benefits to which you are otherwise entitled or affect your future medical care.

Your doctor or the sponsor, St Jude Medical, may decide to withdraw you from the study at any time without your consent. If it is felt to be in your best interest, or if the study is stopped, your doctor may withdraw you from this research. If you have a problem as described in the risks section, or if you become ill during the research, you may have to stop participating in the study, even if you would like to continue. Your study doctor will make this decision. Your study doctor or designee will discuss with you what follow-up is required if you decide to withdraw, or are withdrawn from the study before the study is finished.

If important information is learned during the course of this study, your doctor will be notified by St. Jude Medical. You will be told of any important new information that is learned during the course of this research study that may affect your condition or your willingness to continue to take part in this study.

Questions

If you have any questions about the study or taking part in this study, please contact Dr. _____ at ___-___-_____.

In addition, if you have questions about your rights as a research patient, or if you have complaints, concerns, or questions about the research, please contact _____ at -___-___-_____.

You are making a decision on whether or not to take part in the study. Your signature indicates that you have read the information in this form and have decided to take part in the study. You will be given a signed copy of this form to keep.

_____

Printed Name of Patient

_____ _____

Signature of Patient Date

_____ _____

Signature of Person Obtaining Consent Date