Title: Electrocardiogram for Programming in Cardiac Resynchronization Therapy Trial

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Electrocardiography for Programming In Cardiac Resynchronization Therapy (EPIC) Trial

Principal Investigator: Amit Noheria, MBBS, SM

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Protocol Revision History

Initial Approval Version	**Protocol v1.0**	**XX/XX/XXXX**

Electrocardiography for Programming In Cardiac Resynchronization Therapy (EPIC) Trial

Principal Investigator's Signature Page

The study will be conducted in accordance with the International Conference on Harmonisation guidelines for Good Clinical Practice (ICH E6), the Code of Federal Regulations on the Protection of Human Subjects (45 CFR Part 46), and the NIDCR Clinical Terms of Award. All personnel involved in the conduct of this study have completed human subject's protection training.

The signature below constitutes the approval of this protocol and the attachments, and provides the necessary assurances that this trial will be conducted according to all stipulations of the protocol, including all statements regarding confidentiality, and according to local legal and regulatory requirements and applicable US federal regulations and ICH guidelines.

Signed: _____ Date: _____

Name: Amit Noheria, MD

Title: Principal Investigator

A Introduction

A1 Study Abstract

Heart failure with reduced ejection fraction is a major global health problem. Every year, over 200,000 patients with heart failure receive pacing device implants for cardiac resynchronization therapy (CRT). However, one-third of the patients receiving CRT do not derive any benefit, a large population with refractory heart failure symptoms, high mortality, and tremendous healthcare costs. Our overall objective is to reduce heart failure by physiological individualized optimization of CRT pacing therapy guided by 12-lead electrocardiography (ECG).

Patients with heart failure and left bundle branch block benefit from CRT. This delivers pacing from right ventricle (RV) and left ventricle (LV) synchronously, the resultant ventricular electical resynchrony leading to improved cardiac mechanics and acute hemodynamics, and subsequent reverse structural cardiac remodeling. This leads to reduced heart failure symptoms, hospitalizations and death. It is not known if programming an individually optimized RV-LV pacing offset to maximize electrical resynchrony can improve benefit from CRT.

The proposed study is a *randomized controlled trial* in patients undergoing implant of a CRT pacemaker/defibrillator device for clinical indications to evaluate benefit of RV-LV offset programming using ECG vs. standard nominal CRT programming without RV-LV offset. Patients receiving CRT devices will be randomized to either (A) active intervention of programming individualized RV-LV pacing offset to optimize ECG or to (B) active control of nominally programming CRT device without RV-LV offset. The patients will be followed to evaluate changes in heart failure endpoints including echocardiography, quality-of-life, functional performance and a blood biomarker.

A2 Primary Hypothesis

Among patients receiving CRT, individualized RV-LV offset programming using ECG will result in improvement of heart failure endpoints.

A3 Purpose of the Study Protocol

The results of this study will provide key mechanistic insights on the salutary effects of CRT on reverse cardiac remodeling. Physiologically-tailored individually-optimized CRT therapy would improve individual patient health by improving heart failure outcomes, and decrease the economic burden of refractory heart failure.

B Background

B1 Prior Literature and Studies

CRT can be lifesaving for heart failure patients with left bundle branch block (LBBB) and delayed electrical activation of the LV lateral wall. A pacing device is used to resynchronize the LV with electrical stimulation from implanted electrodes in the RV and in a LV coronary vein.[1-3] CRT results in improved hemodynamics, beneficial reverse cardiac remodeling, and reduction in adverse outcomes like heart failure hospitalizations and death.[4-10] Every year, over 200,000 CRT procedures are performed in heart failure patients worldwide.[11] However, one-third of CRT patients fail to show a clinical response to CRT with a large implication for the quality and quantity of life, and economic healthcare burden.[6-10,12] Non-response to CRT can be attributed to factors

like irreversible scarring of the heart muscle, absence of sufficient baseline electrical dyssynchrony that is amenable to CRT, suboptimal pacing electrode location, non-adherence to heart failure medications, competing cardiac arrhythmias limiting CRT delivery, and importantly, suboptimal CRT delivery due to non-individually optimized programming of the device.[13-15]

Optimizing RV-LV offset: Previous techniques have been evaluated to individually program RV-LV offset to acutely optimize cardiac mechanics and hemodynamic performance with variable results. These methods included transthoracic echocardiography,[16-18] gated SPECT perfusion imaging,[19] invasive hemodynamic measurements,[20,21] non-invasive digital photoplethysmography,[22] and pacemaker lead sensors to measure peak endocardial acceleration.[23,24] However, these techniques have failed on account of being cumbersome, non-standardized, lacking reproducibility, and failure to show improvement in clinical outcomes. Echocardiography to prospectively guide RV-LV offset optimization has not been demonstrated to be superior to simultaneous biventricular pacing without RV-LV offset.[25,26] The aforementioned techniques for RV-LV offset optimization focus on acute mechanical and hemodynamic effects, without any evaluation of the resulting electrical resynchrony. The disappointing results have led experts to surmise that "*an electrical problem requires an electrical solution*".[27] We hypothesize that the salutary long-term effects of CRT are dependent on its impact on electrical rather than mechanical function.

Commercial device algorithms for RV-LV offset: Some device manufacturers have proprietary algorithms that use the RV-LV activation delay to make a recommendation for RV-LV offset programming.[28-30] An adaptive algorithm for fusion of intrinsic right bundle branch conduction with LV only pacing has also been developed.[31,32] These algorithms are based on relative local activation differences at the RV and LV pacing electrodes, and fail to incorporate activation of bulk of the heart muscle. Further limitations include inability to use thse algorithms in setting of atrioventricular block or atrial fibrillation, and lack of validation to assess impact on clinical outcomes.

ECG for optimizing RV-LV offset: 12-lead ECG is a readily available tool to evaluate the electrical activation of the heart and has been retrospectively used to evaluate CRT in many studies (**Table 1**). It is, however, unclear whether the absence of ECG markers that predict a good response to CRT in an individual patient is due to remediable RV-LV offset programming, or is a result of non-programmable factors like electrode location and scarring of heart muscle; and how many patients will convert to a favorable ECG with RV-LV offset optimization.[48]

Table 1. *Retrospectively using ECG after CRT to correlate with good clinical response.*

QRS duration	Lead V1 (or V2)	Lead I (or aVL)	Frontal plane QRS
• Shorter QRSd (absolute or indexed to baseline QRSd); QRSd shortening ≥25 ms[33-40] • QRS normalization[34]	• R wave[34,37,41,42] • R/S ≥1[43] • R wave amplitude (V1 or V2)[44] • Shortening of RS interval; RS shortening ≥10 ms[45]	• S wave[41] • R/S ≤1[43] • Reversal from positive to negative (lead I & aVL)[46]	• Right axis deviation (from baseline left axis deviation)[44] • Vectorcardiogram QRS amplitude half way between LBBB and LV pacing[47]

ECG has been evaluated prospectively in limited-scope small studies for RV-LV offset optimization.[18,39] A shorter biventricular paced QRS duration (QRSd) has been associated with good CRT response.[33-40] However, RV-LV offset programming to minimize the QRSd is not the most suitable method for RV-LV offset optimization.[39] In a study by Vidal et al., RV-LV offset (-30 ms, 0, +30 ms) determined by shortest QRSd did not predict acute mechanical left ventricular resynchrony on tissue Doppler echocardiography.[49] Other "summed" ECG parameters like 3-dimensional QRS area (voltage-time integral) are conceptually appealing but yet to be evaluated prospectively for CRT programming.[50,51]

B2 Rationale for this Study

We propose to study the heart failure effects of ECG-guided RV-LV offset optimization. In a randomized controlled trial, we will determine whether such individualized RV-LV offset optimization using ECG results in improved reverse cardiac remodeling and other heart failure endpoints.

C Study Objectives

C1 Specific Aim

To determine the impact of individualized RV-LV pacing offset to optimize ECG on reverse cardiac remodeling and other heart failure surrogate endpoints:

After CRT implant, we will *randomize* patients to either (A) active intervention of programming individualized RV-LV offset to optimize ECG or to (B) active control of nominally programming CRT device without RV-LV pacing offset. The *primary outcome* will be the reverse cardiac remodeling after 3-12 months, as assessed by *LV end-systolic volume* on echocardiography.[52] The secondary outcomes will include quality-of-life (Kansas City Cardiomyopathy Questionnaire-12, KCCQ-12), functional performance (6-minute hall walk distance) and a prognostic biomarker (serum NT-proBNP).

C2 Rationale for the Selection of Outcome Measures

The primary outcome is echocardiographic LV end-systolic volume. LV end-systolic volume is a reliable surrogate for clinical outcomes in clinical heart failure trials.[52] Secondary outcomes include quality-of-life (KCCQ-12), functional performance (6-minute hall walk distance) and a prognostic biomarker (serum NT-proBNP). KCCQ-12 and 6-minute hall walk are standard metrics to assess quality-of-life and functional status in heart failure research.[53-55] Serum NT-ProBNP strongly predicts improvement in cardiac function and favorable prognosis after CRT.[56]

D Study Design

D1 Overview or Design Summary

Once the eligibility for the study is determined and patient has consented for participation, all study participants will undergo a baseline evaluation (within 6 weeks prior to 2 weeks after CRT device implant/upgrade). Echocardiogram, quality-of-life questionnaire, 6-minute hall walk, blood test, vital signs, ECGs, device interrogation and baseline demographic and medical history including chart review will be obtained. After CRT device implant/upgrade, participants will

undergo physiologic evaluations at various (up to 10 or more) RV-LV offset settings including ECGs and echocardiography. A randomized assignment using a random allocation table in REDCap will be used to program patients to (A) intervention or (B) control RV-LV offset setting. Patients will return for study follow-up between 3-12 months. Follow-up evaluations will include echocardiography, quality-of-life questionnaire, 6-minute hall walk test, blood test, vital signs, ECGs, device interrogation, and follow-up medical history including chart review. The patients will continue to be in extended follow-up through review of their medical charts till the end of the study (12 months from date of CRT implant/upgrade of the the last study participant).

Treatment and control arms: All study patients will receive standard of care clinically indicated medical and device therapy per their treating physicians. After implant of a clinically indicated CRT device or upgrade of a preexisting pacemaker or defibrillator device to CRT system, participants will be randomized 1:1 to treatment arms (A) active intervention of programming individualized RV-LV pacing offset to optimize ECG or to (B) active control of nominally programming CRT device without RV-LV offset. Of note, both intervention and control treatment are active FDA-approved CRT therapies and no investigational device or programming will be used, and no clinically indicated treatment will be withheld from any patient. At any time, if in the judgment of the patient's treating physicians or the research team, any treatment including CRT programming different from the study protocol is necessitated for clinical reasons, the appropriate clinically indicated changes will be made. At the end of the study, if the participant is clinically doing well and the programmed CRT settings are deemed clinically appropriate they will be retained, else the CRT programming may be changed as per standard of care.

Enrolled participants who have a failed or unsatisfactory LV lead implant will not be randomized.

D2 Subject Selection and Withdrawal

2.a Inclusion Criteria

1. Patients ≥18 years of age who are able to give consent.
2. Diagnosis of systolic heart failure.
3. Planned to undergo new CRT device implant (or upgrade of preexisting pacemaker or defibrillator device to CRT system) for standard clinical indications.
4. Expected to have over 95% heart beats resynchronized with CRT (absence of competing arrhythmias or plans to not immediately activate CRT therapy).

2.b Exclusion Criteria

1. Unable to comply with the study follow-up.
2. Life expectancy ≤1 year.

2.c Ethical Considerations

This is a patient-oriented research plan to optimize delivery of CRT in humans. Patients with heart failure undergoing clinically indicated CRT device implant/upgrade would form the study population. Human subjects receiving clinically indicated CRT are needed to evaluate the clinical impact of individulzied RV-LV offset programming of CRT.

2.d Subject Recruitment Plans and Consent Process

- Subjects will be enrolled from patients undergoing CRT device implant/upgrade at Barnes-Jewish Hospital. Patients will provide a signed informed consent prior to participation in the study. Enrollment will be voluntary. No children will be enrolled.
- Informed consent will be obtained by study personel in person with ample opportunity to ask questions, consider options and decline participation. Participants will be educated about

the rationale of the research, logistics and follow-ups for the study, and risks associated with the study. The subjects will sign a Washington University Institutional Review Board approved informed consent document prior to being enrolled in the study. Only adult patients who are personally able to provide informed consent will be enrolled. If a patient is unable to consent, they will not be enrolled.

- No special vulnerable populations will be enrolled.

2.e Randomization Method and Blinding

A 1:1 randomization scheme using a random allocation table in REDCap will be used. The patient and personel assessing study outcomes will be blinded to the randomized assignment.

2.f Risks and Benefits

- Participation in the research study requires a commitment of time by the participants. Every subject will undergo, both at enrollment and at the follow-up visit, evaluations including echocardiography, quality-of-life questionnaire, 6-minute hall walk test, blood test, vital signs, ECGs, device interrogation, and clinical history including chart review. After CRT implant/upgrade, participants will have a physiological assessment of various (up to 10 or more) RV-LV offset settings including ECGs and echocardiography. During study related CRT device evaluation, there is an extremely small risk of inducing cardiac arrhythmias that is similar to the risk entailed in standard routine clinical device interrogations. In the improbable event of an unstable cardiac arrhythmia, the patient will be immediately cardioverted using the implanted pacemaker/defibrillator or using an external defibrillator. A trained clinical electrophysiologist will be present in person during all study related interrogation and programming of CRT device.
- The alternative for human subjects to research participation is to not enroll for the study and undergo standard care with RV-LV offset programming at the discretion of the treating physician. The research question is a state of equipoise where it is not clear whether RV-LV pacing offset optimization using ECG is superior to nominally programming CRT device without any RV-LV offset. It is the intention of this research to investigate if there is any additional CRT benefit with individualized optimization of RV-LV offset.
- Potential benefits of the research to participants include close follow-up required for the trial post CRT system implant. Potential benefit of this research to other CRT recipients would be determination of individualized optimal RV-LV offset programming for maximizing CRT benefit and alleviation of heart failure.
- This outcome of this research will impact >200,000 heart failure patients who receive CRT every year, with more individually optimized delivery of CRT.[11] This will be especially impactful for the large group of patients with refractory heart failure who currently derive no benefit from CRT. Improvement in CRT response would ultimately impact individual patient health by improving heart failure outcomes and reduce the economic burden on healthcare systems.[12]

2.g Early Withdrawal of Subjects

- The participants may withdraw by telling the study team they are no longer interested in participating in the study or by sending in a withdrawal letter.
- The investigator might end a subject's participation in this research study earlier than planned. This may happen for no reason, because in the treating physician or study team's judgment it would not be beneficial for the participant to continue, because the participant's condition has become worse, or because the research has ended.

2.h When and How to Withdraw Subjects

Subjects can be withdrawn from the study at any time by communicating directly to the study team or sending a withdrawl letter.

2.i Data Collection and Follow-up for Withdrawn Subjects

All data collection and follow-up for the purposes of the study will be terminated for subjects withdrawn from the study. At the time of withdrawal, if the participant is clinically doing well and the programmed CRT settings are deemed clinically appropriate they will be retained, else the CRT programming may be changed as per standard of care.

E Study Procedures

E1 Screening for Eligibility

Patients for this study will be screened and approached for participation prior to or after a clinical CRT implant/upgrade procedure at Barnes-Jewish Hospital Clinical.

E2 Schedule of Measurements

The baseline evaluation will encompass one, two or more visits in the time window 6 weeks prior to 2 weeks after CRT device implant/upgrade date. If the patient passes the eligibility screening and signs informed consent, their baseline evaluation will include echocardiogram, quality-of-life questionnaire, 6-minute hall walk, blood test, vital signs, ECGs, device interrogation and baseline demographic and medical history including chart review. After CRT device implant, participants will undergo physiologic evaluations at various (up to 10 or more) RV-LV offset settings including ECGs and echocardiography. The randomized CRT pacing assignment will be programmed.

The follow-up evaluation (usually 3-12 months) will encompass one or more visits and include echocardiography, quality-of-life questionnaire, 6-minute hall walk test, blood test, vital signs, ECGs, device interrogation, and follow-up medical history including chart review. The patients will continue to be in extended follow-up through review of their medical charts till the end of the study (12 months from date of CRT implant/upgrade of the the last study participant).

Table 2.

EPIC Study Calendar

	Baseline Evaluation	**CRT Evaluation**	**Follow-up Evaluation**	**Extended Follow-up**
Timeline (w.r.t. date of CRT device implant/upgrade)	-6 to +2 weeks	0 to +2 weeks	3 to 12 months	Till study completion
Informed Consent	✓			
Medical History	✓		✓	✓
Vital Signs	✓		✓	

Echocardiogram	✓	✓	✓	
KCCQ-12	✓		✓	
6-Minute Hall Walk	✓		✓	
Blood Testing	✓		✓	
Device Interrogation	✓	✓	✓	
12-lead ECGs	✓	✓	✓	
Randomization		✓		
Adverse Event Monitoring	✓	✓	✓	✓

E3 Safety and Adverse Events

3.a Adverse Events and Reporting Requirements

Any adverse or significant events including heart failure hospitalizations, incident arrhythmias, complications and deaths will be tracked during the study participation (i.e. from time of consent through completion of the study). A baseline evaluation of all subjects' current medical problems will be documented and evaluated using the reporting classifications below prior to any baseline procedures. Any exacerbation of these medical problems will be documented as an adverse event. All adverse events will be tracked from time of consent through completion of the study.

i Adverse Event Definitions

Term	Definition
Adverse Event (AE)	An unfavorable medical occurrence in a human subject including any abnormal sign, symptom, or disease.
Serious Adverse Event (SAE)	An adverse experience occurring that results in any of the following outcomes: a. Death b. A life-threatening adverse experience c. Inpatient hospitalization or prolongation of existing hospitalization d. A persistent or significant disability/incapacity (i.e. a substantial disruption of a person's ability to conduct normal life functions) e. A congenital anomaly/birth defect f. Any other experience which, based upon appropriate medical judgment, may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed above

Life-Threatening	An adverse experience that places the subject (in the view of the investigator) at immediate risk of death from the reaction as it occurred, i.e. it does not include a reaction that, had I occurred in a more severe form, might have caused death.

ii Attribution, Anticipation, and Expectedness of AEs

The terms for attribution, expectedness, and severity are defined as follows:

1) Attribution

Classification	Description
Definitely Related	The adverse event, incident, experience or outcome was definitely caused by the procedures involved in the research.
Probably Related	There is a reasonable probability that the adverse event, incident, experience or outcome may have been caused by the procedures involved in the research.
Possibly Related	There is a reasonable possibility that the adverse event, incident, experience or outcome may have been caused by the procedures involved in the research.
Unlikely Related	The adverse event, incident, experience or outcome was unlikely caused by the procedures involved in the research.
Unrelated	The adverse event, incident, experience or outcome was unrelated to the procedures involved in the research.

2) Anticipation

Classification	Description
Anticipated	Any incident, experience, or outcome that is anticipated to occur due to the research (i.e. procedures, investigational medication, etc.).
Unanticipated	Any incident, experience, or outcome that meets <u>all</u> of the following criteria: a. unexpected (in terms of nature, severity, or frequency) given (a) the research procedures that are described in the protocol-related documents, such as the IRB-approved research protocol and informed consent document; and (b) the characteristics of the subject population being studied; b. related or possibly related to a subject's participation in the research; and

	c. suggests that the research places subjects or others at a greater risk of harm (including physical, psychological, economic, or social harm) related to the research than was previously known or recognized.

3) Expectedness

Classification	Description
Expected	Any adverse event that is a known or foreseeable risk associated with the procedures involved in the research or is an expected natural progression of any underlying disease, disorder, or condition.
Unexpected	Any adverse event occurring in one or more subjects in a research protocol, the nature, severity, or frequency of which is not consistent with either: a. the known or foreseeable risk of adverse events associated with the procedures involved in the research that are described in (a) the protocol–related documents, such as the IRB-approved research protocol, any applicable investigator brochure, and the current IRB-approved informed consent document, and (b) other relevant sources of information, such as product labeling and package inserts; or b. the expected natural progression of any underlying disease, disorder, or condition of the subject(s) experiencing the adverse event and the subject's predisposing risk factor profile for the adverse event.

iii Noncompliance and Exceptions

Term	Definition
Noncompliance	Failure to follow an applicable regulation or institutional policies that govern human subjects research or failure to follow the determinations of the IRB. Noncompliance may occur due to lack of knowledge or due to deliberate choice to ignore regulations, institutional policies, or determinations of the IRB.
Serious Noncompliance	Noncompliance that materially increases risks, that results in substantial harm to subjects or others, or that materially comprises the rights or welfare of participants.
Protocol Exceptions	A planned deviation from the approved protocol that are under the research team's control. Exceptions apply only to a single participant or a singular situation.

	Washington University central IRB pre-approval of all protocol exceptions must be obtained prior to the event for both the coordinating center and all participating sites. Participating sites must also follow their local IRB's guidelines for any submission that needs to be made to their local IRB.

All incidences of noncompliance and protocol exceptions will be tracked from time of IRB approval until the close of the study.

iv Reporting Requirements

The Washington University Human Research Protection Office (HRPO) requires that all events meeting the definition of unanticipated problem or serious noncompliance be reported as outlined.

The PI is required to promptly notify the IRB of the following events:

- Any unanticipated problems involving risks to participants or others which occur at WU or any BJH or SLCH institution that impacts participants or the conduct of the study.
- Noncompliance with federal regulations or the requirements or determinations of the IRB.
- Receipt of new information that may impact the willingness of participants to participate or continue participation in the research study

These events must be reported to the IRB within **10 working days** of the occurrence of the event or notification to the PI of the event. The death of a research participant that qualifies as a reportable event should be reported within **1 working day** of the occurrence of the event or notification to the PI of the event.

3.b Safety and Compliance, and Medical Monitoring

i Investigator

- In the unlikely event of any acute adverse events during device programming during study participation, they will be addressed in person by the investigator and plans communicated to the treating team. Any significant adverse events related to the research project will be reported to the data safety monitoring committee and the Washington University IRB. The above sections describes the plan for data and safety monitoring of the clinical trial and adverse event reporting to the IRB, to ensure the safety of subjects.
- No investigational treatments will be used for the study. Participants will receive a clinically indicated CRT device per routine care. The only treatment intervention is optimization of RV-LV offset (programmable setting of CRT system) guided by ECG within parameters on CRT devices and programming approved by the FDA.

ii Independent Data and Safety Monitoring Committee

An independent data and safety monitoring committee (DSMC) chaired by Dr. Edward Geltman will be appointed. Dr. Geltman will choose 2 additional members including a statistician and an electrophysiologist. All members of the DSMC will be completely independent and not involved in the conduct of the study. The committee will have access to the study data, in order to determine patient safety.

Dr. Edward Geltman: Dr. Geltman is an experienced advanced heart failure expert and Professor of Medicine at Washington University. In his clinical practice he follows many advanced heart failure patients and patients with CRT devices. He will be able to

adjudicate if heart failure outcomes are attributable to participation in the research study. He has experience in leading DSMC for other cardiovascular research studies.

Electrophysiologist: The electrophysiologist will be experienced in implantation and management of CRT devices. They will be able to adjudicate if any CRT related outcomes or other complications are attributable to participation in the research study.

Statistician: The statistician will be knowledgable in interim safety analyses.

E4 Study Outcome Measurements and Ascertainment

The primary outcome of LV end-systolic volume will be evaluated by blinded study personel with echocardiography. For secondary outcomes, the patients will fill out quality-of-life KCCQ-12 questionnaire, undergo 6-minute hall walk test, and have blood draw for serum NT-proBNP.

F Statistical Plan

F1 Sample Size Determination and Power

We plan to randomize 200 patients that may require enrollment of up to **250 patients**. This gives us 80% power to detect a between-treatment difference of ≥2±5% in the % reduction in LV end-systolic volume from baseline with a 2-sided α-error 0.05. Previous studies have shown that a reduction in LV end-systolic volume from baseline is associated with an improvement in clinical outcomes.[52] As both the study and control arms will receive CRT, albeit with different approach to programming RV-LV offset, any statistical difference in reverse cardiac remodeling between the two RV-LV offset programming strategies will be clinically important.

F2 Statistical Methods

The primary outcome of interest is the LV end-systolic volume.[52] Secondary outcomes include quality-of-life (KCCQ-12), functional performance (6-minute hall walk distance) and a prognostic biomarker (serum NT-proBNP).[53-55] We will perform **t-tests** to assess for differences in the % change from baseline in primary and secondary endpoints between treatment groups. Sub-analyses will evaluate for effect modification by subgroups based on ischemic vs. non-ischemic cardiomyopathy, sex, and magnitude of RV-LV offset based on ECG. We prespecify evaluation of the subgroup with ECG optimized RV-LV offset ≥40 msec. A two-tailed p-value 0.05 will be considered as threshold for statistical significance.

G Data Handling and Record Keeping

G1 Confidentiality and Security

- No specimens, records, or data will be collected from anyone not participating in the study.
- The human study subjects will provide baseline demographic and historical data related to their heart failure and related medical illnesses. This will be collected from their medical chart, patient interview, and patient questionnaire. The subjects will also provide echocardiography, quality-of-life questionnaire, 6-minute hall walk, blood sample, ECG, CRT device interrogation, and clinical information at baseline and follow-up.

- Only the research staff and the data safety monitoring committee will have access to identifiable private information. Password-secured anonymized data will be stored on secure Washington University server (WUSTL BOX) and in REDCap, and kept in confidential study binders maintainded by the Washington Univeristy Cardiovascular Research core in a locked cabinet in a locked suite.
- The data related to the research project will be collected and managed using the standard protocols to protect PHI. Use of patient identifying information will be minimized and participant information will be identified by study ID number. The collection forms will be labeled only with the study ID number.

G2 Records Retention

The collection forms will be kept in confidential study binders at the Washington University Cardiovascular Research core in a locked cabinet in a locked suite. The data will be entered electronically and stored on secure server (WUSTL Box and REDCap).

H Study Monitoring, Auditing, and Inspecting

H1 Study Monitoring Plan

In compliance with the Washington University Institutional Data and Safety Monitoring Plan, the Data and Safety Monitoring Committee (DSMC) will meet to review data at least annually beginning six months after accrual has begun. The report will be prepared by the study statistician with assistance from the study team and will be reviewed by the DSMC. The report will include:

- HRPO protocol number, protocol title, Principal Investigator name, research coordinator name, and statistician.
- Date of initial HRPO approval, date of most recent consent HRPO approval/revision, date of HRPO expiration, study status, and phase of study.
- History of study including summary of substantive amendments; summary of accrual suspensions including start/stop dates and reason; and summary of protocol exceptions, error, or breach of confidentiality including start/stop dates and reason.
- Study-wide target accrual and study-wide actual accrual.
- Protocol activation date.
- Average rate of accrual observed in year 1, year 2, and subsequent years
- Expected accrual end date
- Objectives of protocol with supporting data and list the number of participants who have met each objective.
- Measures of efficacy.
- Abstract submissions/publications
- Summary of any recent literature that may affect the safety or ethics of the study
- Additional information the DSMC may request

The following information will be monitored and provided to the DSMC:

- Enrollment and follow-up
- Adverse events occurring during follow-up, including hospitalizations and death

The DSMC will have complete access to the raw study data throughout the duration of the study.

The DSMC will have complete discretion for terminating the study for concerns of patient safety.

The investigator and the study coordinators will be responsible to report all Adverse Events, Serious Adverse Events (deaths, hospitalizations, life threatening events and any Unanticipated Problems) to the data safety monitoring committee and IRB as described above.

I Study Administration

I1 Organization and Participating Centers

This is a single centre study at Washington University/Barnes-Jewish Hospital.

I2 Funding Source and Conflicts of Interest

This study is funded through Divisional support and American College of Cardiology Presidential Career Development Award to the PI.

I3 Subject Stipends or Payments

None

I4 Study Timetable

Subjects will be enrolled in 2019-2021 and complete study related follow-up by 2022.

J Publication Plan

The trial results will be submitted for publication in an reputed peer-reviewed cardiology journal.

K Attachments

K1 Informed consent document

K2 KCCQ-12 quality-of-life questionnaire

L References

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