Research Protocol – 2020-0831
HIS-Purkinje Conduction System Pacing Optimized Trial of Cardiac Resynchronization Therapy (HOT- CRT)

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TABLE OF CONTENTS

1 ABBREVIATIONS USED IN THE PROTOCOL

Abbreviation	Term
AF	atrial fibrillation
AV	atrioventricular
BBB	bundle branch block
BVP	biventricular pacing
CRT	Cardiac Resynchronization therapy
ECG	electrocardiogram
EF	ejection fraction
EQ-5D	EuroQoL 5D
HBP	His bundle pacing
HF	heart failure
HFH	Heart Failure Hospitalization
HOT-CRT	HPCSP-optimized Trial of CRT
HPCSP	His-Purkinje conduction system pacing
ICD	implantable cardioverter defibrillator
KCCQ	Kansas City Cardiomyopathy Questionnaire
LBBB	left bundle branch block
LBBP	left bundle branch pacing
LV	left ventricular
LVEF	left ventricular ejection fraction
NYHA	New York Heart Association
RBBB	right bundle branch block
RV	right ventricular
sLVP	synchronized left ventricular pacing
VF	ventricular fibrillation
VT	ventricular tachycardia

2 ABSTRACT

Despite the great impact Cardiac Resynchronization therapy (CRT) utilizing biventricular pacing (BVP) has had on heart failure patients, one-third of patients do not respond to CRT, and CRT may result in worsening heart failure and increased mortality in some patients. We hypothesize that in patients with heart failure (HF) eligible for CRT as part of routine standard-of-care based on accepted Class I or Class II indications, His-Purkinje conduction system pacing (HPCSP)-optimized trial of CRT (HOT-CRT) may not only be safely achieved but will also be associated with superior echocardiographic and clinical outcomes compared to conventional BVP during CRT. We aim to determine the overall rate of successful HOT-CRT at the time of implant of CRT in a pilot study, collecting data in BVP and HOT-CRT on acute and mid-term outcomes at Geisinger. Primary outcomes include freedom from major complications and change in left ventricular ejection fraction (LVEF) at 6 months. To compare the effectiveness of HOT-CRT versus traditional CRT in patients with heart failure, patients will be randomized to either HOT-CRT or BVP and will remain blinded to their treatment allocation. Treating physicians will be aware of assignment in order to facilitate routine device follow-up. Echocardiographic evaluation will also be performed in a blinded manner. Crossover is permitted between treatment group allocation as follows: (1) If CS lead (BVP) cannot be placed due to difficult cannulation of the CS, limited branches at the posterolateral or lateral wall, or phrenic nerve capture, patients may then crossover to HOT-CRT. All efforts will be made to achieve CRT using CS lead. (2) HOT-CRT patients may crossover if HPCSP lead cannot be positioned with adequate stability and reasonable pacing output and acceptable electrical resynchronization cannot be achieved. Echocardiographic response to CRT (improvement in left ventricular ejection fraction) and a combination of clinical, electrocardiographic, and echocardiographic endpoints will be prospectively studied. Any complications will also be assessed prospectively, both acutely and throughout the study period.

3 BACKGROUND AND SIGNIFICANCE

Heart failure (HF) is one of the leading causes of hospitalization, morbidity and mortality in the United States. In addition, healthcare costs of heart failure in the United States exceed $35 billion annually.[1] CRT utilizing BVP has made major improvements to symptoms and mortality in HF patients with New York Heart Association (NYHA) symptoms class II, III or ambulatory IV, left ventricular (LV) ejection fraction (EF) < 35% and widened QRS by electrocardiogram (ECG).[2,3,4] Despite the great impact of CRT in HF, one-third of patients do not respond to CRT.[5] In some patients, CRT may result in worsening heart failure and increased mortality. The anatomic location of the LV lead, patient specific characteristics, myocardial substrate and ECG

characteristics may affect clinical response. Novel approaches to improve CRT outcomes are necessary and several new approaches are evolving. Small studies have examined patients with intact intrinsic atrioventricular (AV) conduction and normal or near-normal conduction via the right bundle branch. In these patients, LV pacing synchronized to produce fusion with the intrinsic activation via the right bundle branch (sLVP) results in superior LV and right ventricular (RV) electrical activation and function compared to biventricular pacing. In a study using sLVP, patients with >50% sLVP had significantly decreased heart failure hospitalization and mortality compared to patients with <50% sLVP.[6] However, this algorithm is limited by the need for patient's intact AV nodal conduction to allow for conduction to occur normally via the right bundle branch. Significant number of patients with heart failure require atrial pacing and or have long PR intervals limiting the utility of this approach. Recent studies suggest improved outcomes with His bundle pacing (HBP).[7] HBP can correct underlying bundle branch blocks and thereby decrease or normalize QRS duration. Studies have shown high rates of hyper-response to CRT utilizing His bundle pacing.[8] A randomized crossover study showed comparable benefits with HBP compared to standard CRT.[9] A recent small pilot study (HisSync) comparing HBP with BVP could not demonstrate superiority with HBP due to high crossover rates.[10] Nonetheless this study showed a trend towards improved clinical and echocardiographic outcomes with HBP compared to BVP. Many patients in these studies show partial correction of left bundle branch block (LBBB) with HBP. HBP can also provide robust AV synchronization in patients with long AV delays or AV nodal block. By maintaining normal conduction through the right bundle and part or most of the left bundle, HBP can provide clinical and hemodynamic benefits. Our early experience shows that His bundle Optimized LV pacing can combine AV synchrony with fusion LV pacing.[11] The QRS duration and morphology can mimic normal physiologic pattern in this situation. Permanent His bundle pacing utilizes FDA-approved clinical tools to precisely position the pacing lead at the His bundle region and stimulates the ventricles through the intrinsic His-Purkinje system, which results in synchronous electrical and mechanical activation. There is great clinical uncertainty for CRT utilization in HF patients "in the middle" with intermediate ECG criteria; QRS duration 130-149ms or non-LBBB morphology; currently Class IIa-IIb indications. This is a significant clinical problem because these patients with intermediate ECG criteria represented 40-45% of those enrolled in the large randomized trials that showed benefit of CRT. Even in these patients with right bundle branch block (RBBB), HBP has been shown to normalize conduction by recruiting the right bundle conduction.[12] Because of the ability of His-Purkinje conduction system pacing to achieve significant electrical resynchronization in the majority of patients undergoing CRT, this form of pacing has the theoretical potential to improve

clinical outcomes compared to BVP. Lack of direct comparison by means of randomized studies are the current limitations of this approach.

3.1 Hypothesis

We hypothesize that:

1. in patients with advanced heart failure and evidence of intraventricular conduction disease who meet criteria for CRT, HOT-CRT may be safely achieved and,
2. HOT-CRT will be associated with superior echocardiographic and clinical outcomes compared to conventional biventricular pacing (BVP) during CRT.

3.2 Specific Aim 1

To determine the overall rate of successful HOT-CRT at the time of implant of CRT. Patients randomized to HOT-CRT but who cannot be successfully implanted with a HPCSP lead will crossover to traditional coronary sinus (CS) lead position.

3.3 Specific Aim 2

To perform a pilot study to collect data in BVP and HOT-CRT on acute and mid-term outcomes at Geisinger. Acute outcomes include change in QRS duration pre-and post-pacing (degree of QRS narrowing) and incidence of major periprocedural complications (pericardial tamponade, need for lead revision, etc.). Mid-term outcomes include echocardiographic response at 6 months along with a composite clinical outcome of heart failure hospitalization, ventricular arrhythmias, crossover, and all-cause mortality.

4 PRELIMINARY DATA

In patients with bundle branch blocks (BBB), capture thresholds to correct the BBB may limit the ability to achieve successful HBP. High pacing thresholds may lead to premature battery depletion. Recently an alternative form of conduction system pacing has gained significant momentum. By pacing distal to the site of conduction block in the proximal left bundle via deep lead placement in the interventricular septum, very low and stable capture thresholds can be achieved.[13,14,15,16,17] This new approach, called left bundle branch pacing (LBBP), has been shown to achieve significant narrowing of the paced QRS and improve clinical outcomes in patients with LV dysfunction and LBBB. In short- and medium-term follow-up, this approach has been shown to be feasible in a very high percentage of patients.

5 STUDY DESIGN

5.1 Description

This is a randomized, prospective, single-blinded trial. Patients will be randomized to HOT-CRT versus BVP and will remain blinded to their treatment allocation. Both treatment options use standard-of-care, FDA-approved devices. The distinction is only in the allocation toward HOT-CRT and BVP. Treating physicians will be aware of assignment in order to facilitate routine device follow-up. Echocardiographic evaluation will also be performed in a blinded manner. Study physicians with the role of completing this evaluation will be blinded to lead placement.

Crossover is permitted between treatment group allocation if:

- CS lead (BVP) cannot be placed due to difficult cannulation of the CS, limited branches at the posterolateral or lateral wall, or phrenic nerve capture. These patients may then crossover to HOT-CRT. All efforts will be made to achieve CRT using CS lead.
- HOT-CRT patients may crossover if HPCSP lead cannot be positioned with adequate stability and reasonable pacing output and acceptable electrical resynchronization cannot be achieved.

Implant procedure will be per routine percutaneous access, as is standard for pacemaker and implantable cardioverter defibrillators (ICDs). All patients will receive FDA-approved cardiac resynchronization therapy pacemaker or defibrillator device, as per standard of care outlined for the patient.

Follow-up will be performed at 2 weeks post-implant for incision check and device interrogation, as is standard of care. In addition, routine device and clinical follow-up will be scheduled at 3, and 6 months, with remote device monitoring between scheduled visits, as needed.

Electrocardiography (i.e., ECG) will be performed pre-implant, prior to hospital discharge, and at 3- and 6-months post-discharge, as is standard of care. Echocardiography will be performed pre-implant, at 6 months to evaluate for change in left ventricular ejection fraction (LVEF), chamber dimension, and wall motion with strain imaging as is standard of care in the treatment of patients with advanced heart failure. NYHA functional class and quality of life, as measured

by the Kansas City Cardiomyopathy Questionnaire (KCCQ) and the EuroQoL 5D (EQ-5D), will be assessed pre-implant and at 6 months.

The primary clinical endpoint for the study (Aim 2) is change in left ventricular ejection fraction at 6 months. The primary safety endpoint (Aim 1) – freedom from major complications such as pericardial tamponade or need for CRT lead revision.

Secondary endpoints are as follows:

- Clinical: Composite of heart failure hospitalization, ventricular tachycardia (VT)/ventricular fibrillation (VF), crossover of treatment and any-cause mortality at 6 months will be assessed. NYHA functional class and quality of life will also be assessed.
- Electrocardiographic: Change in QRS duration between pre-implant and at hospital discharge, and 6 months will be performed. Arrhythmia occurrence (i.e., atrial fibrillation (AF), nonsustained VT, VT or VF requiring device therapy) will be documented throughout the study period.
- Echocardiographic: Change in left ventricular end-systolic volume index, chamber dimension, and tissue-strain pre-implant, and at 6 months will be performed by readers blinded to treatment allocation.

Regarding primary complication endpoints, complications will be assessed prospectively both acutely and throughout the study period, including:

- Procedure-related: pneumothorax, perforation, pericardial effusion, or hemorrhage
- System-related: implant site hematoma, implant site infection
- Lead-related: lead dislodgement, lead fracture, inability to pace due to high threshold, phrenic capture

Patients will be allocated to HOT-CRT or standard BVP (CS lead) prior to implant procedure. Randomization will be performed by the assigned biostatistician and use a randomly permuted block design. Blocks of size 2 and 4 will be randomly generated. Randomization will be stratified by LBBB and non-LBBB and clinical site.

Chart review will be performed for each enrolled patient upon study completion. The following events/data points will be collected to perform a survival analysis curve between the two randomized groups:

- Date of death and cause of death

- Heart failure hospitalization (HFH), date of HFH, and number of HFHs
- Atrial and ventricular arrythmias as per device log
- Complications (i.e., lead revision, infection, device replacement, etc.)
- Last encounter date
- Last withdrawal date

5.2 Study Population

Target Population: Patients with heart failure (HF) eligible for CRT as part of routine standard-of-care based on accepted Class I or Class II indications will be considered for this study.

5.2.1 Approximate Number of Subjects

Approximately 100 Geisinger subjects will participate in this study; approximately 50 in the intervention arm, and approximately 50 in the control arm.

5.2.2 Inclusion Criteria

Eligible patients will be similar to those previously enrolled in the large randomized controlled trials and current Society guidelines[18, 19] which support current indications for CRT. The following are the inclusion criteria for the HOT-CRT study:

1. Patients at least 18 years of age
2. Diagnosis is NYHA Class II, III, and ambulatory Class IV heart failure with either ischemic or nonischemic cardiomyopathy and patients with NYHA Class I symptoms and ischemic cardiomyopathy, with at least one of the following:
    i. LV systolic dysfunction with LVEF ≤ 35% and Evidence of bundle branch block with QRS duration > 120 msec
    ii. LV systolic dysfunction with LVEF ≤ 50% and with need for >40% RV pacing

5.2.3 Exclusion Criteria

The following are exclusion criteria for the HOT-CRT study:

1. Existing CRT device
2. Inability of patient capacity to provide consent for themselves either due to medical or psychiatric comorbidity

3. Pregnancy
4. Participation in other device trials
5. Inability to complete study requirements

5.3 Recruitment

Subjects selected for the study will be recruited from Geisinger Wyoming Valley, Geisinger Medical Center, and Geisinger Community Medical Center for participation in the study. Investigators will identify eligible subjects during one of their initial, standard care visits, describe the study procedures and invite them to participate in the study. The Informed Consent Form (ICF) will be provided to the subject and they will have ample time and opportunity to review and consider participation. Prior to performing any study procedures, the subject will sign the ICF and be considered enrolled at that point. Documentation of the consent process will be entered into the subject's Electronic Health Record (EHR). The subject will be assigned a Study ID Number upon enrollment and their data will be entered into the study's database.

5.4 Study Duration

5.4.1 Approximate Duration of Subject Participation

Subjects will participate in the study for approximately 6 months. This includes the time from consent of the subject through a 6-month follow-up period.

5.4.2 Approximate Duration of Study

This study will be completed in approximately 24 months. This includes 3 months of study start-up, a subject recruitment period of approximately 12 months, 6 months of subject follow-up from the time of last subject enrolled and 3 months for data analysis.

5.5 Procedures & Study Timeline

Patients enrolled in the study will receive a permanent CIED (CRT-pacemaker or CRT-defibrillator) as clinically indicated. Patients will be centrally randomized by the study team with input from the biostatistician.

Procedure:

Patients randomized to biventricular pacing will undergo left ventricular lead placement in the coronary sinus venous branches.

Patients randomized to HOT-CRT will undergo CRT as described below. His bundle pacing lead will be placed initially to achieve CRT. If complete resynchronization is achieved (BBB normalization) but capture thresholds are high (1.5-2V), the lead may be placed in the distal conduction system (left bundle branch area). If only partial QRS narrowing is achieved, a coronary sinus lead may be placed and LV timing may be optimized to achieve maximal resynchronization. This will be at the discretion of the implanting physician.

Visit One - Pre-Implant

Enrolled subjects will undergo the following standard care procedures, unless noted as being completed for research purposes:

1. Clinical physical evaluation
2. Serum or urine pregnancy screen for women of child-bearing potential
3. Serum BNP or pro-BNP, baseline metabolic panel
4. Electrocardiogram
5. Transthoracic Echocardiogram (TEE) will be completed if it has not been done within the previous 3 months prior to Visit One.
6. Kansas City Cardiomyopathy Questionnaire (KCCQ) will be completed by the subject as part of the study
7. EuroQoL 5D (EQ-5D) will be completed by the subject as part of the study
8. Six Minute Walk Test (6MWT) will be administered by study staff to record distance as part of the study
9. NYHA functional class
10. Randomization – Subjects will be randomized by study staff in the study REDCap database to either HOT-CRT or standard BVP lead placement using a permuted block design. Patients will be blinded to randomization arm. Blocks of size 2 and 4 will be

randomly generated. Randomization will be stratified by LBBB and non-LBBB (right bundle branch block, RV pacing or narrow QRS) and by clinical site.

11. Collection of adverse events from time of consent until end of study participation

Visit Two – Day of Implant

1. Implant completed according to the assigned randomization arm by investigator
2. Electrocardiogram completed pre/post procedure
3. Device interrogation completed prior to hospital discharge
4. Adverse event collection

Visit Three – 2-week follow-up

1. Device Interrogation
2. Adverse event collection

Visit Four – 3-month follow-up

1. Clinical physical evaluation
2. Electrocardiogram
3. Device Interrogation
4. Adverse event collection

Visit Five – 6-month follow-up

1. Clinical physical evaluation
2. Electrocardiogram
3. Transthoracic Echocardiogram (TTE)
4. Device Interrogation
5. Kansas City Cardiomyopathy Questionnaire (KCCQ) will be completed by the subject
6. EuroQoL 5D (EQ-5D) will be completed by the subject
7. Six Minute Walk Test (6MWT) will be administered by study staff to record distance.

8. NYHA functional class
9. Adverse event collection

Remote device monitoring will be completed between visits as part of standard care of this patient population. Data from this monitoring will be collected as part of the study.

Any heart failure hospitalization (HFH), sustained ventricular arrhythmias requiring therapy (shock or ATP) or death will be documented. Heart failure hospitalization is defined as an unplanned outpatient or emergency department visit or inpatient hospitalization in which the patient presented with signs and symptoms consistent with heart failure and required intravenous therapy.

5.5.1 Participant Withdrawal

Subjects will be free to withdraw from the study at any time by notifying the study team in writing. If the subject withdraws, no further data will be collected after that timepoint unless needed for safety reporting.

5.6 Primary Endpoints

The primary safety endpoint (Aim 1) – freedom from major complications such as pericardial tamponade or need for CRT lead revision. The primary clinical endpoint for the study (Aim 2) will be change in left ventricular ejection fraction at 6 months.

5.7 Secondary Endpoints

Secondary endpoints are as follows:

- Clinical: Composite of heart failure hospitalization, ventricular tachycardia (VT)/ventricular fibrillation (VF), crossover of treatment and any-cause mortality at 6 months will be assessed. NYHA functional class and quality of life will also be assessed.
- Electrocardiographic: Change in QRS duration between pre-implant and at hospital discharge, and 6 months will be performed. Arrhythmia occurrence (i.e., atrial fibrillation

(AF), nonsustained VT, VT or VF requiring device therapy) will be documented throughout the study period.

- Echocardiographic: Change in left ventricular end-systolic volume index, chamber dimension, and tissue-strain pre-implant, and at 6 months will be performed by readers blinded to treatment allocation.

5.8 Statistics

Geisinger's Biostatistics Core will perform the statistical analyses. The statistician will be responsible for assisting with study design and statistical analysis to understand the role of HOT-CRT in HF patients.

5.8.1 Statistical Analysis Plan

This is a pilot study to collect data and estimate parameters that are needed to design a larger study. Therefore, the sample size is based on estimating the precision of the change in left ventricular ejection fraction (LVEF). If we assume an equal distribution of subjects with LVEF at baseline above or below 35%, then from the BLOCK-HF trial[20] we further assume that the standard deviation of change in LVEF at 6 months will be 7.93. With a sample size of 50 patients in each arm, we can estimate the precision of a 95% confidence interval (i.e., half-width) to be 2.25. A sample size of 50 was chosen due to budget limits.

Survival analysis will be conducted between the two randomized groups to assess time-to-event as an endpoint.

5.8.2 Statistical Power and Sample Size Considerations

Analysis will follow the "intent-to-treat" principle. That is, subjects will be analyzed based on their randomization allocation. A small number of patients might cross-over into the other arm so we will complete a secondary analysis using the per-protocol principle where subjects are analyzed based on their final treatment allocation. Data will be fully described using mean and standard deviation or median and inter-quartile range for continuous measures, and frequency and percentage for categorical variables. Baseline variables will be summarized by randomization arm to assess for balance. Any imbalance will be adjusted for in the estimation of the parameters of interest. Successful placement (Aim 1) will be summarized in the HOT-CRT group among those randomized to this group. The percentage and 95% confidence interval will be estimated. A logistic regression model will be fit to identify baseline factors that associate with success. The primary endpoint in Aim 2, change in LVEF, will be estimated along with the

standard deviation and 95% confidence interval. The difference in change between the randomization arms will also be estimated. No formal statistical inferences will be conducted in this study. Deliverables

Pilot study deliverables will be to establish feasibility, collect preliminary data, and further develop and refine infrastructure to test hypothesis(es) in a fully powered trial. We anticipate being able to identify specific clinical and health care utilizations endpoints during the pilot trial, which will be important to further investigate in a larger, powered trial. We hope to publish our findings and add to the generalizable knowledge to inform physicians, policy-makers, and the healthcare community of real-world outcomes.

5.9 Data Management

5.9.1 Data Collection and Storage

Only IRB-approved study staff will have access to data collected for this research. Electronic data will be stored on Geisinger's secure network. Any hard copy data will be secured in a locked area. The following data, including relevant dates, will be collected:

- Names
- Medical record number
- Date of birth/date of death
- Information relevant to all encounters, admissions/discharges, clinical procedures, medications administered, problem list entries, device interrogations and lab values
- Baseline demographic variables of patients (age, sex, ethnicity, tobacco use, comorbidities)
- Clinical outcomes and procedural related complications

5.9.2 Records Retention

Records of data generated in the course of the study shall be retained for at least 6 years and could be used for future research studies submitted and approved by the IRB.

6 SAFETY MONITORING

6.1 Adverse Event Reporting

Clinical adverse events (AEs) will be monitored throughout the study. The date and time of onset and outcome, course, intensity, action taken, and causality to study treatment will be assessed by the study PI. In the event of a serious AE (SAE), this will be reported to the Geisinger IRB (GIRB) according to the GIRB guidelines.

Definitions:

An **adverse event** (AE) is any untoward, undesired, or unplanned event in the form of signs, symptoms, disease, or laboratory or physiologic observations occurring in a person given a test article or in a clinical study. The event does not need to be causally related to the test article or clinical study.

An AE includes, but is not limited to, the following:

- Any clinically significant worsening of a preexisting condition.
- An AE occurring from abuse (e.g., use for nonclinical reasons) of a test article.
- An AE that has been associated with the discontinuation of the use of a test article.

A **serious adverse event** (SAE) is an AE that:

- Results in death.
- Is life-threatening (see below).
- Requires inpatient hospitalization or prolongation of an existing hospitalization (see below).
- Results in a persistent or significant disability or incapacity (see below).
- Results in cancer.
- Results in a congenital anomaly or birth defect.
- Additionally, important medical events that may not result in death, be life-threatening, or require hospitalization may be considered SAEs when, based on appropriate medical judgment, they may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such events include allergic bronchospasm requiring intensive treatment in an emergency

room or at home, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

Life-threatening refers to immediate risk of death as the event occurred per the reporter. A life-threatening experience does not include an experience, had it occurred in a more severe form, might have caused death, but as it actually occurred, did not create an immediate risk of death. For example, hepatitis that resolved without evidence of hepatic failure would not be considered life-threatening, even though hepatitis of a more severe nature can be fatal. Similarly, an allergic reaction resulting in angioedema of the face would not be life-threatening, even though angioedema of the larynx, allergic bronchospasm, or anaphylaxis can be fatal.

Hospitalization is official admission to a hospital. Hospitalization or prolongation of a hospitalization constitutes criteria for an AE to be serious; however, it is not in itself considered an SAE. In absence of an AE, a hospitalization or prolongation of a hospitalization should not be reported as an SAE by the participating investigator. This is the case in the following situations:

- The hospitalization or prolongation of hospitalization is needed for a procedure required by the protocol.
- The hospitalization or prolongation of hospitalization is part of a routine procedure followed by the center (e.g., stent removal after surgery). This should be recorded in the study file.

In addition, a hospitalization for a preexisting condition that has not worsened does not constitute an SAE.

Disability is defined as a substantial disruption in a person's ability to conduct normal life functions.

If there is any doubt about whether the information constitutes an SAE, the information is treated as an SAE.

A **protocol-related adverse event** is an AE occurring during a clinical study that is not related to the test article but is considered by the investigator or the medical monitor (or designee) to be related to the research conditions, i.e., related to the fact that a subject is participating in the study. For example, a protocol-related AE may be an untoward event occurring during a washout period or an event related to a medical procedure required by the protocol.

Other Reportable Information. Certain information, although not considered an SAE, must be recorded, reported, and followed up as indicated for an SAE. This includes:

- Pregnancy exposure to a test article, except for exposure to prenatal vitamins. If a pregnancy is confirmed, use of the test article must be discontinued immediately. Information about pregnancy exposure includes the entire course of pregnancy and delivery, and perinatal and neonatal outcomes, even if there are no abnormal findings. Both maternal and paternal exposure are considered other reportable information. For exposure involving the female partner of a male subject, the necessary information must be collected from the subject, while respecting the confidentiality of the partner.
- Lactation exposure to a test article with or without an AE.
- Overdose of a test article as specified in this protocol with or without an AE. Baby formula overdoses without any AEs are excluded.
- Inadvertent or accidental exposure to a test article with or without an AE.

6.2 Recording and Reporting

A subject's AEs and SAEs will be recorded and reported from the signing of the informed consent form to conclusion of patient follow-up in accordance with GIRB policy guidelines.

6.3 Serious Adverse Event Reporting

The PI will notify GIRB of all study SAEs in accordance with policy guidelines. If an SAE has not resolved at the time of the initial report, a follow-up report including all relevant new or reassessed information (e.g., concomitant medication, medical history) will be submitted to GIRB. An SAE will be followed until either resolved or stabilized.

7 PROTECTION OF HUMAN SUBJECTS

7.1 Informed Consent and HIPAA Authorization

The investigator will provide for the protection of the subjects by following all applicable regulations. The informed consent/authorization form will be submitted to the IRB for review and approval.

Before any procedures specified in this protocol are performed, a subject must:

- Be informed of all pertinent aspects of the study and all elements of informed consent.
- Be given time to ask questions and time to consider the decision to participate.
- Voluntarily agree to participate in the study.

- Sign and date an IRB-approved informed consent form.

7.2 Potential Risks/Benefits and Protection of Human Subjects Against Risks

Potential Risks

Risks associated with both CS lead position and HBP which include, but are not limited to, the risk for cardiac perforation, tamponade, lead dislodgement, fracture, and site infections. Early data indicate that the two technologies are comparable with respect to risk profile.

All electronic study data will be kept in password-protected computer files and hard copy data will be stored in a locked environment that is only accessible only to the study team members. Data will be coded by linking a unique study identification number to patients' medical record numbers. Analysis will be performed using the coded data. Only aggregate data without personal identifiers will be included when presenting results or submitting manuscripts for publication.

Benefits

There will be no direct benefit to patients who are included in this study. We hope that what is learned from this study will help others in the future.

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