

CHILDREN'S HEART FOUNDATION

LAY SUMMARY

The diagnosis and treatment for the most serious congenital heart defects (CHDs) involve surgery shortly after birth. Currently, pediatric cardiothoracic surgeons rely primarily on mentally taking 2D data (cardiac ultrasound, MRI and CT scans) and converting it into a 3D mental image of their patient's heart. As skilled as surgeons are at imagining the heart, the mental reconstruction of such complex, miniscule structures oftentimes does not adequately prepare the doctors for surgery before entering the OR.

Furthermore, studies have disclosed that the duration of time a child spends on a heart-lung machine (cardiopulmonary bypass, or CPB, circulates the patient's blood and oxygen to vital organs throughout her body) during surgery and the length of hospitalization have a negative impact on the child's quality of life, health and abilities, both cognitive and physical. Among children who underwent bypass, prolonged time on the machine led to more severe brain injury.

The production of a patient-specific, three-dimensional (3D) printed model displays a patient's unique heart defects, intricacies, vessels and valves with unmatched certainty. If a doctor can accurately visualize and plan a surgery prior to the surgical date with a physical heart he can manipulate in his hands, then he will be able to better utilize the critical time during which his patient is on a CPB machine, and ultimately perform a better repair with better short- and long-term outcomes.

This multi-center clinical trial aims to evaluate whether pre-procedural planning of surgeons exposed to a patient-specific 3D printed heart model will decrease CPB time, surgical complications, and mortality. Three hundred and seventy-six (376) pediatric cardiac patients from 18 sites will be included in the trial. Eligible study participants ("subjects") will be randomly split between two groups: the treatment group (surgeon will receive a patient-specific 3D printed heart model along with standard imaging and data prior to surgery) and the control group (surgeon will perform existing preoperative planning without use of a 3D heart model). Data collection will occur at four key points: 1) screening and enrollment; 2) within 24 hours prior to surgery; 3) within 24 hours following surgery; and 4) 30-day post-surgery follow-up.

The primary measurement will be the difference between the treatment and control groups in the amount of time (in minutes) a subject spends on CPB during surgery. This information will show whether the use of a 3D heart model during preoperative planning aided the surgeon to the point that the patient was on the heart-lung machine for a shorter amount of time. The second measurement will be the difference in total OR time, frequency of relevant complications up to 30 days post-surgery, and surgeons' feedback on the use of the 3D heart model. This data will further illustrate the impact of a surgeon's exposure to a patient-specific 3D heart replica prior to actually performing surgery, specifically focusing on decreased risk of brain injury and long-term complications.

It is anticipated that results of this study will help develop and validate the use of 3D printed models in surgical planning which will benefit all CHD patients, and will translate to other cardiac diseases as well as non-cardiac disease.

RESEARCH PLAN

SPECIFIC AIMS

Patient-specific, 3D printed models have been occasionally utilized in preoperative planning for many years. Among researchers and clinicians, there is a perception that preoperative exposure to 3D printed models, derived from patient images (CT or MRI), aid in procedural planning. 3D printed models for heart surgery have the potential to improve a clinician's preparedness and therefore may reduce surgically-related morbidity and mortality. Toward this aim, a randomized clinical trial where surgeons are exposed to a patient-specific 3D printed model will assess whether pre-procedural planning will decrease CPB time and reduce morbidity and mortality.

The primary objective of this study is to assess the clinical efficacy of pediatric cardiac surgeon's preoperative exposure to patient-specific, 3D printed models as measured by the difference in CPB time between treatment and control groups, over a two-year treatment period (or until 376 patients covered by the trial). Secondary objectives include assessment of: (1) clinical efficacy of preoperative exposure to patient-specific, 3D printed models as measured by the prevalence of surgical complications and mortality; and (2) assessment of 3D print utility according to the surgeon as measured by pre- and post-surgical questionnaires. The hypothesis to be tested is that utilization of 3D printed models in presurgical planning will demonstrate improved outcomes such as less CPB time, fewer days in recovery, fewer complications requiring reoperations, and lower mortality.

3D heart models have the potential to improve surgical outcomes as they display the relationship of septal defects, outflow tracts and valves with certainty, in an unambiguous manner. Greatest benefit may be seen for heart defects which involve a complex two-ventricle repair, including double outlet right ventricle, transposition of the great arteries with ventricular septal defect, truncus arteriosus with ventricular septal defect and congenitally corrected transposition of the great arteries with pulmonary stenosis. By aiding the surgeon in planning for a surgery, 3D printed models have the potential to decrease CPB time. In addition, reduction in surgical times may lead to lower morbidity and mortality, especially through the reduction of duration-associated (surgical time, operating room time, etc.) infections (Gelijns et al., 2014).

While improving patient care by reducing morbidity and mortality is the primary aim this trial, direct patient and hospital-related costs are important considerations regarding the use of technology. Shorter time in the operating room and subsequent length of stay in hospital can substantially reduce costs. Costs related to morbidity post-surgery are offset by the patient/patient-family, insurance companies, and hospitals. In addition, the time allocated for an operation has an associated cost; either a direct cost per time unit or indirect cost per procedure (depending on the hospital's business model) (Cardoen, Demeulemeester, & Beliën, 2010; Dexter & Macario, 2002; Does, Vermaat, Verver, Bisgaard, & Van Den Heuvel, 2009). By reducing the time of surgery or CPB, the patient is at a lower risk of infection; thereby, the hospital will save both money and resources that would have likely been consumed in a longer operation and resources that would have been used to treat post-surgical complications. 3D printed models have the potential to reduce surgical duration and indirectly save on resources.

BACKGROUND & SIGNIFICANCE

Congenital heart disease is the most common birth defect; an average of 1% of babies born each year in the U.S. have at least one congenital heart defect (CHD). Annually, 20,000 newborns will require open-heart surgery, and nearly 5,000 will not celebrate their first birthday.

To fully appreciate what a pediatric cardiac surgeon faces in the OR and the impact of accurate presurgical planning, the reality of pediatric cardiac surgery must be considered. A baby's heart is the size of a strawberry. The vessels that surgeons cut and sew are as thin as hair. The surgeon is required to envision not only how his handiwork will hold up in four hours, when blood floods the reassigned vessels, but in ten years, when his patient races down the soccer field. The longer a child is on CPB during surgery, the more likely serious problems develop, including organ failure or brain damage. Thus, a surgeon is tasked with an almost Herculean feat. And currently he is handicapped by relying on antiquated 2D images, which fail to convey the subtleties of a patient's heart and their unique defect.

As imaging technology advances, opportunities arise to improve accuracy and quality of current surgical planning methods. The advent of 3D printing now offers surgeons a tool whereby they can create a more reliable and accurate roadmap for intricate surgical repair, providing a tremendous difference regarding how surgeons repair defects, the child's quality of life or even if she will survive.

Preliminary studies demonstrate potential for clinical impact of 3D models on patient care and patient outcomes. 3D models have long been shown to enhance education and communication of anatomy (Ejaz et al., 2014; Weidenbach et al., 2009). Sodian et al report fabrication of a model of the aortic arch in perioperative planning (Sodian et al., 2007). Mottl-Link et al describes the use of physical models pre-operatively in congenital heart repair (Mottl-Link et al., 2008). The physical model helped with pre-operative localization of the coronary arteries, providing more spatial information for the surgeons. In 2008 Kim et al reviewed 3D printed models as an emerging technology in management of congenital heart disease, and also suggests that physical models may also help enhance patients and physicians' understanding of congenital heart disease (Kim, Hansgen, Wink, Quaife, & Carroll, 2008). Participating institutions have also published on the clinical and educational value of these 3D heart models (Costello et al., 2014, 2015; Ejaz et al., 2014; Olivieri, Krieger, Chen, Kim, & Kanter, 2014; Ryan et al., 2015). To date, no systematic, prospective trial identifying the value of 3D models on procedural planning has been published.

This randomized clinical trial aims to fill the knowledge gap in evaluating whether pre-procedural planning of pediatric cardiothoracic surgeons exposed to a patient-specific 3D printed heart model will decrease CPB time, surgical complications, and mortality.

PRELIMINARY STUDIES

Participating institutions have also published on the clinical and educational value of these 3D heart models (Costello et al., 2014, 2015; Ejaz et al., 2014; Olivieri, Krieger, Chen, Kim, & Kanter, 2014; Ryan et al., 2015). To date, no systematic, prospective trial identifying the value of 3D models on procedural planning has been published.

RESEARCH DESIGN & METHODS

This is a multi-center, single-blind, randomized clinical trial evaluating the efficacy of preoperative exposure to 3D printed models on surgical outcomes. Three hundred and seventy-six (376) subjects from 18 sites will be inclusion into the trial. Each subject will be identified by a participating institution as 1) having a double outlet right ventricle (DORV) or similar –type lesion and 2) having appropriate CT or MRI scans necessary for 3D reconstruction and 3D printing.

Subjects will be randomly assigned to a preoperative plan using an a priori randomized order. Based on this order, surgeons for the subjects will either have 1) preoperative exposure to a patient-specific 3D heart model or 2) no exposure to a patient-specific 3D heart model. All surgeons will have preoperative exposure to traditional imaging (traditional imaging is defined here as imaging already present at the center and imaging that is clinically indicated).

Sites and Investigators

The study team is comprised of the following PIs, Site Leaders, and experts providing 3D support and study coordination, in addition to 20 clinicians at the listed participating sites:

Principal Investigators

- [REDACTED]
- [REDACTED]
- [REDACTED]
- [REDACTED]

Site Leaders

- [REDACTED]
- [REDACTED]
- [REDACTED]
- [REDACTED]
- [REDACTED]
- [REDACTED]
- [REDACTED]
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- [REDACTED]
- [REDACTED]
- [REDACTED]
- [REDACTED]

3D Expertise and Support

- [REDACTED]
- [REDACTED]
- [REDACTED]

Coordination and Support

- Data Coordinating Center (DCC): [REDACTED]
- Image Reconstruction Center (IRC): [REDACTED]
- Management: [REDACTED]
- Coordination: [REDACTED]
[REDACTED]

Evaluation

The primary efficacy endpoint for the clinical trial is the difference in CPB time in minutes between the study and control groups.

The secondary efficacy endpoints for the clinical trial include differences in total OR time, as well as the frequency of the following morbidities up to 30 days post-surgery:

- Intraoperative death or intraoperative death
- Unexpected Cardiac arrest during or following procedure (Periop/Periprocedural = Intraop/Intraoperative and/or Postop/Postoperative)
- Bleeding, Requiring reoperation
- Sternum left open, Unplanned
- Unplanned cardiac reoperation during the postoperative or postoperative time period, exclusive of reoperation for bleeding
- Unplanned non-cardiac reoperation during the postoperative or postoperative time period
- Postoperative/Postoperative mechanical circulatory support (IABP, VAD, ECMO, or CPS)
- Arrhythmia necessitating pacemaker, Permanent pacemaker
- Renal failure - acute renal failure, Acute renal failure requiring dialysis at the time of hospital discharge
- Renal failure - acute renal failure, Acute renal failure requiring temporary dialysis with the need for dialysis not present at hospital discharge
- Renal failure - acute renal failure, Acute renal failure requiring temporary hemofiltration with the need for dialysis not present at hospital discharge
- Sepsis
- Seizure
- Stroke
- Vocal cord dysfunction (possible recurrent laryngeal nerve injury)
- Other operative/procedural complication

Additionally, a technology acceptance survey will be deployed at three time points: immediately before surgery, immediately following surgery, and 30 days following the surgery. This tool will be used to measure voluntary use of, or intent to adopt, a new technology (i.e., 3D heart model). Perceived usefulness is the perception that using the particular technology will be advantageous over the status quo; with regards to the trial, status quo is traditional medical imaging without 3D printing. Perceived ease-of-use is the perception that the utilization of the new technology will be relatively non-obtrusive to implement. This measure is an attempt to quantify these behavioral responses either for understanding users' intent or to inform future design iterations.

Subject Selection

Subjects with a diagnosis of DORV or DORV-variant congenital heart lesion who meet the inclusion and exclusion criteria will be eligible for participation in this study. Inclusion and

exclusion criteria, risks and benefits, and consent procedures are detailed in the Human Subjects section.

Study Treatments

Method of Assigning Subjects to Treatment Groups

A total of 376 eligible patients will be randomly assigned to have a 3D heart model constructed and provided to their surgeon as part of their preoperative preparation. Randomization will be block randomized by site, with a 1:1 allocation ratio to the treatment (3D heart model) or the control (no 3D heart model) groups, using a SAS-based computer-generated randomization scheme. The randomization will be placed in site-coded envelopes handled by the Image Reconstruction Center. Before randomization the images will be checked at the IRC and if inadequate, the patient will not be randomized.

Blinding

To prevent potential bias and protect clinical staff, the trial's patients (participants) and families will not be informed of the group they were randomly assigned to; thus, the trial is designed as single blinded. The study blind will be broken after completion of the clinical study and lock of the study database.

Imaging Protocol

For all study participants, the clinically-indicated and/or preferred MRI scan, 2D studies of cardiovascular anatomy, flow and function, 3D angiograms, contrast enhanced cardiovascular MRI studies, and cardiac CT may be performed. As randomization of patients will be stratified by site, possible biases due to site-level differences in imaging protocols will be minimized. Further imaging details are available in the Human Subjects section.

Formulation of Test Product (3D Model)

CT and MRI source images will be exported anonymously and stored on a password protected drive dedicated to image storage. Images will be uploaded into commercially available, FDA-approved image segmentation software (Mimics, Materialise Corporation). Cardiac segmentation will be performed by an experienced cardiac segmentation expert at the IRC. Segmentation will be achieved through thresholding and dynamic region growing. The segmentation will be exported as an STL file, and undergo post-processing in a computational engineering software suite to ensure print viability. Participating sites will have 24 hours following completion of reconstruction to recommend any changes prior to printing. The 3D file will be verified by the IRC and a PI, then loaded onto a 3D printer for preparation and printout.

The 3D model will be printed, and provided to the surgeon in advance of the planned procedure, to enable surgical planning based on knowledge of the intra-cardiac anatomy from both standard means (echo, MRI, cardiac catheterization) and the 3D heart model. The intended turn-around time between MR imaging and receipt of the 3D model will be under six business days. Each 3D heart model will be labeled with a unique ID for each subject; the ID will be different from the MRN to ensure patient privacy. The unique key, linking the unique ID to the MRN, will be held by the IRC.

Formulation of Control Product (Traditional Medical Imaging)

Surgeries for subjects, who will not have a 3D heart model for preoperative exposure, will undergo existing preoperative planning schemes. This scheme will differ from center to center but may feature CT, MRI, or echocardiographic images. As randomization of patients will be stratified by site, possible biases due to site-level differences in imaging protocols will be minimized.

Timeline of Evaluations and Data Collection

The data collection forms to be utilized in the study are available for review upon request. The following evaluation and data collection activities will be performed with both the study and control groups:

Screening and Enrollment

1. Review the study with the subject (subject's legal representative) and obtain written informed consent and HIPAA authorization and assent, if appropriate.
2. Record demographics data (date of birth and gender)
3. Record medical history
 - a. Date of scan
 - b. Prior cardiothoracic operations
 - c. Primary preoperative diagnosis and secondary diagnoses
 - d. Intended primary procedure
 - e. Preoperative factors including chromosomal abnormalities and syndromes
4. Send images, CT/MRI report, and CRF 1 to IRC and DCC
5. IRC evaluates the images for adequacy.
6. If adequate, the IRC assigns a study ID number and determines whether the subject will receive a 3D heart model based on the randomization scheme and informs originating center.
7. A 3D heart model is created as described.

Within 24 Hours prior to Surgery

1. Surgeon plans his/her operation following exposure to the 3D printed model (if the subject receives one).
2. Clinician completes pre-surgical questionnaire.

Within 24 Hours following Surgery

1. Record medical information about the surgery
 - a. Date of surgery
 - b. Actual primary procedure
 - c. Operative times:
 - i. Skin incision time and closure time
 - ii. Operating room entry time and leave time
 - iii. Initial extubation time
 - iv. CPB time
 - v. Cross-clamp time
 - vi. Circulatory arrest time
2. Surgeon completes post-surgical questionnaire
3. Send CRF 2 and 3 to IRC

Follow-up 30-day Post-Surgery

1. Record medical history
 - a. Date of surgery
 - b. Actual primary procedure
 - c. 30-day operative follow-up:
 - i. Date of hospital discharge
 - ii. Readmission within 30 days of surgery (yes/no)
 - iii. Status at 30-day post-surgery (alive, diseased, unknown)
 - iv. Date of death (if applicable)
 - d. Cardiac related complications
2. Surgeon completes post-surgical questionnaire
3. Send CRF 4 to IRC within 90 days post-surgery

Adverse Experience Reporting And Documentation

The Investigator will probe, via discussion with the subject, for the occurrence of adverse events (AEs) during each subject visit and record the information in the site's source documents. AEs will be recorded in the patient CRF. AEs will be described by duration (start and stop dates and times), severity, outcome, treatment and relation to study drug, or if unrelated, the cause. AEs are reported to the IRB according to the rules and regulations adopted by the site IRB. CPB time significantly elevated by model inaccuracy as assessed by surgeon questionnaire will require immediate notification of the IRB.

Discontinuation And Replacement Of Subjects

A subject may be discontinued from study treatment at any time if the subject or the investigator feels that it is not in the subject's best interest to continue. All subjects are free to withdraw from participation at any time, for any reason, specified or unspecified, and without prejudice. Accrual and safety data will be monitored by the site Principal Investigator, and the study coordinator. The protocol will be continuously evaluated for any unusual or unpredicted complications with the aim of detecting and preventing unacceptable increase in morbidity and mortality over and above that anticipated. Subjects who withdraw from the study treatment will be replaced to ensure that the sample size required to achieve statistical analyses will be reached.

Protocol Violations

When a protocol violation occurs, it will be discussed with the investigator and a Protocol Violation Form detailing the violation will be generated. This form will be signed by an Investigator. Protocol violations for this study include, but are not limited to: failure to meet inclusion/exclusion criteria; breach of PHI security; and failure to comply with Good Clinical Practice guidelines.

Statistical Methods

Statistical analyses will be performed according to the "intention-to-treat" principle, and following the guidelines provided by the Consolidated Standards of Reporting Trials (CONSORT) statement (www.consort-statement.org). All statistical tests will be 2-sided with overall (accounting for interim analyses) statistical significance evaluated at 5% level.

Descriptive Analyses of Baseline Factors

The distribution of demographic and baseline characteristics will be summarized for the intervention (3D heart model) and control (no model) groups using count and percent for

categorical variables, and the mean and standard deviation or the median and interquartile range for continuous measures.

Comparisons of Primary and Secondary Outcomes

Differences in the mean CPB time (minutes) between treatment groups will be tested using a two-sample T-test. Secondary outcomes (mortality and surgical complications) will be similarly compared by T-tests or Fisher's exact test and reported with 95% confidence intervals based on Wilson's method as appropriate. Multivariable linear regression will be applied to compare CPB time between the 3D printed heart and control groups adjusting for patient age and center as covariates. Also, multivariable logistic regression will be used to compare surgical complications and mortality between the two treatment groups adjusting for patient age and center as covariates and reporting odds ratios and 95% confidence intervals (Harrell, 2015). Counts of safety and AEs will be coded by body system and MedDra classification term. These will be tabulated by treatment group and will include the number of patients for whom the event occurred, the rate of occurrence, and the severity and relationship to intervention under study.

Interim Analysis

An interim analysis (nQuery Advisor version 7.0, Statistical Solutions, Cork, Ireland) will be performed after half of the patients in each group (i.e., 94 per group) are enrolled with 30 days of follow-up after cardiac surgery. Stopping of the trial early will be based on evidence of >15% difference in 30-day mortality between the 3D heart model and control groups. Therefore, consideration of early stopping will not be based on the primary endpoint of CPB time, but rather on patient safety. At the interim analysis, based on expected sample sizes of 94 patients per group (50% of the planned final enrollment), the statistical power will be 80% for detecting a minimum 15% difference in 30-day mortality between the two groups using a Pearson chi-square statistic with continuity correction and a conservative 2-tailed alpha level less than 0.01 to ensure clinical and statistical evidence to justify the possibility of early termination of the trial.

Sample Size Determination

The total proposed sample size is 376 subjects; 188 subjects within each treatment and control groups. This sample size is sufficient for a T-test to detect a difference of at least 15 minutes in the primary outcome of CPB time between groups, with 90% power assuming an overall 1% type I error rate, and a standard deviation of 40 for the CPB time within both groups. (Hulley, Cummings, Browner, Grady, & Newman, 2013)

Additional Analyses to Assess and Correct Possible Bias

Theoretically, randomization should yield similar distributions of baseline factors among the intervention and control groups. However, due to chance, baseline factors may not be balanced between treatment groups. Balance in the distribution of baseline factors between treatment groups will be tested using the Chi-square or Fisher exact test, and the T-test or the Wilcoxon Rank Sum test, as appropriate for the variable distribution. Factors with evidence of imbalance will be considered as potential confounders. To assess and correct for possible bias, multivariable linear regression models will assess effect of preoperative exposure to a 3D heart model and CPB time with and without adjustment for possible confounding factors. Similarly, appropriate multivariable regression methods will be applied to compare secondary outcomes between treatment groups.

Data Collection, Retention And Monitoring

Data Collection Instruments

The Investigator will prepare and maintain adequate and accurate source documents designed to record all observations and other pertinent data for each study subject. Study personnel at each site will enter data from source documents corresponding to a subject's visit into the protocol-specific paper CRF when the information corresponding to that visit is available. Subjects will not be identified by name in the study database or on any study documents to be collected, but will be identified by a site number, subject number and initials. Elements of date will also be released as a way to calculate important outcomes. The Investigator is responsible for all information collected on subjects enrolled in this study. All data collected during the course of this study must be reviewed and verified for completeness and accuracy by the Investigator. A copy of the CRF will remain at the DCC at the completion of the study.

Data Management Procedures

The data will be entered into password-protected database at the DCC. The DCC will be responsible for data processing, in accordance with procedural documentation. Database lock will occur once quality assurance procedures have been completed. All procedures for the handling and analysis of data will be conducted using good computing practices meeting FDA guidelines for the handling and analysis of data for clinical trials.

Archival of Data

The database is safeguarded against unauthorized access by established security procedures; appropriate backup copies of the database and related software files will be maintained. Databases are backed up by the database administrator in conjunction with any updates or changes to the database. At critical junctures of the protocol (e.g., production of interim reports and final reports), data for analysis is locked and cleaned per established procedures.

Availability and Retention of Investigational Records

The Investigator must make study data accessible to the IRB/IEC and Regulatory Agencies (e.g., FDA) inspectors upon request. A file for each subject must be maintained that includes the signed Informed Consent, HIPAA Authorization and Assent Form (if applicable) and copies of all source documentation related to that subject. The Investigator must ensure the reliability and availability of source documents from which the information on the CRF was derived. All study documents (patient files, signed informed consent forms, copies of CRFs, Study File Notebook, etc.) must be kept secured for a period of two years following marketing of the investigational product.

Subject Confidentiality

In order to maintain subject confidentiality, only a site number, subject number and subject initials will identify all study subjects on CRFs and other documentation submitted to the Sponsor. Elements of date will also be released as a way to calculate important outcomes. Additional subject confidentiality issues (if applicable) are covered in the Clinical Study Agreement.

Administrative, Ethical, Regulatory Considerations

The study will be conducted according to the Declaration of Helsinki, Protection of Human Volunteers (21 CFR 50), Institutional Review Boards (21 CFR 56), and Obligations of Clinical Investigators (21 CFR 312).

To maintain confidentiality, all laboratory specimens, evaluation forms, reports and other records will be identified by a coded number and initials only. All study records will be kept in a locked file cabinet and code sheets linking a patient's name to a patient identification number will be stored separately in another locked file cabinet. Clinical information will not be released without written permission of the subject, except as necessary for monitoring by the FDA. The Investigator must also comply with all applicable privacy regulations (e.g., Health Insurance Portability and Accountability Act of 1996, EU Data Protection Directive 95/46/EC).

Protocol Amendments

Protocol amendments cannot be implemented without prior written IRB/IEC approval except as necessary to eliminate immediate safety hazards to patients. A protocol amendment intended to eliminate an apparent immediate hazard to patients may be implemented immediately, provided the IRBs are notified within five working days.

Institutional Review Boards and Independent Ethics Committees

The protocol and consent form will be reviewed and approved by the IRB/IEC of each participating center prior to study initiation. Serious adverse experiences regardless of causality will be reported to the IRB/IEC in accordance with the standard operating procedures and policies of the IRB/IEC, and the Investigator will keep the IRB/IEC informed as to the progress of the study. The Investigator will obtain assurance of IRB/IEC compliance with regulations.

Any documents that the IRB/IEC may need to fulfill its responsibilities (such as protocol, protocol amendments, Investigator's Brochure, consent forms, information concerning patient recruitment, payment or compensation procedures, or other pertinent information) will be submitted to the IRB/IEC. The IRB/IECs written unconditional approval of the study protocol and the informed consent form will be in the possession of the Investigator before the study is initiated. This approval must refer to the study by exact protocol title and number and should identify the documents reviewed and the date of review.

Protocol and/or informed consent modifications or changes may not be initiated without prior written IRB/IEC approval except when necessary to eliminate immediate hazards to the patients or when the change(s) involves only logistical or administrative aspects of the study. Such modifications will be submitted to the IRB/IEC, and written verification that the modification was submitted and subsequently approved will be obtained.

The IRB/IEC must be informed of revisions to other documents originally submitted for review; serious and/or unexpected adverse experiences occurring during the study in accordance with the standard operating procedures and policies of the IRB; new information that may affect adversely the safety of the patients of the conduct of the study; an annual update and/or request for re-approval; and when the study has been completed.

Informed Consent Form

Informed consent will be obtained in accordance with the Declaration of Helsinki, ICH GCP, US Code of Federal Regulations for Protection of Human Subjects (21 CFR 50.25[a,b], CFR 50.27, and CFR Part 56, Subpart A), the Health Insurance Portability and Accountability Act (HIPAA, if applicable), and local regulations.

As this is a multi-center study, each institution will be responsible for the generation of the informed consent form and HIPAA authorization prior to submission to the IRB/IEC. The written consent document will embody the elements of informed consent as described in the International Conference on Harmonisation and will also comply with local regulations.

Each subject will receive oral and written explanation of the purposes, procedures, and risks of this study in language appropriate for the individual's level of understanding. The participants may be approached when they are undergoing their clinically-indicated preoperative cardiac MRI or cardiac catheterization for any cause when referred by their cardiologist.

Information should be given in both oral and written form and subjects (or their legal representatives) must be given ample opportunity to inquire about details of the study. A copy of the signed consent form will be given to the subject or legal representative of the subject and the original will be maintained with the subject's records at the DCC.

If the participant decides to be a part of the study and signs the consent, they will be given a copy of the consent/ assent after both parties have signed.

Publications

The publication or presentation of any study results shall comply with all applicable privacy laws, including, but not limited to, the Health Insurance Portability and Accountability Act of 1996.