NETWORK FOR CT SURGICAL INVESTIGATIONS

SURGICAL INTERVENTIONS FOR MODERATE ISCHEMIC MITRAL REGURGITATION

MANUAL OF PROCEDURES

Version 4.3

April 2011

Sponsored By NHLBI, NINDS & ICHR

CT Surgery Network Research Group

Data Coordinating Center:
International Center for Health Outcomes and Innovation Research
Department of Health Policy
Mount Sinai School of Medicine
New York

TABLE OF CONTENTS

1. STUDY TEAM ROSTER……..…..… 7
2. CLINICAL CENTERS……..…..8
3. TRAINING PLAN…….……..9
4. COMMUNICATIONS PLAN…….…..…10
5. STUDY ORGANIZATION AND RESPONSIBILITIES…….……....10
6. RECRUITMENT……...10
7. STUDY FLOW……..11
8. SCREENING AND ELIGIBILITY CRITERIA……...…11
9. INFORMED CONSENT, HIPAA, RELEASE OF MEDICAL INFORMATION……..12
10. RANDOMIZATION……..…13
11. STUDY INTERVENTION……..…..14
12. MASKING…….…...14
13. PARTICIPANT EVALUATIONS AND FOLLOW-UP…….….14
14. PARTICIPANT RETENTION……..14
15. CONCOMITANT INVESTIGATIONAL MODALITIES……...…15
16. SAFETY REPORTING…….....15
17. EVENT ADJUDICATION COMMITTEE……...……17
18. DATA AND SAFETY MONITORING RESPONSIBILITIES……17
19. STUDY COMPLIANCE……...17
20. DATA COLLECTION AND STUDY FORMS……18
21. REGULATORY DOCUMENTATION……28
22. ELECTRONIC DATA MANAGEMENT…….30
23. QUALITY CONTROL PROCEDURES……...30
24. STUDY COMPLETION AND CLOSEOUT PROCEDURES…….30
25. POLICIES……..……31
26. MOP MAINTENANCE…….31
27. APPENDIX I: Limited Echocardiographic Image Acquisition Protocol…….....32
28. APPENDIX II: CTSN Trial Patient Contact Log …….…….…….…….34

Table of Changes

Revision	Section	Change	Reason	Page
2.0	Study Team Roster	Changed "study" to "Network" chairs	Clarification	6
2.0	Study Flow	Study Design Figure: Deleted EROA as criterion for degree of MR	Internal consistency with eligibility modification	10
2.0	Data Collection Schedule	Added visit window definitions	MOP refinement for clarity	16
2.0	Screening and Baseline	Added information on audiotape storage and destruction under "Neurocognitive Testing" sub-heading	MOP refinement for clarity	20
2.0	Post-Randomization Data Collection	Added Proposed Revascularization form	MOP update for consistency with protocol modification	21
2.0	Post-Randomization Data Collection	Added Study Visits section	MOP refinement for clarity	21
2.0	Post-Randomization Data Collection	Deleted note to finalize Blood, Urine, and Tissue Sample Collection section	MOP update	22
2.0	Post-Randomization Data Collection	Removed old Blood, Urine, and Tissue Sample Collection Schedule	As per request of NHLBI biorepository team	22
2.0	Post-Randomization Data Collection	Added new Blood, Urine, and Tissue Collection Schedule	As per request of NHLBI biorepository team	22
2.0	Post-Randomization Data Collection	Added information on audiotape storage and destruction under "Neurocognitive Testing" sub-heading	MOP refinement for clarity	25
3.1	Table of Contents	Added Event Adjudication Committee	MOP update	2
3.1	Table of Contents	Added Appendix I	MOP update	2
3.1	Study Team Roster	Added MD to Dr. D'Alessandro's name	MOP update	6
3.1	Training Plan	Added Training information for the EDC	MOP update	8
3.1	Training Plan	Deleted old NIH Stroke Scale Training description and added new training information	MOP refinement for clarity	8
3.1	Training Plan	Added new information on full and limited echo acquisition	MOP update	8
3.1	Training Plan	Added description of cMRI Training	MOP update	8
3.1	Communications Plan	Changed language for Coordinator and Steering committee Conference Calls	MOP refinement for clarity	9
3.1	Study Flow	Updated Study Flow diagram	MOP update	9
3.1	Screening and Eligibility Criteria	Updated eligibility criteria	MOP update	10
3.1	Informed Consent, HIPAA, Release of Med Information	Added "HIPAA sensitive" to screening activity prior to informed consent	MOP update	12
3.1	Masking	Added clarification of masking procedures	MOP refinement for clarity	13

3.1	Participant Evaluation and Follow-up	Added description of patient follow-up visits	MOP refinement for clarity	13
3.1	Safety Reporting	Added clarification of safety reporting processes and AE reporting diagram	MOP refinement for clarity	14
3.1	Event Adjudication Committee	Added section on Event Adjudication Committee	MOP update	15
3.1	Study Compliance	Changed Project Leader to Clinical Trial Manager	MOP refinement for clarity	15
3.1	Data Collection Schedule	Added baseline cMRI for sub-study patients	MOP update	16
3.1	Data Collection Schedule	Added assessment point for Surgical Procedure under Event Driven Data	Internal consistency within protocol	16
3.1	Screening and Baseline	Added “Pre-Screening/Screening Failure Form”	MOP update	17
3.1	Screening and Baseline	Updated title to “Demographics Form” and updated unique identification code section	MOP update	17
3.1	Screening and Baseline	Deleted fourth bullet point under “Demographics Form”	MOP refinement for clarity	17
3.1	Screening and Baseline	Added bullet point under Functional Status sub-heading, detailing CPX training and credentialing	MOP refinement for clarity	18
3.1	Screening and Baseline	Deleted reference to Appendix III under Functional Status sub-heading	MOP refinement for clarity	18
3.1	Screening and Baseline	Added “CTSN” to second bullet point under Echocardiogram sub-heading	MOP refinement for clarity	18
3.1	Screening and Baseline	Deleted ERO and added “degree of MR” for echo eligibility and added detail regarding shipping of CDs to core lab	MOP update	18
3.1	Screening and Baseline	Added cMRI sub-heading and guidelines	MOP update	18
3.1	Screening and Baseline	Added description of medications	MOP update	20
3.1	Screening and Baseline	Deleted reference to resident under Physical Exam due to redundancy	MOP refinement for clarity	20
3.1	Screening and Baseline	Updated Laboratory Assessment values	MOP refinement for clarity	21
3.1	Screening and Baseline	Deleted “Screening Outcome” sub-heading	MOP refinement for clarity	21
3.1	Procedure	Added reference to trial protocol	MOP refinement for clarity	21
3.1	Post-Randomization Data Collection	Added remote assessment language for 6 and 24 month follow-up to Study Visits section	Consensus of Network PIs	21
3.1	Post-Randomization Data Collection	Added PCWP to Hemodynamics Section	MOP refinement for clarity	22
3.1	Post-Randomization Data Collection	Deleted reference to “Appendix I” under Blood, Urine, and Tissue Sample Collection sub-heading	MOP refinement for clarity	22
3.1	Post-Randomization Data Collection	Added remote assessment language to echocardiogram section	Consensus of Network PIs	24
3.1	Post-Randomization Data Collection	Added information detailing CPX training, credentialing, and documentation to Functional Status section	MOP refinement for clarity	24

3.1	Post-Randomization Data Collection	Deleted reference to Appendix III in Functional Status section	MOP refinement for clarity	24
3.1	Post-Randomization Data Collection	Added “protocol” to reference of Appendix VI in Quality of Life section and information on patients with remote ECHO assessments	MOP refinement for clarity	25
3.1	Event Drive Data Collection	Added “follow-up” to surgical procedures section	MOP refinement for clarity	25
3.1	Event Drive Data Collection	Added description of adverse events	MOP refinement for clarity	25
3.1	Regulatory Documentation	Added IATA Training	MOP update	28
3.1	Event Driven Data Collection	Added ERB	MOP update	27
3.1	Quality Control Procedures	Deleted reference to Appendix I under first bullet point	MOP refinement for clarity	28
3.1	Quality Control Procedures	Deleted reference to Appendix II under second bullet point	MOP refinement for clarity	28
3.1	Quality Control Procedures	Added bullet point three	MOP refinement for clarity	28
3.1	Quality Control Procedures	Deleted reference to Appendix III under fourth bullet point	MOP refinement for clarity	28
3.1	Study Completion and Closeout Procedures	Deleted reference to medications	MOP refinement for clarity	29
3.1	Appendix I	Added Appendix I: Limited Echocardiographic Image Acquisition Protocol	MOP update	30
3.2	Entire Document	Deleted references to the cMRI sub-study	Consensus of Network PIs	All
3.2	Clinical Centers	Updated the CTSN core, affiliated, and ancillary clinical centers	MOP update	8
3.2	Training Plan	Clarified that inability to complete neurocognitive testing does not preclude a patient from enrollment	MOP update	9
3.2	Training Plan	Clarified that inability to complete quality of life testing does not preclude a patient from enrollment	MOP update	9
3.2	Informed Consent	Clarified the process for reviewing the informed consents	MOP refinement for clarify	12
3.2	Screening Activity	Clarified that data collected on pre-screened patients is recorded in the Pre-Screening Failure Form	MOP refinement for clarify	13
3.2	Safety Reporting	Clarified the process for reporting AEs and added UAPs	MOP update	15
3.2	Event Adjudication Committee	Clarified that the EAC will adjudicate the relatedness to the surgical procedure and investigational intervention	MOP update	16
3.2	Screening & Baseline	Updated the title and explanation of the Pre-Screening Failure Form	MOP refinement for clarify	18
3.2	Echocardiogram	Added the echo core lab’s shipping address	MOP refinement for clarify	19

3.2	Quality of Life	Clarified that inability to complete QoL does not preclude a patient from enrollment	MOP update	21
3.2	Neurocognitive Testing	Clarified that inability to complete quality of life testing does not preclude a patient from enrollment	MOP update	21
3.2	Eligibility Criteria	Added the Eligibility Evaluation Form and description to the second on Eligibility Criteria	MOP update	22
3.2	Hemodynamics	Added clarification of PA O2sat	MOP refinement for clarity	23
3.2	Blood, Urine, and Tissue Sample Collection	Deleted the Biorepository Specimen Collection Schedule	MOP refinement for clarity	23
3.2	Neurocognitive Testing	Clarified that inability to complete quality of life testing does not preclude a patient from enrollment	MOP update	26
3.2	Quality of Life	Clarified that inability to complete QoL does not preclude a patient from enrollment	MOP update	26
3.2	Adverse Events	Clarified the reporting of an AEs relatedness to the surgical procedure vs. investigational intervention	MOP update	27
4.3	Study Team Roster/Clinical Centers	Updated Study Team Roster to include correct investigators and Satellite Sites	MOP update	7-8
4.3	Event Reporting	Updated Adverse Event reporting processes	MOP update	15-17
4.3	Data Collection Schedule	Removed Boston Naming Test		18
4.3	Data Collection Schedule	Removed baseline and 24 month CPX assessment	MOP update	18
4.3	Functional Status	Removed baseline CPX assessment	MOP update	20
4.3	New York Heart Association Classification (NYHA)	Changed to allow non-blinded personnel to complete assessment	MOP update	21
4.3	Angina Class - Canadian Cardiovascular Society Classification (CCSC)	Changed to allow non-blinded personnel to complete assessment	MOP update	21
4.3	Neurocognitive Testing	Removed Boston Naming Test	MOP update	22
4.3	Laboratory Assessment	Changed baseline laboratory assessment window from 7 to 30 days	MOP update	22
4.3	Post-Randomization Data Collection	Added reference to Patient Contact Log	MOP update	23
4.3	Functional Status	Removed 24 month functional status assessment	MOP update	26
4.3	Neurocognitive Testing	Removed Boston Naming Test	MOP update	26
4.3	Regulatory Documentation	Added to list of documents required for new personnel	MOP update	29
4.3	Appendix II	Added Appendix II: Patient Contact Log	MOP Update	34

1. STUDY TEAM ROSTER

A complete directory for the Cardiothoracic Surgery Network (CTSN) and all documents approved for the network may be found at the following website address:
http://www.ctsurgerynet.org/

Data Coordinating Center

The International Center for Health Outcomes and Innovation Research (InCHOIR), Mount Sinai School of Medicine Department of Health Policy (Michael K. Parides, PhD; Annetine Gelijns, PhD; Deborah D. Ascheim, MD; Alan J. Moskowitz, MD; Ellen Moquete, RN; Alejandra Guerchicoff, PhD; Lopa Gupta, MPH; Janine Lynch, MS, MPH; Karen O'Sullivan, MPH; Paula Williams, MS)

Network Chair, Co-Chair

Timothy J. Gardner, MD; Christiana Medical Center
Patrick T. O'Gara, MD; Brigham and Women's Hospital

Study Sponsors

National Heart Lung and Blood Institute (Marissa Miller, DVM MPH; Wendy Taddei-Peters, PhD, Albert Lee, PhD Neal Jeffries, PhD, Nancy Geller, PhD)
Canadian Institute of Health Research (Ilana Gombos, PhD)
National Institute of Neurological Diseases and Stroke (Claudia Moy, PhD)

Protocol Development Committee

Peter Smith, MD (Chair); Deborah D. Ascheim, MD (DCC, InCHOIR, Mount Sinai School of Medicine); Michael Acker, MD (University of Pennsylvania); David D'Alessandro, MD (Montefiore Einstein Heart Center); John Dent, MD (University of Virginia); Nancy Geller, PhD (NHLBI); Daniel Goldstein, MD (Montefiore Einstein Heart Center); Robert Gorman, MD (University of Pennsylvania); Robert Michler, MD (Co-Chair, Montefiore Einstein Heart Center); Michael Parides, PhD (DCC, InCHOIR, Mount Sinai School of Medicine); John Puskas MD (Emory University); Vinod Thourani, MD (Emory University); Joseph Woo, MD (University of Pennsylvania)

Electronic Data Capture Center (EDC)

For technical support, please contact:
Ron Levitan, M. Sc, (ron.levitan@mountsinai.org) Cell: 646-271-1829
Edlira Kumbarce (edlira.kumbrace@mountsinai.org)
Phone 1: 212-659-9556
Phone 2: 212-659-9567

Mount Sinai School of Medicine Department of Health Evidence and Policy
One Gustave L. Levy Place, Box 1077
New York, NY 10029
Phone: 212-659-9567
Fax: 212-423-2998

2. CLINICAL CENTERS

The study will be conducted in the following highly experienced clinical centers participating in the CT Surgery Network:

Core Clinical Centers
Cleveland Clinical Foundation (Eugene Blackstone, MD)
Columbia University Medical Center (Michael Argenziano, MD)
Duke University (Peter Smith, MD)
Emory University (John Puskas, MD)
Montefiore Medical Center - Albert Einstein College of Medicine (Robert Michler, MD)
Montreal Heart Institute (Louis Perrault, MD)
University of Pennsylvania (Michael Acker, MD)
University of Virginia Health Systems (Irving L. Kron, MD)

Affiliated and Ancillary Clinical Centers
Centre Hospitalier de l'Université de Montréal (Nicolas Noiseux, MD)
East Carolina Heart Institute (T. Bruce Ferguson, MD)
Hôpital du Sacré-Cœur de Montréal (Pierre Pagé, MD)
Inova Heart & Vascular Institute (Alan M. Speir, MD)
Institut Universitaire de Cardiologie de Québec (Hôpital Laval) (Pierre Voisine, MD)
NIH Heart Center at Suburban Hospital (Keith Horvath, MD)
The Ohio State University Medical Center (Chittor Sai Sudhakar, MD)
The Valley Hospital (Alexander Zapolanski, MD)
WellStar Health System, Kennestone Hospital (William A. Cooper, MD)

Satellite Clinical Centers
Baylor Research Institute (Michael Mack, MD)
Brigham and Women's Hospital (Fredrick Chan, MD)
Jewish Hospital and St Mary's Healthcare (Mark Slaughter, MD)
Mission Hospital (Mark Groh, MD)
University of Maryland Medical Center (James Gammie, MD)
University of Southern California University Hospital (Vaughn Starnes, MD)
Washington University School of Medicine (Ralph Damiano, MD)

Each clinical center will be required to obtain IRB approval for the protocol and consent revisions in a timely fashion, recruit patients, obtain informed consent from each subject and protect their rights, collect data and accurately enter it in the electronic data capture (EDC) system, faithfully follow the protocol and adhere to the standards of Good Clinical Practice (GCP)/Human Subjects Research. In addition, centers will be required to provide the Data Coordinating Center (DCC) the information necessary for interim, annual, and final reports, source documents, data and regulatory documents to study monitors, respond promptly to DCC inquiries, and participate in analyses and reporting of study results.

A trial roster for all surgeons, cardiologists, coordinators and other investigators in the study, including hospital affiliation, address, telephone, fax, beeper and email information will be maintained by the DCC. The principal investigator, co-investigator and coordinator must email or fax their CV, Conflict of Interest Statement and Financial Disclosure Certification, Institutional Health Insurance Portability and Accountability Act (HIPAA) and Institutional GCP/Human Subjects Certificates when available to the

DCC. All surgical investigators must complete a Surgical Certification form signed by the surgical Principal Investigator at their site. FWA (Federal Wide Assurance) number for the local governing IRB must be provided to the DCC along with the DUNS numbers for relevant investigators.

3. TRAINING PLAN

All clinical site investigators and coordinators must be trained by the DCC in the specifics of the protocol at a site initiation visit, or an in-person coordinators meeting and investigators conference call, in advance of patient enrollment. All participants must review the training slides and sign the attestation that they completed training. This document should be filed in the site regulatory binder and a copy should be forwarded to the DCC.

Electronic Data Capture System Training

All site coordinators will be trained to input the data for the protocol into the web-based electronic data capture system. This training will consist of an in person demonstration, web-based teleconference demonstrations and a web-based training site: (https://www.inchoir.org/ctsn-train/main).

Neurocognitive Training

Study coordinators must be trained by the CTSN Neurocognitive Core Lab personnel in the administration of the neurocognitive testing, and sites must receive certification from the core lab. The certificate should be filed in the site regulatory binder, and a copy should be forwarded to the DCC. The neurocognitive batteries used in this trial have been validated in English and French. For patients who do not speak English or French as a first language and therefore cannot perform the batteries, this will not preclude them from participating in the trial and completion of the batteries for these patients will not be required.

NIH Stroke Scale (NIHSS) Training

The NIHSS must be administered at the time of a neurological adverse event (within 72 hours following the event) and 90 days following the event to document the presence and severity of neurological deficits. The study coordinators must receive on-line training in the NIHSS in order to administer this scale. A certificate can be printed and should be filed in the site regulatory binder at the completion of the training. A copy should be forwarded to the DCC. The certification program can be found at: http://www.nihstrokescale.org/

Quality of Life Training

The study coordinators will be instructed during the protocol training to teach the study subject to complete the quality of life questionnaires independently and without input from family members/significant others. The quality of life measures selected for this study are to be self-administered. In the event a study subject is unable to read the questionnaires, the coordinator may read the documents, word for word, to them. It is important that the coordinator not add any description or explanation to the questions being asked. For this trial, the SF-12 and MLHF are available in English, Spanish and

French. The DASI and Euroqol are available in English and French. Inability to read and complete these instruments in the available languages does not preclude a patient from enrollment in the trial (a family member may assist in completing the QOL questionnaires).

Echocardiographic and Cardiopulmonary Exercise Testing Training
The Echocardiography Core lab and the Cardiopulmonary Exercise (CPX) Testing Core lab will train the designated echocardiographer at each site and the designated cardiopulmonary testing personnel at each site in the protocol, the Standard Operating Procedures (SOPs), and transmission of data. Training will include image acquisition for the full and limited image collection and transmission of data. (Please see the Echo MOP for information on training, transmission of data, and full and limited image acquisition.)

4. COMMUNICATIONS PLAN

The DCC will coordinate and facilitate communication amongst all participating clinical centers, committees, and governing bodies via email, telephone conference calls, and the study website. Such communications will include monthly Steering Committee and monthly PI calls, as well as bi-weekly Coordinator Conference calls.

5. STUDY ORGANIZATION AND RESPONSIBILITIES

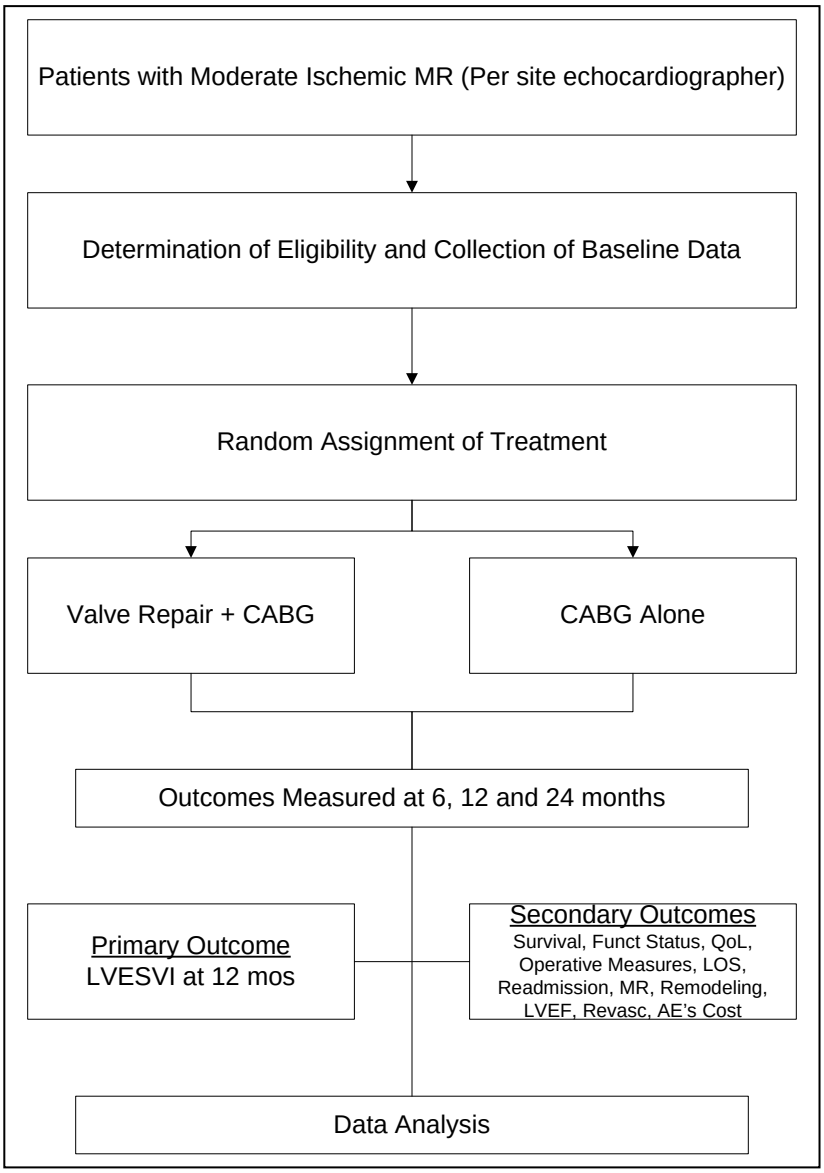
Please refer to the Network for CT Surgical Investigations Administrative Manual of Procedures (MOP) Section I: CTSN ORGANIZATION.

6. RECRUITMENT

Please refer to the protocol sections “Recruitment Strategies” and “Inclusion of Women and Minorities” and/or to the Network for CT Surgical Investigations Administrative Manual of Procedures, Section 9.4, “Inclusion of Women and Minorities as Subjects”. Investigators will be required: (1) to document the number of women and minorities screened and enrolled via screening/exclusion logs, which will be monitored monthly by the DCC; and (2) if necessary, participate in the implementation of outreach programs designed to recruit adequate numbers of women or minorities.

7. STUDY FLOW

See diagram below.



8. SCREENING AND ELIGIBILITY CRITERIA

All patients who are diagnosed with moderate ischemic mitral regurgitation and clinically significant coronary artery disease with a clinical indication for coronary artery bypass grafting (CABG), regardless of gender, race or ethnicity, are potential candidates for this trial and should be screened for study entry according to the protocol.

- The judgment of the investigator is critical for identifying those subjects suitable for study enrollment.

- The baseline echo must be a transthoracic study, performed at the clinical center. A trans-esophageal echo cannot serve as a baseline echo study.
- The ERO will be calculated and the degree of MR by integrative method will be determined by the clinical center echocardiography laboratory for determination of eligibility (Criterion #1), and a copy of the screening echo will be forwarded to the CTSN Echo Core Lab. (Please see the Echo Core Lab MOP for Echo Core Lab shipping procedures and instructions.)
- Inclusion criterion number 1 requires particular attention by the investigator with respect to patient selection.
- Exclusion criteria 1, 2, 9, 10, and 15 require particular attention by the investigator with respect to patient selection.

9. INFORMED CONSENT, HIPAA, RELEASE OF MED. INFORMATION

Informed consent is a process that involves:

- Providing participants with adequate information concerning the study procedures and purpose of the research study, expected duration of participation, and the risks and benefits of participation;
- Providing opportunity for a potential participant to consider all available treatment options which include information about any appropriate alternative treatments that could possibly benefit the subject;
- Responding to individual's questions and concerns;
- Ensuring that all information provided is understood by the potential study subject;
- Obtaining the individual's written voluntary consent.

Informed Consent Form

The consent form documents the willingness of the individual to participate in the study. It contains the signature of the subject and the signature of the investigator giving information on the research. The CTSN sample informed consent form provides the essential elements to ensure that a patient participating in the study is appropriately informed of the risks and potential benefits of study participation. Site investigators may modify the sample consent form to meet the individual Institutional Review Board (IRB) requirements, with approval from the DCC.

Obtaining Informed Consent

Informed consent will be obtained according to individual institutional guidelines. Patients should be encouraged to have family or other support available during the informed consent process. They should be assured that declining to sign an informed consent document will in no way compromise their care, and that should they consent to participate in the study, they may revoke that consent at any time. All patients will be required to sign informed consent to participate in this study. As part of the informed consent process, all patients will be given the opportunity to opt in or out of the biological specimen collection process.

Timing for the informed consent process must be consistent with the center's institutional IRB and privacy policies, and in accordance with the CTSN guidelines, *the consent*

process (and its documentation) must begin at least the day before the surgical procedure. This is to ensure that all subjects will be given adequate time to review the informed consent document, and consider participation in the trial.

As part of the informed consent process, the investigator must:

- Obtain informed consent before baseline studies are performed
- Document any questions addressed with the patient and/or family during the informed consent process in the medical chart
- Confirm that all signatures on the informed consent are complete and dated
- Place one copy of the signed informed consent in the medical chart
- Provide one copy of the signed informed consent to the patient
- File the original signed informed consent in the Case Report Binder

Screening Activity Prior to Informed Consent

In preparation for participation in the study, with local IRB/Privacy Board approval, the investigator can review patient charts for the purpose of identifying potential research candidates and will record HIPAA compliant data on all pre-screened patients who are not enrolled in the Pre-Screening Failure form. *HIPAA sensitive data cannot be extracted or screening studies performed until written informed consent is obtained.*

HIPAA and Release of Medical Information Forms

- The HIPAA Clinical Research Authorization and Release of Medical Information forms may either be incorporated into the consent form as separate documents or as dictated by institutional requirements.
- The HIPAA Clinical Research Authorization form, approved by the IRB or Privacy Board, allows investigators to approach, screen, and enroll patients in the study.
- The Release of Medical Information form authorizes release of medical records to the study investigators, monitors, NHLBI, NINDS, CIHR, and the DCC.

10. RANDOMIZATION

The randomization procedure will be performed intra-operatively, following sternotomy and before cannulation of aorta. This is to minimize the likelihood of enrolling patients in the study with unexpected surgical contra-indications to mitral valve repair.

Randomization Procedure

- Randomization will be performed through the web-based electronic data capture (EDC) system, which automates the delivery of the randomization codes. This code will be generated once the checklist of inclusion and exclusion criteria has been completed and verified.
- The treatment assignment will be immediately visible to the coordinator in the EDC.
- Electronic verification (signature) of the treatment assignment via the EDC will be required before proceeding with the treatment intervention.
- A printed version of the randomization form should be signed and kept in the clinical center patient study binder.

- From the time of randomization on, the primary efficacy endpoint will be analyzed by intention-to-treat; that is, patients will be grouped by their assignment at randomization whether or not they actually received the treatment to which they were assigned.

11. STUDY INTERVENTION

Patients will be randomly assigned, as described above, to one of two treatment groups: (a) mitral valve repair using an FDA-approved annuloplasty ring in addition to coronary artery bypass (CABG) surgery or (b) CABG alone. Please refer to the protocol section labeled "PROCEDURE".

12. MASKING

Neither patients nor investigators will be blinded to treatment assignment due to the nature of treatment intervention. Investigators will, however, be blinded to all data from other clinical sites, except for serious, unexpected AEs for IRB reporting purposes. All echocardiograms and cardiopulmonary testing results will be analyzed by core laboratory personnel who will be blinded to clinical outcomes.

13. PARTICIPANT EVALUATIONS AND FOLLOW-UP

All patients who meet the eligibility criteria and are enrolled in the study will follow the same study visit schedule.

- Follow-up will occur at 6, 12, and 24 months post randomization.
- *Remote Follow-up*: Patients who are unable to return to the clinical site for **the 6 and 24 month assessments** because of extreme geographic distance can obtain a limited echo at a remote site (see Limited Echocardiographic Image Acquisition Protocol, Appendix I), or they may go to an alternative CTSN site. However, follow-up at a remote site should be avoided whenever possible, and the clinical coordinator should strongly encourage patients to return to a CTSN clinical site for the follow-up echos. (Please see the "Remote Echo Assessment" section blow.)
- **All patients must return to a CTSN site for follow-up at 12 months.** If patients are unable to return to the clinical site where they are enrolled in the study, they may go to an alternative CTSN site for the 12 month follow-up. Patients *cannot* obtain a limited echo at a remote site for the 12 month visit.

14. PARTICIPANT RETENTION

Every effort will be made by all clinical investigators to have each randomized subject complete all aspects of the study to study completion.

15. CONCOMITANT INVESTIGATIONAL MODALITIES

Medications and medical substances and devices not approved by the FDA for study subjects are prohibited while the subject is on the study.

16. SAFETY REPORTING

Definitions

Unanticipated Problems

According to the Office for Human Research Protections (*OHRP*), an Unanticipated Problem (UP) generally includes any incident, experience, or outcome that meets **all** of the following criteria: (1) 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; *and* (2) Related or possibly related to participation in the research (in this guidance document, *possibly related* means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); *and* (3) Suggests that the research places subjects or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

Based on the definitions above and as illustrated below (per OHRP guidance), many adverse events are not unanticipated problems, and many unanticipated problems are not adverse events. However, some adverse events are also unanticipated problems. For example, a serious adverse event that is unexpected and at least possibly related to study participation is also by definition an unanticipated problem. As stated above, an unanticipated problem may not necessarily be an adverse event, which is the case when the problem does not cause actual physical harm to participants. For example, if a laptop computer with sensitive, identifiable study data is stolen, this theft places the participants at greater *risk* of psychological or social harm; this is an unanticipated problem that is not an adverse event. Another example of an unanticipated problem that is not an adverse event is if the FDA announces that one of the study drugs is tainted (e.g., with paint chips), yet no participant experiences any adverse effects.

Adverse Events

An adverse event (AE) is any undesirable clinical occurrence in a study patient, whether or not it is related to the study intervention. Any condition that was recorded as pre-existing is *not* an AE unless there is a change in the nature, severity or degree of the condition.

Serious Adverse Event

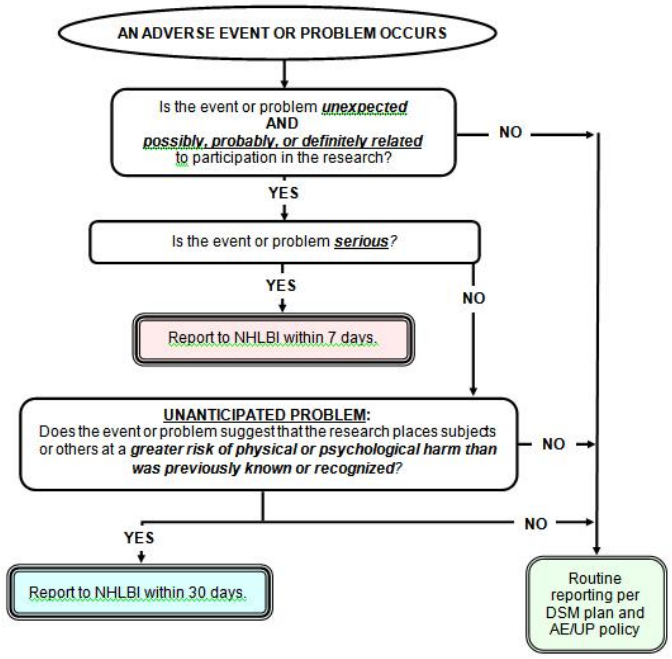
Serious adverse events (SAEs) are defined by FDA regulation as any experience that results in a fatality or is life threatening; results in significant or persistent disability; requires or prolongs a hospitalization; results in a congenital anomaly/birth defect; or represents other significant hazards or potentially serious harm to research subjects or others, in the opinion of the investigators. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse event when, based upon appropriate medical judgment, they may jeopardize the patient

and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias, or convulsions that do not result in inpatient hospitalization.

All investigators conducting clinical studies supported by the NHLBI must report both expected (protocol-defined) and unexpected SAEs. All AE reporting should proceed as follows:

- All ***protocol defined*** AEs must be reported directly to the clinical center's Institutional Review Board (IRB)/Ethics Review Board (ERB) and the DCC within **10 business days** of knowledge of the event, or as dictated by the specific IRB/ERB policy, whichever is sooner. The study coordinator will send an email to the clinical trials manager at the DCC to document the SAE and enter the data into the Electronic Data Capture system as soon as the information is available.
- All ***deaths*** and ***unexpected SAEs*** must be reported to the DCC and the clinical center's IRB within **24 hours** of knowledge of the event, or as dictated by the specific IRB policy, whichever is sooner. The study coordinator will call the clinical trials manager at the DCC to notify the DCC of the death. The DCC may request that de-identified source documentation regarding the event be sent via secure fax line for the Medical Monitor to create the pre-adjudication report to the NHLBI. The data will be entered into the Electronic Capture system as soon as the information is available by the site coordinator.
- All ***unexpected SAEs*** **that are** ***unlikely related to the study intervention*** must be reported to the DCC and the clinical center's IRB within **5 business** days of knowledge of the event, or as dictated by the specific IRB policy, whichever is sooner.

Figure 2



The DCC will notify the NHLBI program officer of any unexpected SAEs that are possibly or probably related to the study intervention and all deaths (regardless of relatedness and expectedness) via e-mail within 24 hours of receipt of the event. The program officer will report these events to the DSMB chair within 72 hours of notification. All serious AEs will be reported to the DSMB at least semi-annually, at the discretion of the DCC medical monitor.

Reporting of Unanticipated Problems
All *UPs* that are also SAEs, which are at least possibly related to the study intervention, must be reported to the DCC within 24 hours of knowledge of the event. All UPs that are not SAEs must be reported to the DCC within 5 calendar days of knowledge of the event, or as dictated by the specific IRB policy, whichever is sooner.

17. EVENT ADJUDICATION COMMITTEE

All mortalities and protocol defined and serious adverse events will be adjudicated by an independent Event Adjudication Committee (EAC). The committee will adjudicate adverse event classifications, seriousness and relatedness to the surgical procedure and the investigational intervention (MV repair) as reported by the site PI, as well as the reported primary and underlying causes of mortality events. The DCC will provide de-identified source documentation supplied by the clinical sites to the committee to support each event and mortality to be adjudicated. The optimal procedure for the clinical site personnel in this process is to file source documentation supporting each reported AE in the Patient Source Binder as the events are reported. All events will be fully monitored prior to presentation to the EAC for adjudication.

18. DATA AND SAFETY MONITORING RESPONSIBILITIES

The conduct of the study will be overseen by an independent Data and Safety Monitoring Board (DSMB) appointed by NHLBI. Please refer to the Network for CT Surgical Investigations Administrative Manual of Procedures, Section 1, “NETWORK ORGANIZATION”.

19. STUDY COMPLIANCE

Efforts to maximize adherence to the study protocol will be made through careful and comprehensive training, early review of study data submitted via the EDC system, and routine communication with all site investigators. Despite the best efforts of the clinical investigators, protocol deviations and/or violations may occur. They may include but are not limited to randomizing an ineligible study participant, failing to obtain informed consent, failing to maintain IRB and related study documents, or administering the wrong treatment. Relevant violations will be reported to the DCC, who will notify appropriate parties, including the study site Principal Investigator, NHLBI, NINDS, CIHR, and/or DSMB. The DCC will instruct each clinical center to maintain a log of protocol deviations and/or violations and report them routinely to the Clinical Trial Manager.

20. DATA COLLECTION SCHEDULE

Assessment	Screening/ Baseline	Intra-Operative	POD#1	6 Mos (± 14 days)	12 Mos (± 14 days)	24 Mos (± 14 days)	Event Driven
General							
Informed Consent	X						
Release of Medical Information	X						
Screening Log and Registration	X						
Medical History	X						
Medications	X			X	X	X	X
Physical Exam	X			X	X	X	
Laboratory Assessment	X						
Eligibility Criteria	X						
Screening Outcome	X						
Cardiac							
NYHA Heart Failure Class	X			X	X	X	
CCSC Angina Class	X			X	X	X	
Peak VO_2 (Cardiopulmonary stress test)				X	X		
TTE (Trans-thoracic Echocardiogram)	X			X	X	X	
TEE (Transesophageal Echocardiogram)		X					
Hemodynamics		X	X				
Biological Specimen Collection		X		X	X		
Quality of Life (QOL)							
MLHFQ	X			X	X	X	
SF-12	X			X	X	X	
EuroQol	X			X	X	X	
DASI	X			X	X	X	
Neurocognitive Testing							
Hopkins Verbal Learning Test	X				X		
Trailmaking Tests A and B	X				X		
MCG Complex Figures	X				X		
Digit Span	X				X		
Digit Symbol Substitution Test	X				X		
Event Driven Data							
Surgical Procedure		X					X
Adverse Events							X
Hospitalization	X						X
Missed Visit							X
Mortality							X
Study Completion/Early Termination							X
End of Study/Investigator Statement							X
Cost							
UB-92 Forms & Hospital Bills							X*

*Costing data will be collected by the DCC on a quarterly basis.

Screening and Baseline

Pre-Screening Failure Form

Prior to informed consent

- Prior to approaching a patient to begin the informed consent process, the study personnel will review data on prospective patients to determine eligibility for inclusion in the trial.
- All pre-screened patients (patients who are not consented) who are not enrolled are recorded in the Pre-Screening Failure form. Reasons for screening failure are collected.
- The data collected is HIPAA compliant and does not include patient identifiers.
- The data collected include screening quarter, screening year, age, gender and reason not eligible.

Demographics Form

At initiation of screening

- A screened patient is defined as someone (a consented patient) who was referred to, or identified at a clinical site for consideration of entry into the study, and for whom some preliminary (i.e. medical record) data have been collected and/or reviewed.
- For all patients screened, the first, middle, and last initial, date of birth, sex, ethnic origin, racial category, health insurance, level of education, and handedness will be captured on the screening form.
- The EDC will generate a unique 10-digit identification code (e.g., AAA-01-M-0001) that will identify the patient throughout the course of the study. The code is composed of three patient initials (if no middle initial, a dash is acceptable), site number (auto-populated by the EDC), the trial initial "M", and the consecutive patient enrollment count at the site (also auto-populated).

Consent

Prior to screening data collection and *protocol-defined procedures*

- Prior to screening, a thorough explanation of the risks and benefits of the study will be outlined by the investigator or designee to the potential study subject.
- Study personnel will begin the informed consent process as soon as possible during the preoperative evaluation phase for each patient.
- Timing for the informed consent process must be consistent with the center's institutional IRB and privacy policies, and in accordance with the CTSN guidelines, *the consent process must begin at least the day before the surgical procedure*. This is to ensure that all subjects will be given adequate time to review the informed consent document, and consider participation in the trial.
- All questions will be answered to the satisfaction of the subject prior to signing the informed consent document.
- Site source records will include documentation of the informed consent process for each subject.
- No study specific procedures will be performed prior to signing the informed consent document.
-

HIPAA and Release of Medical Information Form

Prior to screening data collection and *protocol defined procedures*

- The patient must sign HIPAA and the Release of Medical Information form or equivalent that authorizes release of medical records, including hospital costing data, to the study sponsors, investigators and monitors.

Functional Status

Within 30 days prior to randomization

- The site Exercise Physiology lab must be trained by the Cardiopulmonary Exercise Core Lab in advance of performing any study. Each CTSN site will be credentialed according to the CTSN CPX Core Lab (Henry Ford Hospital) Manual of Operations (MOO).

Echocardiogram

Within 30 days prior to randomization

- The site echocardiography lab must be trained by the Echo Core Lab in advance of performing any study echocardiograms, and each test must be performed by the trained technician within the lab. (Please see the "Training Sessions" section of the Echo Core Lab MOP.)
- A complete transthoracic echocardiogram will be performed at the CTSN clinical center, according to the specifications defined in the Echocardiographic Image Acquisition Protocol at each of the designated time points.
- A trans-esophageal echo cannot serve as a baseline echo study.
- ***The pre-randomization echo will be read by the clinical site echocardiography investigator to assess the degree of MR which will determine echocardiographic eligibility for participation in the trial.***
- After this initial assessment, the study echo will be sent to the Echocardiography Core Lab for centralized reading by a blinded core lab investigator.
- Pre-labeled CDs for copying the echo and pre-labeled mailing slips for shipping studies to the core lab will be provided to the clinical sites by the core lab.
- Baseline echo studies will be shipped to the core lab within 7 days of randomization. Please ship the echo to:

  ATTN: Judy Hung
  55 Fruit Street
  Massachusetts General Hospital
  Echocardiography Blake 256
  Boston, MA 02114

Medical History

Within 7 days prior to randomization

- This form captures the information pertaining to the study subject's cardiovascular history, cardiovascular procedure history, cerebrovascular history, history of "other" medical conditions, and current medical condition.

New York Heart Association Classification (NYHA)
Within 7 days prior to randomization

- The presence of heart failure will be assessed and, when present, classified according to the NYHA scale.
- NYHA classification will be determined by investigative center personnel. The personnel identified at the site to perform the NYHA must be documented on the site signature and delegation log.
- The NYHA classification scheme is detailed in Appendix II of the trial protocol.

Angina Class - Canadian Cardiovascular Society Classification (CCSC)
Within 7 days prior to randomization

- The presence of angina will be assessed and, when present, classified according to the CCSC scale.
- The CCSC will be determined by investigative center personnel. The personnel identified at the site to perform the CCSC must be documented on the site signature and delegation log.
- The CCSC classification scheme is detailed in Appendix IV of the trial protocol.

Medications
Within 7 days prior to randomization

- This form captures all protocol-defined medications taken within 7 days prior to randomization.
- "Other Medication" entered should include those medications that are clinically relevant in the judgment of the investigator (e.g., antibiotics, immunosupressants, etc).
- It is not necessary to list *all* non-clinically relevant medications (e.g., vitamins, stool softeners, GI prophylaxis, nutraceuticals, etc.).

Physical Examination
Within 7 days prior to randomization

- This form captures the comprehensive physical examination including vital signs, anthropometrics (height, weight and BSA), cardiopulmonary examination, abdominal examination, and nutritional assessment.
- The physician or his/her delegate (including another physician, PA, and NP) can perform this exam.

Quality of Life
Within 7 days prior to randomization

- The Minnesota Living with Heart Failure Questionnaire (MLHFQ), Duke Activity Status Index (DASI), SF 12, and EuroQol (Appendix VI of protocol) questionnaires will be completed by the patient to assess quality of life.
- Data regarding completeness of QoL data collection and reasons for missing responses to questionnaires will be collected on the QoL Checklist.
- Inability to read and complete these instruments in the available languages does not preclude a patient from enrollment in the trial (a family member may assist in completing the QOL questionnaires).

Neurocognitive Testing

Within 7 days prior to randomization

- Cognitive performance will be assessed at baseline using the following battery of tests: Hopkins Verbal Learning Test, Trailmaking Tests A and B, MCG Complex Figures, Digit Span, and Digit Symbol Substitution Test.
- Study personnel trained in accordance with the respective neurocognitive tool must conduct these tests and document the results on the appropriate forms. Testing for the purposes of this protocol will not require a neurologist or neuro-psychologist.
- The testing will take a total of 45 minutes.
- Results from these tests will be independently scored by investigators from the CTSN Neurocognitive Core Lab.
- After QA is completed (as detailed in the Neurocognitive Core Lab's "Nurses' Cognitive Training Directive"), all tests and audiotapes will be stored at Duke University Medical Center until the end of the study when all data analyses are completed at which point the audio tapes will be destroyed. Prior to that point, tapes will be destroyed upon receipt of a formal request for destruction from the Data Coordinating Center or from an enrolled patient.
- The neurocognitive batteries used in this trial have been validated in English and French. For patients who do not speak English or French as a first language and therefore cannot perform the batteries, this will not preclude them from participating in the trial and completion of the batteries for these patients will not be required.

Laboratory Assessment

Within 30 days prior to randomization

- White blood cell *($10^3/\mu l$)(K/uL)*
- Hemoglobin *(g/dl)*
- Hematocrit *(%)(L/L)*
- Platelet count *($10^3/\mu l$) (K/uL)*
- Prothrombin time (PT/sec), partial thromboplastin time (PTT/sec)
- International Normalized Ratio (INR)
- Blood chemistries, including sodium *(mM/L)*, potassium *(mM/L)*, blood urea nitrogen *(mg/dl)*, creatinine *(mg/dl)*
- Liver function tests, including total bilirubin *(mg/dl)*, alanine aminotransferase (ALT *U/L)*, aspartate aminotransferase AST *(U/L)*, albumin (g/dl), lactate dehydrogenase (LDH).
- Urine or serum beta HCG *(IU/L)* is required for women who have the potential to become pregnant

Eligibility Criteria/Eligibility Evaluation Form

Prior to randomization

- The inclusion and exclusion criteria will be documented by the clinical site study coordinator and verified with the site Principal Investigator.
  - All screened patients (patients who are consented) who are not randomized in the trial will be documented in the Eligibility Evaluation form. Reasons for non-randomization are collected.

- The data collected is HIPAA compliant.

Proposed Revascularization
Prior to the surgical intervention

- The coronary anatomy will be described by the surgical investigator including the degree of coronary obstruction.
- Each artery/territory will be described *pre-operatively* as amendable or not amenable to bypass.
- The proposed revascularization plan of each territory must be reported *pre-operatively*.

Randomization

- A representative from the DCC will be available to discuss any questions regarding patient eligibility.
- **The randomization procedure will be performed intra-operatively, following sternotomy and before cannulation of aorta (see section 10 above).**

Procedure

Surgical Procedure*
Patients will be randomized to either:

a. Mitral valve repair + CABG
   or
b. CABG alone

**See trial protocol for additional detail regarding the surgical procedure.*

Post-Randomization Data Collection

Attempts to reach patients via telephone will be documented in the Trial Patient Contact Log (Appendix II).

Study Visits

- Post-Op Day 1
- 6, 12 and 24 months post-op (+/- 14 days)
  - Patients who are unable to return to the clinical site for the *6 and 24 month* assessments because of **extreme geographic distance** can obtain the required echocardiogram from a remote clinical site outside of the core CTSN sites (see Limited Echocardiographic Image Acquisition Protocol, Appendix I). ***However, this should be avoided whenever possible, and the clinical coordinator should strongly encourage patients to return to one of the core CTSN sites.***
    - The remote clinical site *must* be identified in advance of discharge from the index hospitalization, and all efforts must be made to perform all follow-up visits at a CTSN clinical site.
  - Patients can, when necessary, go to another CTSN site for 6, 12, and 24 months post-op follow-up if desired.

- *All 12 month (Primary Endpoint) assessments must be performed at a CTSN clinical site.*

Hemodynamics

Intra-operative assessment at initiation of TEE and POD #1

- Hemodynamics will be measured prior to surgical intervention by the intra-operative right heart catheter
- The following will be recorded: CVP, PA_S, PA_D, PA_M, PCWP, CO, CI, SVR, and pulmonary artery O_2 sat (PA O_2 sat)

Blood, Urine, and Tissue Sample Collection

Intra-operative and at 6 and 12 months post randomization

- Patients must provide a separate consent for participation in the biological specimen collection portion of the trial. This discrete consent may be included in the trial consent form, but requires separate signature.
- For those patients who consent, the following will be collected at time points specified in the protocol:
  - Blood
  - Urine
  - Tissue
- The samples will be banked by the NHLBI Blood and Tissue Repository service (operated by SeraCare Bio Services, 217 Perry Parkway, Gaithersburg, Maryland 20877).
- See Biorepository MOP for detailed information on sample collection, handling and shipping procedures.

Surgical Procedures

Initial surgical intervention and event driven

- The initial surgical procedure and all subsequent operations must be reported on the surgical procedure form within 48 hours of knowledge of the event.
- If the operation is to address a complication, the coordinator must also complete an adverse event report.

Hospitalizations

Index hospitalization and event driven

- The index (baseline) hospitalization and all subsequent hospital admissions (for any reason) must be reported.
- For each hospitalization limited information about procedures, length of stay, days in intensive care, and discharge if applicable, as well as patient condition and disposition will be collected.

Medications

At 6, 12, and 24 months post randomization and event driven

- All cardiovascular medications will be recorded at each study visit and, as indicated, at the time of associated adverse events.

Physical Examination
At 6, 12, and 24 months post randomization

- In this limited physical examination vital signs and cardiopulmonary examination will be captured.

New York Heart Association Classification
At 6, 12, and 24 months post randomization

- NYHA classification will be determined by a clinical site coordinator, not otherwise involved in this trial, who will be blinded to the treatment assignment.
- The personnel identified at the site to perform the NYHA must be documented on the site signature and delegation log.

Angina Class - Canadian Cardiovascular Society Classification (CCSC)
At 6, 12, and 24 months post randomization

- The CCSC will be determined by a clinical site coordinator, not otherwise involved in this trial, who will be blinded to the treatment assignment.
- The personnel identified at the site to perform the CCSC must be documented on the site signature and delegation roster.

Echocardiogram
At 6, 12, and 24 months post randomization

- A complete transthoracic echocardiogram will be performed at the CTSN clinical site, according to the specifications defined in the Echocardiographic Image Acquisition Protocol, at each of the designated time points (protocol Appendix I).
- If desired patients can, when necessary, go to another CTSN site for 6, 12, and 24 months post-op follow-up.
- Patients who are unable to return to the clinical site for the 6 and 24 month assessments because of extreme geographic distance can obtain a limited echo at a remote site (see MMR MOP Appendix I). However, this should be avoided whenever possible, and the clinical coordinator should strongly encourage patients to return to a CTSN clinical site for the follow-up echos.
- *All 12 month (Primary Endpoint) assessments must be performed at a CTSN clinical site.*
- All study echos will be sent to the Echocardiography Core Lab for centralized reading by a blinded investigator.

Remote Echo Assessments:
At 6 and 24 months post randomization ONLY

- *The remote clinical site must be identified by the coordinator in advance of discharge from the index hospitalization*
- The remote image acquisition site contact information, including primary contact person, must be documented on the Remote Image Acquisition Contact form. The form must be faxed to the DCC prior to patient discharge and filed in the Patient Study Binder.
- 30 days prior to the image acquisition assessment date the clinical site coordinator will:

- Contact the patient and the remote image acquisition center to confirm that the echo is scheduled
- Send (1) the limited echo acquisition protocol (See Echocardiography Core Lab SOP), (2) pre-labeled recording material for copying the echo, and (3) pre-labeled mailing slips for shipping studies to the core lab to the remote acquisition center contact person

Functional Status

At 6 and 12 months post randomization

- The site Exercise Physiology lab must be trained by the Cardiopulmonary Exercise Core Lab in advance of performing any study. Each CTSN site will be credentialed according to the Henry Ford CPX Core Lab Manual of Operations (MOO).
- Functional status as assessed by a CPX test will be evaluated, and the peak oxygen uptake will be recorded.
- If patients are unable to undergo a CPX test (e.g. on inotropic therapy), the reason for non-performance will be documented in the CRF.
    - Patients who were followed remotely for the 6 ~~and 24~~ month ECHO assessments will not have functional status tests at 6 ~~and 24~~ months.
- The metabolic cart data will be sent to the CPX Core Lab for centralized analysis by a blinded core lab investigator.
- Details regarding the CPX protocol and data transfer are provided in the CPX MOO and protocol.

Neurocognitive Testing

At 12 months post randomization

- Cognitive performance will be assessed at baseline using the following battery of tests: Hopkins Verbal Learning Test, Trailmaking Tests A and B, MCG Complex Figures, Digit Span, and Digit Symbol Substitution Test.
- Study personnel trained in accordance with the respective neurocognitive tool must conduct these tests and document the results on the appropriate forms. Testing for the purposes of this protocol will not require a neurologist or neuro-psychologist.
- Results from these tests will be independently scored by investigators from the CTSN Neurocognitive Core Lab.
- After QA is completed (as detailed in the Neurocognitive Core Lab Nurses' Neurocognitive Training Directive), all tests and audiotapes will be stored at Duke University Medical Center until the end of the study when all data analyses are completed at which point the audio tapes will be destroyed. Prior to that point, tapes will be destroyed upon receipt of a formal request for destruction from the Data Coordinating Center or from an enrolled patient.
- The neurocognitive batteries used in this trial have been validated in English and French. For patients who do not speak English or French as a first language and therefore cannot perform the batteries, this will not preclude them from participating in the trial and completion of the batteries for these patients will not be required.

Quality of Life

At 6, 12, and 24 months post randomization

- The Minnesota Living with Heart Failure Questionnaire (MLHFQ), Duke Activity Status Index (DASI), SF 12, and EuroQol (protocol Appendix VI) questionnaires will be completed by the patient to assess quality of life.
- Data regarding completeness of QoL data collection and reasons for missing responses to questionnaires will be collected on the QoL Checklist.
- If the patient is unable to return to the CTSN investigative center for their 6 and 24 month follow-up visit:
    - The coordinator will send the QoL questionnaires to the patient with a postage paid, self addressed return envelope.
    - The coordinator will telephone the patient to remind them to complete and return the QoL questionnaires.
- Inability to read and complete these instruments in the available languages does not preclude a patient from enrollment in the trial (a family member may assist in completing the QOL questionnaires).

Cost

- Direct costing data from UB-92 forms and hospital billing sheets for all patients will be obtained by the DCC on a quarterly basis.
- The coordinator will provide a list of medical record numbers to the financial data administrator, at their institution, who will generate the UB-92 forms and hospital bills.
- For Medicare-eligible enrollees, CMS billing data will also be collected.

Event Driven Data Collection

Follow-up Surgical Procedures

Event Driven

- All operations must be reported on the surgical procedure form within 48 hours of the knowledge of the event.
- If the operation is to address a complication, the coordinator must also complete an adverse event report.
- All intra-operative transfusion requirements must be documented.

Adverse Events

Event Driven

- Detailed information regarding protocol-defined and serious adverse events will be recorded at the time an adverse event occurs.
- Investigators must classify the events according to the seriousness and relationship of the event to the surgical procedure (CABG) and the investigational intervention (MV repair).
    - If a patient did not receive an investigational intervention (i.e. randomization to CABG alone), please indicate this in the EDC (i.e.

Adverse Events Form). In this case, an event could not be classified as related to the investigational intervention.

- All adverse events will be recorded until completion of the trial.

National Institute of Health Stroke Scale and Modified Rankin Scale
Event Driven

- NIHSS and Modified Rankin Scale must be administered within 72 hours of a neurological event (as defined in the protocol) and 90 days following the event to document the severity of neurological deficits.

Missed Visit Assessment
Event Driven

- A missed visit form must be completed if a patient is unable to return for follow-up before the closure of a study visit window.
- The reasons for missing the visit must be documented.

Mortality
Event Driven within 24 hours of knowledge of event

- The following information must be collected:
  - Date of death
  - Immediate cause of death
  - Primary underlying cause of death
  - Notation of autopsy being performed
  - Clinical narrative of the event

Study Completion/Early Termination
Event Driven

- The date and reason for study completion or early termination will be recorded.
- Examples of reasons for a patient to be withdrawn from this study will be recorded, including:
  - Patient's request
  - Physician's discretion

Investigator's Statement
End of study

- The Principal Investigator will review all of the electronic case report forms (eCRFs) and patient summaries. Their electronic signatures attest to the accuracy and completeness of the data collected.

21. REGULATORY DOCUMENTATION

Regulatory requirements:
Each site will maintain a regulatory binder for each protocol. The DCC must have the following documents on file prior to site approval and initiation of the study:

- Clinical study agreement with Mount Sinai School of Medicine

- Nondisclosure agreement with Mount Sinai School of Medicine and the DCC
- Copy of IRB approval for protocol, informed consent, HIPAA, and Release of Medical information forms
- Investigator and Co-Investigator Curriculum Vitaes (CVs)
- GCP and HIPAA certification for all study personnel
- IRB(US)/Ethics Committee (non-US) roster and IRB/Ethics Committee verification
- FWA and DUNS numbers
- Clinical site laboratory certification and laboratory normal values
- Clinical site echocardiography laboratory accreditation
- Specialized Training Certifications:
    - Surgical Certification Form
    - Coordinator Neurocognitive Training Certification
    - NIHSS Training Certificate
    - IATA Training Certificate

Ongoing study documents:
All sites must retain a regulatory binder that must be updated as new revisions of study documents are made and approvals are renewed. Study documents include:

- Copies of all revisions of the protocol
- Copies of all revisions of the informed consent
- All IRB(US)/Ethics Committee (non-US) correspondence
- IRB approvals for the protocol and informed consent
- Printed copies of blank electronic case report forms
- Clinical Study agreements
- New Investigator and Co-Investigator CVs
- IRB Correspondence
- Monitor site visit log
- Site signature and delegation log
- Correspondence with DCC

Ongoing IRB requirements:

- The DCC will send clinical centers a reminder letter 90 days prior to IRB approval expiration date.
- The DCC will provide the sites with DSMB protocol approval letters.
- The protocol must be reviewed annually by the IRB.
- Informed consent must be re-approved in accordance with the clinical center's IRB, or at least annually.
- A copy of the IRB letter of re-approval must be forwarded to the DCC.

Changes in CTSN personnel:
The DCC should be informed of any personnel changes in Principal investigator, co-investigator, and/or coordinators.

Complete documentation for the new study personnel should be sent to the Project Manager at the DCC. This should include:

- Role in CTSN Study

- Complete contact information including telephone, fax, email address, and beeper number
- Curriculum vitae
- GCP and HIPAA certification
- Clinical Study agreement, as applicable
- Specialized Training Certification, as applicable (e.g. Neurocognitive, NIHSS)
- Conflict of Interest Form (COI)
- Site Attestation Form
- Signature on Delegation of Duties Log

22. ELECTRONIC DATA MANAGEMENT

The primary data collection tool within the Network for forms-based data is a web-based forms management system that has been developed by the DCC's system development team. The system design is based on an industry-standard three-tier architecture consisting of the user's web browser, an SSL-enabled application server with the Apache web server, the Java-based Tomcat servlet engine, and a relational database server.

23. QUALITY CONTROL PROCEDURES

The training of investigators/coordinators will occur at site initiation and yearly investigator meetings. Every effort will be made to implement quality control measures for all procedures, diagnostic tests, and samples obtained. To this end, documents specific to the CTSN have been created and should be referenced as applicable.

These documents include:

- Biological Specimen Manual of Procedures
- Echocardiography (Echo) Core Lab Manual of Procedures
- Limited Echocardiographic Image Acquisition Protocol (Appendix I)
- Cardiopulmonary Exercise Testing Core Lab Manual of Operations
- Neurocognitive Core Lab Nurses' Neurocognitive Training Directive
- Surgical Certification Form: All surgical investigators will complete a surgical certification form which will be reviewed and signed by each site PI. The site PI will be responsible for overseeing the performance of each participating surgeon at their site over the course of the trial. (See CTSN Website Documents)

24. STUDY COMPLETION AND CLOSEOUT PROCEDURES

The monitoring team will determine the study completion status following the study close-out visit. This visit will occur once the study is completed and all data and finalized CRFs are submitted. The DCC policy for maintaining records is reviewed with the Clinical site at this time. Additionally, the return of study supplies is completed. A final report indicating the completion of the study is prepared by the DCC following this visit.

25. POLICIES

Confidentiality Procedure (See the Certificate of Confidentiality on the CTSN Website)

26. MOP MAINTENANCE

The DCC will review the MOP annually for updated information and communicate these changes with the sites.

APPENDIX I: Limited Echocardiographic Image Acquisition Protocol

- All images should be acquired during quiet respiration.
- At least 3 cardiac cycles are requested for 2D imaging, spectral pulsed wave (PW) and continuous wave (CW) Doppler.
- For patients in atrial fibrillation, a minimum of 2 captures of 3 consecutive cardiac cycles are required.
- Harmonic imaging should be employed to optimize visualization of endocardial borders.
- A sweep speed of 100 mm/sec is required for PW, CW Doppler and M-mode recordings.
- Color Doppler Nyquist limits will be adjusted to the range of 50 –70cm/sec.

I. Protocol for Transthoracic Echocardiogram (TTE)

1. **PLAX**
   a. 2D image for measurements of LV, LA, LVOT and Ao dimension
   b. Color Doppler at MV with Zoom (for MR vena contracta assessment)
   c. Color Doppler at AV

2. **RV inflow**
   a. 2D
   b. Color Doppler at TV
   c. CW of TR jet (if jet imaged parallel to beam)

3. **PSAX**
   a. 2D images at the AV level, MV level, papillary muscle level and apex of LV
   b. Color Doppler at PV and TV
   c. PW at PV at AV level

4. **Apical 4 chamber**
   a. Full sector (including the entire LA, LV, RA, RV)
   b. Zoom of the LV
   c. Zoom of the LA
   d. Color Doppler of MV
   e. Zoom of the MV with color, shift baseline between 30-40 cm/sec to maximum
      i. PISA radius, record 3-5 cardiac cycles as well as still frame of maximum PISA
      ii. radius. **(Apply to patients with mitral valve repair only).**
   f. CW of MR jet with the maximal peak velocity **(Apply to patients with mitral valve repair only).**
   g. CW at the tip of MV

h. PW at the tip of MV
i. PW at 1 cm within one pulmonary vein
j. PW-tissue Doppler imaging of mitral annulus (septal and lateral)
k. Color Doppler of TV
l. PW at the tip of TV
m. CW of TR jet

5. Apical 5 chamber

n. Color Doppler at AV
o. CW at AV
p. PW at LVOT

6. Apical 2 chamber

q. Full sector (including the entire LA and LV)
r. Zoom the LV
s. Zoom the LA
t. Color Doppler at MV

7. Apical long-axis

u. Full sector (including the entire LA and LV)
v. Color Doppler at MV and AV

NOTE: Occasionally eccentric CW jets may require interrogation of additional views (e.g., PLAX, Apical 2C view) to obtain the true maximal jet velocity.

ABBREVIATIONS

AV	Aortic valve
LA	Left atrium
LV	Left ventricular
LVOT	Left ventricular outflow tract
MR	Mitral regurgitation
MV	Mitral valve
PV	Pulmonary valve
TDI	Tissue Doppler imaging
TR	Tricuspid regurgitation
TV	Tricuspid valve

Appendix II: CTSN Trial Patient Contact Log

Subject ID	Person Initiating Contact	Date	Time	Method of Contact (e.g. in-person visit, phone call, email, certified letter w/ return receipt, etc.)	Issue Discussed	Comments

Rev 2.0
Dated 6/8/10