Network for CT Surgical Investigations

Protocol

EVALUATION OF OUTCOMES FOLLOWING MITRAL VALVE REPAIR/REPLACEMENT IN SEVERE CHRONIC ISCHEMIC MITRAL REGURGITATION

Sponsored By NHLBI, NINDS & CIHR

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	Data Collection	Collection Schedule	NHLBI biorepository team	
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ACRONYMS & ABBREVIATIONS

ACE	Angiotensin converting enzyme antagonist
AE	Adverse event
AICD	Automatic implantable cardioverter defibrillator
ARB	Angiotensin receptor blocker
ASD	Atrial septal defect
CABG	Coronary artery bypass grafting
CPB	Cardiopulmonary bypass
CHF	Congestive heart failure
CIHR	Canadian Institutes of Health Research
CSA	Cross sectional area
CCSC	Canadian Cardiovascular Society Classification
CW	Continuous wave
DASI	Duke Activity Status Index
DCC	Data Coordinating Center
EAC	Event Adjudication Committee
EDC	Electronic data capture system
EDV	End diastolic volume
ERO	Effective Regurgitant Orifice area
EQ-5D	EuroQoL (5D)
ESV	End systolic volume
ESVI	End systolic volume index
GCP	Good Clinical Practice
HF	Heart failure
HIPAA	Health Insurance Portability and Accountability Act
IMR	Ischemic mitral regurgitation
InCHOIR	International Center for Health Outcomes & Innovation Research
LA	Left atrium
LBBB	Left bundle branch block
LOS	Length of stay
LV	Left ventricle
LVAD	Left ventricular assist device
LVEF	Left ventricular ejection fraction
LVESVI	Left ventricular end systolic volume index
MACE	Major adverse cardiac event
MI	Myocardial infarction
MLHF	Minnesota Living with Heart Failure questionnaire
MR	Mitral regurgitation
MV	Mitral valve
NIH	National Institutes of Health
NHLBI	National Heart Lung & Blood Institute
NINDS	National Institute of Neurological Disorders and Stroke
NYHA	New York Heart Association
PA	Pulmonary artery
PCWP	Pulmonary capillary wedge pressure

PFO	Patent foramen ovale
PISA	Proximal isovelocity surface area
POD	Post-op day
PR	Pulmonic regurgitation
PV	Pulmonic valve
PW	Pulsed wave
QOL	Quality of Life
RV	Right Ventricle
RVol	Regurgitant volume
SAX	Short axis
SF12	Short Form 12
TAPSE	Tricuspid annular plane systolic excursion
TEE	Trans-esophageal echocardiography
TR	Tricuspid regurgitation
TTE	Transthoracic echo
TV	Tricuspid valve
TVI	Tissue velocity imaging
VTI	Velocity time integral

ABSTRACT

Objectives	To evaluate the safety and efficacy of mitral valve repair and mitral valve replacement for patients with severe ischemic mitral regurgitation (MR)
Study Design	Randomized multi-center trial
Target Population	Patients diagnosed with severe ischemic MR in need of surgical intervention
Rx arms	(a) mitral valve repair with annuloplasty and a sub-valvular procedure for severe tethering (b) mitral valve replacement and complete preservation of the sub-valvular apparatus
Sample Size	250 subjects; 90% power to detect an absolute difference of 15 ml/m^2 in LVESVI (based on a 35% (replacement) v. 20% (repair) reduction in LVESVI)
Duration	24 months following randomization
1° Endpoints	Degree of left ventricular remodeling, as assessed by Left Ventricular End Systolic Volume Index (LVESVI) at 12 months
2° Endpoints	o All-cause mortality (*Principal secondary endpoint*) o Operative time, cardiopulmonary bypass (CPB) and cross clamp time o Blood loss and transfusion o MACE (death, stroke, worsening heart failure (+1 NYHA Class), CHF hospitalization, mitral valve re-intervention) o NYHA Classification and CCSC Angina class o Peak VO$_2$ (assessed by cardio-pulmonary stress test) o LOS for the index hospitalization and discharge location o Re-admission rates and days alive out of hospital o Echo parameters o Adequacy of revascularization o Change in quality of life (QOL) o Neurocognitive outcomes o Cost and cost effectiveness o Incidence of serious adverse events o Re-operation for MR and freedom from re-operation in general
Selected Inclusion Criteria	o Chronic severe ischemic mitral regurgitation by echocardiography using an integrative method o Eligible for surgical repair and replacement of mitral valve o Coronary artery disease with or without the need for coronary revascularization
Selected Exclusion Criteria	o Any evidence of structural mitral valve disease or ruptured papillary muscle o Prior mitral valve repair o Severe pulmonary hypertension o Contraindications to CPB o Inability to derive ERO and ESVI by transthoracic echocardiography o Planned concomitant intra-operative procedures (except closure of PFO, ASD or Maze procedure) o Clinical signs of cardiogenic shock at the time of randomization o Treatment with chronic intravenous inotropic therapy at the time of randomization o ST segment elevation MI requiring intervention within 7 days prior to randomization o Congenital heart disease (except PFO or ASD) o Evidence of cirrhosis or hepatic synthetic failure

DATA COLLECTION SCHEDULE

Assessment	Screening/ Baseline	Intra-Op	POD #1	POD #30 (± 3 days)	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	X
Physical Exam	X			X	X	X	X	
Laboratory Assessment	X							
Eligibility Criteria	X							
Screening Outcome	X							
Cardiac								
NYHA Heart Failure Class	X			X	X	X	X	
CCSC Angina Class	X			X	X	X	X	
Peak VO$_2$ (Cardiopulmonary stress test)					X	X		
TTE (Trans-thoracic Echocardiogram)	X			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	X	
SF-12	X			X	X	X	X	
EuroQol	X			X	X	X	X	
DASI	X			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.

OBJECTIVES

The overall objective of this study is to evaluate the safety and efficacy of mitral valve repair and mitral valve replacement for patients with severe ischemic mitral regurgitation (MR). Specifically, this study compares mitral valve repair with annuloplasty and a sub-valvular procedure for severe tethering to mitral valve replacement and complete preservation of the sub-valvular apparatus.

° The primary aim of this trial is to evaluate the impact of these two surgical approaches on left ventricular remodeling.

° Secondary aims of this trial include assessment of the impact of these two surgical interventions on cardiac performance, mortality, adverse events, quality of life, functional status, severity of MR, and health resource use.

BACKGROUND AND SIGNIFICANCE

Ischemic MR, especially severe, has long been associated with poor health outcomes in cardiac patients. Ischemic (also known as functional) MR is a complication of myocardial infarction (MI) and has been estimated to affect 1.6-2.8 million people in the United States in 2004 [1]. As the population ages and the survival rate for MI increases, so will the number of people with ischemic MR[2]. The presence of ischemic MR portends an adverse prognosis. As demonstrated by the Survival and Ventricular Enlargement (SAVE) trial, the presence of even mild ischemic MR post MI significantly increases mortality at 3.5 years (29% versus 12%, $p < 0.001$)[3]. Severe ischemic MR has been associated with a 1-year mortality of 40% [4]. Others have demonstrated a 5-year survival of $29 \pm 9\%$ in the presence of severe MR [5]. Leading professional societies recommend (Class I) in their recent practice guidelines that the severe MR patients targeted in this trial be treated surgically either by replacement or repair.[6, 7]

Post-infarction changes in ventricular structure and function often create ischemic MR secondary to two distinct processes. Locally, inferior and posterior remodeling causes displacement of the papillary muscles away from the mitral valve annulus, promoting leaflet tethering and restriction of motion. This inhibits the leaflets' ability to close effectively at the level of the annulus. Globally, annular enlargement secondary to left ventricular (LV) dilatation causes central malcoaptation at the level of the annulus. This is compounded by LV dysfunction, which decreases the force available to close the leaflets in opposition to the increased tethering forces noted above [1, 8, 9].

Revascularization does not significantly reduce moderate to severe MR; one study reported that moderate to severe MR persisted in 77% of patients [10]. Mitral valve replacement was the preferred approach in early studies. However, suboptimal results were demonstrated, in part secondary to the lack of preservation of the subvalvular apparatus. Large retrospective studies performed by Grossi and Gillinov demonstrated that repair and replacement eliminated MR immediately post-operatively; however, repair was associated with a lower perioperative mortality [11, 12].

The surgical approach to mitral valve repair has evolved over time. Therapy directed to reducing the annular size alone has a demonstrated 6 month recurrence of severe MR of 28-30% [13, 14]. The long-term recurrence rates are in the 72% range [13]. Significant mitral annulus undersizing has been attempted; however, these long-term results are still not optimal [15]. There are several new rings available that attempt to reshape the annulus specific to ischemic MR. However, the major concern remains that reduction annuloplasty alone does not address the subvalvular changes or the tethering mechanism.

Alternative surgical options have been explored including extraventricular Dacron patches and balloons [16]; external infarct plication sutures [17]; reduction of leaflet tethering by cutting a limited number of secondary chordae [18, 19]; edge-to-edge suture creating a double orifice valve [20]; LV restoration procedure with improvement of papillary muscle orientation [21]; and suture relocation of the posterior papillary [22].

In sum, several studies have compared replacement to repair in patients with severe MR, but considerable controversy remains regarding the optimal surgical approach for these patients. Available evidence is limited to observational studies and case series, where correction for significant and substantial imbalances in baseline patient characteristics is problematic. These studies are also limited by short-term outcome measures, inclusion of patients with different types of mitral valve disease, and lack of information on important secondary outcomes, such as quality of life. Importantly, the recently published ACC/AHA guidelines for CABG and Valve Disease all avoid addressing the decision algorithm for IMR [21]. Although there is general agreement about the need to surgically treat patients with symptomatic severe MR, the long-term benefits of repair versus replacement are unknown. This has led to significant variations in surgical practice. Given the prevalence of this high-mortality condition, a randomized trial that would address the relative benefits of repair versus replacement could have a significant impact on patient management and health outcomes.

ENDPOINTS
Primary
The primary endpoint for the trial is the degree of left ventricular remodeling, as assessed by Left Ventricular End Systolic Volume Index (LVESVI) at 12 months.

Secondary
This trial assesses several secondary endpoints. The principal secondary endpoint for the trial is *all-cause mortality*. This endpoint provides complementary clinical information to the primary physiological endpoint for assessing the overall benefits of treatment.

Additional secondary endpoints for the trial are as follows:

Functional Status, Neurocognition and Hospitalizations
- o MACE (death, stroke, worsening heart failure (+1 NYHA Class), CHF hospitalization, mitral valve re-intervention)
- o NYHA Classification
- o Peak VO_2 (assessed by a cardio-pulmonary stress test)

- o Angina class
- o Neurocognitive outcomes
- o LOS for the index hospitalization and discharge location
- o Re-admission rates (within 30 days and long term for all, cardiovascular, and heart failure re-admissions) and days alive out of hospital (as a percent of survival)

Physiologic Measures
- o Echo
    - o Quantification of MR (Effective Regurgitant Orifice Area [ERO])
    - o Quantification of mitral valve area
    - o MV and subvalvular assessments
    - o LV size, function and geometry (including, but not limited to LVEF, LVESVI, LV sphericity)
    - o RV size and function
    - o LA dimension
    - o MV tethering
    - o Intracardiac pressures
    - o Regional wall motion (LV function and viability assessment)
- o Adequacy of revascularization

Quality of Life and Economic Measures
- o Change in quality of life (QOL)
    - o Minnesota Living with Heart Failure (MLHF) score
    - o SF-12
    - o EuroQoL
    - o DASI

- o Cost and cost effectiveness

Safety
- o Incidence of serious adverse events
- o Reoperation for MR and freedom from re-operation in general

Peri-operative Measures
- o Operative time, cardiopulmonary bypass (CPB) and cross clamp time
- o Blood loss and transfusion

Figure 1: Trial Design Schematic

Patients with Severe Ischemic MR (Per site echocardiographer)

Determination of Eligibility and Collection of Baseline Data

Random Assignment of Treatment

Mitral Ring Annuloplasty ± CABG (subvalvular procedure for severe tethering)

Mitral Valve Replacement ± CABG (complete subvalvular preservation)

Outcomes Measured at 1, 6, 12, and 24 months

Primary Outcome
LVESVI at 12 mos

Secondary Outcomes
Survival, Funct Status, QoL, Operative Measures, LOS, Readmission, MR, Remodeling, LVEF, Revasc, AE's Cost

Data Analysis

STUDY DESIGN
This is a parallel design, prospective, multi-center, randomized controlled clinical trial. The trial will be conducted in highly experienced clinical centers participating in the NIH/CIHR-supported CT Surgery Network. The estimated enrollment period is 24 months (n=250 see below) and all patients will be followed for 24 months post-randomization. Endpoints will be measured at 30 days, 6, 12, and 24 months.

RANDOMIZATION
Patients will be randomly assigned (1:1) to mitral valve repair or mitral valve replacement. The randomization procedure will be performed intra-operatively, following sternotomy and before cannulation of aorta, in order to minimize the likelihood of enrolling patients in the study with unexpected surgical contra-indications to mitral valve repair. Randomization will be controlled centrally and performed through a Web-based data collection system that automates the delivery of the randomization codes. The treatment assignment will be sent to the site coordinator electronically, in a secure fashion, and electronic verification of the treatment assignment will be required before proceeding with the treatment intervention. From that point on, primary efficacy will be analyzed by intention-to-treat; that is, the patients will be grouped by their assignment at randomization whether or not they actually received the treatment to which they were assigned.

MASKING
The nature of the treatment precludes blinding of patients and their clinicians. Investigators will, however, be blinded to all data from other clinical sites, except serious unexpected AEs for IRB reporting purposes. All echocardiograms will be analyzed by core laboratory personnel. Adverse events will be adjudicated by an Event Adjudication Committee and trial oversight will be provided by an independent DSMB.

STUDY POPULATION

Characterization of Patient Population
The patient population for this trial consists of patients with severe ischemic mitral regurgitation with and without the need for concomitant coronary artery bypass surgery. All patients who meet the eligibility criteria may be included in the study regardless of gender, race or ethnicity.

Inclusion Criteria
1. Chronic severe ischemic mitral regurgitation (often with tethering as a major mechanism) in the judgment of the clinical site echocardiographer, assessed by transthoracic echocardiogram. Assessment of mitral regurgitation will be performed using an integrative method (Zoghbi W. et al. J. American Society of Echocardiography. 2003:16:777-802. see appendix). Quantitative guidelines as proposed would be: ERO ≥ 0.4 cmsq. If ERO < 0.4, then the degree of mitral regurgitation will be guided by other color Doppler quantitative methods (jet area/left

atrial area ratio, vena contracta, supportive criteria in an integrated fashion (See Appendix I).

2. Eligible for surgical repair and replacement of mitral valve

3. Age ≥ 18 years

4. Able to sign Informed Consent and Release of Medical Information forms

5. Coronary artery disease with or without the need for coronary revascularization

Exclusion Criteria

1. Any evidence of structural (chordal or leaflet) mitral valve disease or ruptured papillary muscle

2. Prior mitral valve repair

3. Severe irreversible pulmonary hypertension in the judgment of the investigator

4. Contraindications to CPB

5. Inability to derive ERO and ESVI by transthoracic echocardiography

6. Planned concomitant intra-operative procedures (with the exception of tricuspid valve repair, closure of patent foramen ovale [PFO] or atrial septal defect [ASD], or Maze procedure)

7. Clinical signs of cardiogenic shock at the time of randomization

8. Treatment with chronic intravenous inotropic therapy at the time of randomization

9. ST segment elevation MI requiring intervention within 7 days prior to randomization

10. Congenital heart disease (except PFO or ASD)

11. Evidence of cirrhosis or hepatic synthetic failure

12. Excessive surgical risk (in the judgment of the surgical investigator)

13. Recent history of psychiatric disease (including drug or alcohol abuse) that is likely to impair compliance with the study protocol, in the judgment of the investigator

14. Therapy with an investigational intervention at the time of screening, or plan to enroll patient in additional investigational intervention study during participation in this trial

15. Any concurrent disease with life expectancy to < 2 years

16. Pregnancy at the time of randomization

Recruitment Strategies
Based on a survey of the clinical sites, it is estimated that approximately 120-130 patients could be enrolled annually through active screening and recruitment by the participating Network centers. These strategies may include: mailings to referring physicians of the study hospitals, symposia and health care events targeted towards this population; as well as telephone calls to neighboring health care facilities. The DCC will regularly assess actual enrollment in relation to pre-specified goals, and additional interventions to increase enrollment will be implemented as needed. The Screening Log will identify numbers of patients screened and reasons for non-enrollment in the trial.

Inclusion of Women and Minorities
The inclusion of women and minorities in clinical trials is critical for scientific, ethical, social reasons, and for the generalizability of trial results. The Network is strongly committed to ensuring a balanced recruitment of patients regardless of sex or ethnicity. The CT Surgery Network will recruit at least 30% women and 25% minorities. The following measures will be employed to ensure adequate representation of these groups: (1) documentation of the number of women and minorities screened and enrolled via screening/exclusion logs; (2) monitoring of such logs from each clinical center on a monthly basis; and (3) if necessary, the development and implementation of outreach programs designed to recruit adequate numbers of women or minorities.

TREATMENT INTERVENTIONS

Mitral Valve Replacement Group
Mitral valve replacement will include complete preservation of the subvalvar apparatus. The technique of preservation, choice of prosthetic valve, and technique of suture placement will be dependent on the surgeon's preference. The prosthetic valve will be tested for paravalvular leaks using the left ventricular saline infusion test.

Mitral Valve Repair with Annuloplasty Group
The annuloplasty ring will be chosen by the surgeon. The ring is sized to the anterior leaflet and intertrigonal distance. A semi-rigid or rigid annuloplasty ring will be used and. If tethering is present, a subvalvar procedure may be performed.

DEFINITIONS AND MEASUREMENT OF ENDPOINTS

Primary Endpoint
The primary endpoint for the trial is the degree of left ventricular remodeling, as assessed by change in Left Ventricular End Systolic Volume Index (LVESVI) between

randomization and 12 months post-surgical intervention, measured with transthoracic echocardiography (see Appendix I).

Secondary Endpoints
The principal secondary endpoint is:
Survival
       All-cause mortality will be assessed

Additional secondary endpoints for the trial are defined as follows:

Perioperative Measures
       Operative time, cardiopulmonary bypass time, cross clamp time, blood loss, and transfusions will be measured.

Functional Status

MACE (Major Adverse Cardiac Events)
MACE is defined as a non-weighted composite score comprised of the following components:
- Death
- Stroke
- Worsening heart failure (+1 NYHA Class)
- CHF hospitalization
- Mitral valve re-intervention

New York Heart Association (NYHA) Classification
Functional status will be assessed by the NYHA Classification scale. Complete NYHA classification guidelines can be found in Appendix II.

Peak VO$_2$
In addition, in those patients without a clinical contraindication for exercise testing (e.g. unstable angina or left main disease), functional status will be measured by maximal oxygen uptake (VO$_2$ Peak) assessed by cardiopulmonary stress test at the pre-determined time intervals. Patients will be uniformly encouraged to exercise to volitional exhaustion using a standardized protocol for verbal encouragement. For those patients who are unable to achieve an RER $\geq$ 1.0, the addition of Borg's CR10 RPE (rate of perceived exertion) to complement the level of effort attained would be beneficial. Therefore, RPE will be assessed and collected every 2 minutes for all patients using the 0-10 RPE scale. Scripted instructions for the patient on the use of the RPE scale will be utilized for all study related exercise tests, and standardized laminated cards depicting the scale and demonstrating its use will be displayed to each patient during the test. Cardiopulmonary stress tests will be performed according to a standardized protocol and will be analyzed by the CPX Core Lab. Appendix III includes the standardized protocol for cardiopulmonary stress testing.

A test will be considered a maximal test if the patient achieves a peak RER $\geq$ 1.0. If, however, the achieved RER is < 1.0 but > than .99, then a test will be

considered maximal if the RPE is > 8. This dual criterion of utilizing both peak RER and peak RPE will ensure that a maximal test is a reflection of the physiologic response of the patient as well as the patient's best effort.

Angina Class
Angina class will be assessed by the Canadian Cardiovascular Society Classification (CCSC). The CCSC guidelines are detailed in Appendix IV.

Re-operation
All re-operations and re-operation for mitral regurgitation in particular will be recorded and freedom from re-operation will be analyzed using a time-to-event analysis.

Neurocognition
Neurocognition will be compared between treatment groups. Cognitive performance will be assessed 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 (Appendix VII). Neurocognitive testing will be administered by clinical site personnel trained by experienced neuropsychologists identified at each site by the Core Lab. All neurocognitive test scoring will be performed centrally by the CTSN Neurocognition Committee.

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.

Hospitalization
Index Hospitalization
Overall length of stay for the index hospitalization will be measured (and broken down by days spent in the ICU versus days spent on telemetry and regular floors). In addition, we will capture discharge location.

Readmission
Readmission rates will be calculated for the first 30 days following intervention and for the duration of follow-up. Hospitalizations will be classified for all causes, including for cardiovascular and heart failure readmissions. Classification of a readmission as heart failure related requires *at least 2* out of the following signs and symptoms of acute decompensated heart failure:

- o Dyspnea felt related to HF
- o Treatment with intravenous diuretic, vasodilator or inotropic therapy
- o X ray evidence of pulmonary edema or pulmonary vascular congestion
- o Rales on physical exam
- o PCWP or LVEDP > 18 mmHg

All readmissions will be classified by the investigator and adjudicated by the Event Adjudication Committee (EAC).

Days Alive and Out of Hospital
The total number of days alive and out-of-hospital (as well as the days out-of-hospital as a percentage of total days alive post randomization) will be compared between the treatment groups.

Physiologic Measures
Echocardiographic Measurements (Appendix I)

Presence and severity of mitral regurgitation will be assessed by measuring the effective regurgitant orifice area (EROA) by both the proximal isovelocity surface area (PISA) and the quantitative flow methods.

Mitral valve apparatus and quantification of valve area will be assessed by evaluating annular shape and motion, tethering angle and tenting area, papillary muscle position and separation, and calculation of mean trans-mitral stenotic gradient by mitral inflow continuous wave Doppler.

LV size, geometry and function will be assessed by the following measures: LV dimensions, ejection fraction (biplane Simpson's rule), LV end-systolic volume index using the biplane volumetric method, LV mass, LV sphericity, radial strain, and twist.

RV size and function will be assessed by the following measures: tricuspid annular plane systolic excursion (TAPSE), peak systolic velocity, diastolic E and A velocity (by tissue doppler), and fractional area change.

Intracardiac pressures and hemodynamics, including pulmonary artery pressures and pulmonary capillary wedge pressure will be assessed by Doppler flow studies.

Regional Wall Motion (LV function and viability assessment) will be assessed at baseline and again at one year following surgical intervention to evaluate the extent of baseline viability and the effect of revascularization when applicable.

Left atrial dimension, mitral valve tethering length and area, *tethering angle*, *papillary muscle* position and separation will be assessed echocardiographically.

Adequacy of Revascularization
Coronary territories will be identified as amendable or not amenable to bypass pre-operatively, and the bypass status of each territory will be reported post-operatively. The territories will be defined as follows: LAD proximal, LAD distal, proximal diagonal, distal diagonal, proximal circumflex, distal circumflex, distal dominant circumflex, right posterolateral, right posterior descending. See Appendix V.

Quality of Life

The change in quality of life (QOL) from baseline will be measured, using the disease-specific Minnesota Living with Heart Failure (MLHF) score, the disease-specific Duke Activity Status Index (DASI), the Short Form-12 general health status index, and EuroQol 5-D measures of health state preference from the individual and societal perspective. The Minnesota Living with Heart Failure Questionnaire is a disease specific instrument that measures the perception of the physical, psychological and social effects of heart failure (HF) and HF treatment on the patient. The DASI questionnaire measures a broad level of cardiovascular stresses across the four major domains of adult activity that correlate with oxygen uptake: 1) personal care, 2) ambulation, 3) household tasks, and 4) sexual function and recreation. The SF-12 is a general health status measure. This instrument examines 8 quality of life dimensions (physical activity, social activity, role/physical, body pain, general mental health, role/emotional, vitality and general health perception). The EuroQoL 5-D is a standardized instrument for measuring health-related quality of life. This questionnaire provides a simple descriptive profile that consists of 5 dimensions. The 5 domains are anxiety/depression, pain/discomfort, usual activities, self care, and mobility. The instrument also has a self-assessment of health status. A copy of these instruments can be found in Appendix VI.

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). Copies of these instruments can be found in Appendix VI.

Economic Measures

Inpatient costs will be measured through UB-92 forms and hospital billing sheets. In addition to index hospitalization costs, costs associated with subsequent readmissions will also be included in the study. Patients will also be asked at each follow-up if they have been hospitalized at another hospital and if yes for how long. Costs related to hospitalization at non-Network institutions will be imputed based on the average per day cost of hospitalization of study patients at Network hospitals. Outpatient costs incurred at non-Network hospitals will not be captured.

Safety

Re-operation

All re-operations and re-operation for mitral regurgitation in particular will be recorded and freedom from re-operation will be analyzed.

Adverse Events

The incidence of serious adverse effects over the course of the trial will be compared between the two treatment groups. All serious and all protocol-defined adverse events (AE) will be adjudicated by an Event Adjudication Committee (EAC). The endpoints for safety will be reported as the frequencies of occurrence of each adverse event, the rate of adverse events per patient/year and time to each

event. In addition, the number of patients with each serious adverse event type will be recorded. Safety data will be collected throughout this study and the incidence of each event type will be computed along with the 95% confidence intervals.

An adverse event 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. Furthermore, for a pre-existing condition that is not protocol defined to be reported as an adverse event, a change in severity must meet the criteria for being serious (see definition below).

Serious Adverse Event
Serious adverse events 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.

Unanticipated Serious Adverse Event
An unanticipated (unexpected) serious adverse event is any serious adverse event that is not protocol-defined. Expedited reporting is required for serious adverse events that are unexpected.

Event Recording
The following adverse events will be captured throughout the period of trial participation:
   o   Protocol-defined (as described below)
   o   Serious unanticipated events (serious *"Other"* adverse events)

Causality
The investigator will assess the relationship of an adverse event to the surgical intervention. If possible, the investigator should distinguish the relationship between the event and (a) the surgical procedure and (b) the investigational intervention (MV repair or replacement). Causality will be defined as follows:

> *Probable*
> Adverse events that, after careful medical evaluation, are considered with a high degree of certainty to be related to the surgical intervention (MV repair or replacement). The following characteristics will apply:

o A reasonable temporal relationship exists between the event and the surgical intervention, and
o The event is a known reaction to the surgical intervention and cannot be explained by an alternative etiology commonly occurring in the population/individual.

Possible
Adverse events that, after careful medical evaluation, do not meet the criteria for a probable relationship to the surgical intervention, but for which a connection cannot be ruled out with certainty. The following characteristics will apply:

o The event occurs after surgical intervention, and
o The event is not a known reaction to surgical intervention, but cannot be explained by a commonly occurring alternative etiology.

Unlikely
Adverse events that, after careful medical evaluation, do not meet the criteria for a possible or probable relationship to surgical intervention and for which a connection is unlikely. The following characteristics will apply:

o The event does not follow a reasonable temporal sequence from administration of the surgical intervention, or
o May have been produced by environmental factors, and there is no apparent pattern of response to the surgical intervention.

Reporting of Serious Adverse Events
All investigators conducting clinical studies supported by the NHLBI must report both expected (protocol-defined) and unexpected serious adverse events. All serious protocol-defined adverse events must be reported directly to the clinical center's IRB and the Data Coordinating Center (DCC) within 10 working days of knowledge of the event, or as dictated by the specific IRB policy, whichever is sooner. All deaths and unexpected serious adverse events 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 DCC will provide preliminary notification to the NHLBI program director of all deaths and any unexpected serious adverse events 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 adverse events will be reported to the DSMB at least semi-annually, at the discretion of the DCC medical monitor.

In addition, the investigators are expected to comply with their institutional policies with regard to reporting to the FDA any serious, unexpected drug events for any (non-research related) drug used in patients participating in this protocol. This reporting should be submitted on a MedWatch Online Voluntary Reporting form (3500) at

https://www.accessdata.fda.gov/scripts/medwatch/. A copy of this form should be faxed to the DCC within 10 working days of reporting to the FDA.

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 (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 <u>serious</u> adverse event that is <u>unexpected</u> and at least <u>possibly related</u> 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 participant(s). 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.

Specific Adverse Event Definitions

Bleeding
       A bleeding event is defined by any one of the following:

         o   Transfusion of > 5 units RBC within the first 24 hours following surgery
         o   Death due to hemorrhage
         o   Re-operation for hemorrhage or tamponade

       NOTE: Hemorrhagic stroke is considered a neurological event and not as a separate bleeding event.

Cardiac Arrhythmias
       Any documented arrhythmia that *results in clinical compromise* (e.g., hemodynamic compromise, oliguria, pre-syncope or syncope) that requires

hospitalization or requires a physician visit or occurs during a hospital stay. Cardiac arrhythmias are classified as one of two types:

1. Sustained ventricular arrhythmia requiring defibrillation or cardioversion

2. Sustained supraventricular arrhythmia requiring drug treatment or cardioversion

Pericardial Fluid Collection

Accumulation of fluid or clot in the pericardial space that requires surgical intervention or percutaneous catheter drainage. This event will be subdivided into those with clinical signs of tamponade (e.g. increased central venous pressure and decreased cardiac output) and those without signs of tamponade.

Pleural Effusion

Accumulation of fluid or clot in the pleural space documented by chest radiogram or chest CT that requires evacuation with surgical intervention or chest tube placement.

Pneumothorax

Presence of gas in the pleural space, documented by chest radiogram or chest CT, which requires evacuation or prolongs the duration of chest tube drainage.

Hepatic Dysfunction

An increase in any two of the following hepatic laboratory values (total bilirubin, aspartate aminotransferase/AST and alanine aminotranferease/ALT) to a level greater than three times the upper limit of normal for the hospital, (or if hepatic dysfunction is the primary cause of death).

Major Infection

A new clinical infection accompanied by pain, fever, drainage and/or leukocytosis that is treated by anti-microbial agents (non-prophylactic). A positive culture from the infected site or organ should be present unless strong clinical evidence indicates the need for treatment despite negative cultures. The general categories of infection are listed below:

Localized Infection

Infection localized to any organ system or region (e.g. mediastinitis) without evidence of systemic involvement (see sepsis definition), ascertained by standard clinical methods and either associated with evidence of bacterial, viral, fungal or protozoal infection, and/or requiring empirical treatment.

Endocarditis

Signs, symptoms and laboratory findings consistent with endocarditis, including but not limited to fever $\geq 38.0^{o}$ C, positive blood cultures, new regurgitant murmurs or heart failure, evidence of embolic events (eg, focal neurologic impairment, glomerulonephritis, renal and splenic infarcts, and septic pulmonary

infarcts), and peripheral cutaneous or mucocutaneous lesions (eg, petechiae, conjunctival or splinter hemorrhages, Janeway lesions, Osler's nodes, and Roth spots). Echocardiographic evidence of a new intra-cardiac vegetation with or without other signs and symptoms should be considered adequate evidence to support the diagnosis of endocarditis. TEE should be the modality of choice for diagnosis of prosthetic valve endocarditis.

Sepsis
Evidence of systemic involvement by infection, manifested by positive blood cultures and/or hypotension.

Myocardial Infarction

Myocardial infarction (MI) should be classified when there is evidence of myocardial necrosis in a clinical setting consistent with myocardial ischemia. Under these conditions, any one of the following criteria meets the diagnosis for myocardial infarction[1]:

o **Myocardial Infarction**
Detection of rise and/or fall of cardiac biomarkers (preferably troponin) with at least one value above the 99th percentile of the upper reference limit (URL) together with evidence of myocardial ischemia with at least one of the following:

> o Symptoms of ischemia;
>
> o ECG changes indicative of new ischemia (new ST-T changes or new left bundle branch block [LBBB]);
>
> o Development of pathological Q waves in the ECG;
>
> o Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality.

o **Peri-CABG Myocardial Infarction**
For CABG in patients with normal baseline troponin values, elevations of cardiac biomarkers above the 99th percentile URL are indicative of peri-procedural myocardial necrosis. By convention, increases in biomarkers > 5 x 99th percentile URL plus either new pathological Q waves or new LBBB, or angiographically documented new graft of native coronary artery occlusion, or imaging evidence of new loss of viable myocardium have been designated as defining CABG-related MI.

o **Peri-Percutaneous Intervention (PCI) Myocardial Infarction**
For PCI in patients with normal baseline troponin values, elevations of cardiac biomarkers above the 99th percentile URL are indiciative of peri-procedural myocardial necrosis. By convention, increases in biomarkers > 3 x 99th percentile

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[1] Joint ESC/ACCF/AHA/WHF Task for the Redefinition of Myocardial Infarction, *Circulation*.2007;116:2634-2653.

URL have been designated as defining PCI-related MI. A subtype related to a documented stent thrombosis is recognized.

o   Sudden unexpected cardiac death, involving cardiac arrest, often with symptoms suggestive of myocardial ischemia, and accompanied by presumed new ST elevation or new LBBB, and/or evidence of fresh thrombus by coronary angiography and/or autopsy, with death occurring before blood samples obtained, or at a time before the expected appearance of cardiac biomarkers in blood will be classified as a mortality due to MI.

Neurologic Dysfunction

Any new, temporary or permanent, focal or global neurological deficit ascertained by a standard neurological examination (administered by a neurologist or other qualified physician and documented with appropriate diagnostic tests and consultation note). The examining physician will distinguish between a transient ischemic attack (TIA), which is fully reversible within 24 hours (and without evidence of infarction), and a stroke, which lasts longer than 24 hours (or less than 24 hours if there is evidence of infarction). The Modified Rankin Scale and the NIH Stroke Scale must be administered at time of event (within 72 hours following the event) and 90 days following the event to document the presence and severity of neurological deficits.

Each neurological event must be subcategorized as:

o   Transient Ischemic Attack defined as an acute event that resolves completely within 24 hours with no imaging evidence of infarction.
o   Ischemic or Hemorrhagic Stroke (Cerebrovascular Accident), defined as an event that persists beyond 24 hours or less than 24 hours associated with infarction on an imaging study. Hemorrhagic conversion of an ischemic stroke should be classified as ischemic.
o   Toxic Metabolic Encephalopathy defined as a disorder of the brain function that arises from abnormal systemic metabolism or exogenous substances, altering awareness and/or consciousness, in which there is a non-focal neurological examination and a negative brain image.
o   Other

Renal Events

Two categories of renal events will be identified:

Renal Dysfunction

Abnormal kidney function defined by > 100% rise in serum creatinine (Cr) from baseline, and Cr > 2.0

Renal Failure

New requirement for hemodialysis related to renal dysfunction. This definition excludes aquapheresis for volume removal alone.

Respiratory Failure

       Impairment of respiratory function requiring re-intubation, tracheostomy or the inability to discontinue ventilatory support within 48 hours post-surgical intervention. This <u>excludes</u> intubation for re-operation or temporary intubation for diagnostic or therapeutic procedures.

Heart Failure

Signs of inadequate organ perfusion or congestion, or a syndrome of compromised exertional tolerance manifested by dyspnea or fatigue that requires

    a) intravenous therapy (diuretics or inotropic support) *and* prolongs hospital stay in the judgment of the investigator, *or*

    b) introduction of intravenous therapy (diuretics or inotropic support) at any point following discharge from the index hospitalization, *or*

    c) readmission for heart failure

Arterial Non-CNS Thromboembolism

       An acute systemic arterial perfusion deficit in any non-cerebrovascular organ system due to thromboembolism confirmed by one or more of the following:

         o Standard clinical and laboratory testing
         o Operative findings
         o Autopsy findings

       This definition <u>excludes</u> neurological events.

Venous Thromboembolic Event

       Evidence of venous thromboembolic event (e.g. deep vein thrombosis, pulmonary embolism) by standard clinical and laboratory testing.

Wound Dehiscence

       Disruption of the apposed surfaces of a surgical incision, excluding infectious etiology, and requiring surgical repair.

Other

       An event that causes clinically relevant changes in the patient's health, or any event that is life-threatening, results in a fatality, results in permanent disability, requires hospitalization, or prolongs an existing hospital stay.

CLINICAL CENTERS

The study will be conducted in up to 24 clinical centers participating in the NIH/CIHR supported Cardiothoracic Surgery Network. Each clinical center will be required to obtain IRB approval for the protocol and consent (and their revisions) in a timely fashion, to recruit patients, to collect data and enter it accurately in the electronic data capture

(EDC) system, to faithfully follow the protocol and adhere to the standards of Good Clinical Practice (GCP). In addition, centers will be required to provide the Data Coordinating Center (DCC) with the information necessary for interim, annual, and final reports, to provide source documents, data and regulatory documents for study monitors, provide prompt responses to DCC inquiries, and to participate in analyses and reporting of study results.

Investigator Profile
All surgeons, cardiologists, coordinators and other investigators in the study must complete the Investigator Profile form, including hospital affiliation, address, telephone, fax, beeper and email information. The surgeon, cardiologist and coordinator must email or fax their CV, Conflict of Interest Statement and Financial Disclosure Certification, and Institutional Health Insurance Portability and Accountability Act (HIPAA) Certificates when available to the DCC.

Qualifications and Training
Clinical investigators will be cardiothoracic surgeons with expertise in surgical repair of mitral valve and cardiologists with experience in caring for ischemic and valvular heart disease. To qualify as a participating surgeon, the surgical investigators must have performed at least 10 mitral valve repair procedures annually (averaged over a 2 year period). The certified surgeon will either perform the mitral procedure on their own patient, or participate in the mitral procedure of an enrolled patient whose surgeon is not certified. Surgical qualifications for all participating surgical investigators will be collected on the Surgical Certification Form and faxed to the DCC prior to accreditation. The clinical site Principal Investigator will be responsible for overseeing the ongoing performance of the other participating surgical investigators at that site over the course of the study. In addition, each surgical investigator will participate in at least one of the bi-annual meetings of the Clinical Management Committee.

All clinical site echocardiography personnel involved in image acquisition for this trial will be certified by the Echocardiography Core Lab, as defined below.

All clinical site investigators and coordinators will be trained by the DCC in the specifics of the protocol at a site initiation visit in advance of patient enrollment. The study coordinators will be trained by the CTSN Neurocognition Core Lab to administer the neurocognitive testing. In addition, the investigators and coordinators will undergo a separate training session to gain familiarity with the electronic data capture system.

Signature Verification
Investigators will input an electronic signature into the electronic data capture system (EDC). It will be updated throughout the study as new site personnel are approved.

Conflict of Interest and Financial Disclosure Agreement
This statement verifies that all investigators have no conflict of interest with any institution that may influence their participation in this study. All investigators need to complete this statement. Investigators will also submit a financial disclosure agreement.

Site Approval to Enroll Patients

The following documents must be collected prior to approval:

- Clinical Study Agreement

- Clinical site IRB roster

- Clinical site IRB approval, version and date for protocol and consent

- Clinical site Laboratory Certification and Laboratory normal values

- Clinical site Echocardiography Laboratory Accreditation

Patient Confidentiality

All patients' records will be kept confidential according to HIPAA guidelines. Study Investigators, site Institutional Review Boards (IRBs), and the DCC and NHLBI personnel may review source documentation as necessary, but all unique patient and hospital identifiers will be removed. The aggregate data from this study may be published as per publication policy documented in the trial agreements; however, no data with patient identifiers will be published.

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. The data collected is HIPAA compliant and does not include patient identifiers but does include screening quarter, screening year, age, gender and reason not eligible or not enrolled.

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 of the informed consent document.

Release of Medical Information Form
Prior to screening data collection and *protocol defined procedures*
The patient must sign the Release of Medical Information form or equivalent that authorizes release of medical records, including hospital costing data, to the study sponsors, investigators, monitors, and the FDA.

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, ethnic origin, and sex will be captured on the registration form.   The EDC will generate a unique 8-digit identification code that will identify the patient throughout the course of the study.

Echocardiogram
Within 30 days prior to randomization
A complete transthoracic echocardiogram will be performed, according to the specifications defined in the Echocardiographic Image Acquisition Protocol (Appendix I) at each of the designated time points. ***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 investigator. The site echocardiography lab must be accredited by the Echo Core Lab in advance of performing any study echocardiograms, and each test must be performed by the accredited technician within the lab.

Medical History
Within 7 days prior to randomization
This form captures the information pertaining to the medical history, including but not limited to previous myocardial infarction, myocardial revascularization, arrhythmias, AICD, permanent right ventricular or biventricular pacemaker, stroke and other comorbidities such as diabetes and peripheral vascular disease. Information regarding the current medical condition is also captured, including but not limited to disposition at time of screening (outpatient, inpatient, ICU monitoring, etc) and IABP use.

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 and documented on the "New York Association Classification" form. The NYHA classification scheme is detailed in Appendix II.

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 Classification will be determined by investigative center personnel. The CCSC class will be documented on this form. The CCSC classification scheme is detailed in Appendix IV.

Medications
Within 7 days prior to randomization
This form captures all protocol-defined medications taken within 7 days prior to randomization.

Physical Examination
Within 7 days prior to randomization
This form captures the comprehensive physical examination including vital signs cardiopulmonary examination, abdominal examination, and anthropometrics (height, weight and BSA).

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) questionnaires will be completed by the patient and used 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.

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. The testing will take a total of 45 minutes, will involve a trained technician but will not require a neurologist or neuro-psychologist and can be performed with a minimal amount of special equipment. Results from these tests will be independently scored by investigators from the CTSN Neurocognition Committee. All neurocognitive batteries will be tape recorded and the de-identified recordings sent to the Duke University neurocognitive core lab for quality assurance evaluation.

Laboratory Assessment
Within 30 days prior to randomization

- White blood cell *($10^3/\mu l$)*
- Hemoglobin *(g/dl)*
- Hematocrit *(%)*
- Platelet count *($10^3/\mu l$)*
- 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 in the Eligibility Evaluation Form. All screened patients (patients who are consented) who are not randomized in the trial will have the reasons for non-randomization documented in the Eligibility Evaluation Form. The data collected is HIPAA compliant and includes reason for not being randomized.

A representative from the DCC will be available to discuss any questions regarding patient eligibility.

Proposed Revascularization
Prior to the surgical intervention
Coronary anatomy will be described, including the degree of coronary obstruction. Each artery/territory will be described *pre-operatively* as amendable or not amenable to bypass, and 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 first incision and before cannulation of aorta.** Randomization to the study assignment will be generated by the Electronic Data Capture (EDC) system once the checklist of inclusion and exclusion criteria has been completed and verified. For the purpose of the primary analysis, patients are considered enrolled in the study once they are randomized and an identification code is generated. Patients must undergo their study defined surgical intervention within 72 hours after randomization.

PROCEDURE
Patients will be randomized to either (a) mitral valve repair using an FDA-approved undersized annuloplasty ring or (b) complete chordal-sparing mitral valve replacement.

After induction of anesthesia, all patients will undergo trans-esophageal echocardiography (TEE) and pulmonary artery catheterization. Central hemodynamics will be recorded and TEE performed under loading conditions as close as possible to the

patient's baseline. Intra-operative TEEs will be performed according to standardized procedures (See Appendix I) that will also be provided to the site and affixed to the operating room echo machine. **The site must forward a sample intra-operative TEE to the Echo Core Lab in advance of performing any study echocardiograms, in order to assure adequacy of image acquisition and transfer to the Core Lab**. The site must receive Echo Core Lab approval in advance of performing any study related TEEs.

To prevent anesthetic effects, blood pressure and pulmonary artery pressures should be maintained with phenylephrine and volume during the TEE evaluations. For patients randomized to MV annuloplasty, tethering of the anterior and posterior leaflets by the posterior papillary muscle and adjacent left ventricle is confirmed.

All procedures will be performed with full or partial sternotomy, or a right thoracotomy using cardiopulmonary bypass via institutional routines. Dual venous cannulation can be performed either percutaneously or directly. Antegrade and/or retrograde cardioplegia is utilized and coronary artery bypass grafting is performed as per surgeon preference. The adequacy of the revascularization will be evaluated by the surgeon.

The mitral valve may be approached by either the left atrium via the Waterston's groove or using a biatrial approach. The mitral valve shall be inspected to confirm no organic pathology (myxomatous, rheumatic, or endocarditic changes).

Coronary Artery Bypass Grafting (CABG)
Coronary artery bypass grafting will be performed using standard techniques and two-stage venous cannulation. Conduit selection and harvesting methods will not be prescribed, except that utilization of the LIMA is recommended when an LAD graft is indicated. The technical details of bypass grafting will not be prescribed. Complete revascularization will be performed, within the judgment of the surgical investigator.

Mitral valve repair using an undersized annuloplasty ring
Exposure of the mitral valve is obtained through the Sondergaard or Waterston groove or through a transseptal approach (biatrial approach). The mitral annuloplasty ring should be complete and rigid or semi-rigid by any manufacturer. Nonpledgeted 2-0 braided sutures are placed circumferentially in the mitral valve annulus. Generally, 4 to 6 sutures are placed in the anterior annulus and 6 to 8 in the posterior annulus. Sizing of the annuloplasty ring is determined according to the surface area of the anterior mitral leaflet measured by determination of the intertrigonal distance and anterior leaflet height. Annuloplasty ring sizes 24 to 28 mm are typically used, sized 2 ring sizes smaller than the measurement (on average, this will be a 28mm in males, and a 26mm in females). Sutures are passed through the ring with appropriate spacing, then the ring is lowered into position and the sutures are tied. Finally, the ventricle is pressurized with saline solution to test for a residual regurgitation.

An additional subvalvular procedure can be added in case of severe tethering according to the surgeon's judgement and experience.

There are 2 circumstances where a mitral valve repair may be converted to a mitral valve replacement (which constitutes a cross-over): (1) *If the valve is judged to be unrepairable upon direct examination during the procedure or (2) if the TEE demonstrates greater than mild residual MR.* The amount of residual MR is measured on immediate post-CPB TEE.

The closure will include standard epicardial atrial and ventricular pacing wires according to the preferences of the operating surgeon. In addition, mediastinal and pleural drains will be placed and removed as per institutional routines.

Perioperative hemodynamic support may be necessary and are at the discretion of the surgeon.

Details of the entire surgery, including the mitral valve intervention and any additional surgical procedures will be collected on the CRF.

Complete chordal-sparing mitral valve replacement
Exposure of the mitral valve is obtained through the Sondergaard or Waterston groove or through a transseptal approach (biatrial approach). The anterior mitral leaflet is divided at its mid-point. Pledgetted 2-0 braided sutures are placed so as to incorporate mitral annulus and the divided parts of the anterior leaflet, resulting in plication of the chords to the annulus. In the posterior annulus, sutures incorporate both the annulus and the posterior leaflet, imbricating any redundant tissue. Sizing is performed with the usual manufacturer's sizers. In cases of excessive anterior leaflet tissue, to avoid left ventricular outflow tract obstruction or interference with mechanical valve mechanism, a central ellipse-shaped portion of the anterior leaflet is excised, leaving a 5 to 10 mm rim of leaflet free edge attached to the primary chordae tendineae. This strip of leaflet is incorporated in the valve sutures, as described above. Subsequently, the size of the mitral annulus is measured with standard valve sizers. The prosthesis is lowered into position and the sutures are tied. Finally, unrestricted motion of the prosthetic leaflets is confirmed. Rotation of the valve is performed as needed in the case of a mechanical prosthesis. The type of prosthesis (mechanical versus bioprosthesis) is left to the surgeon's judgement but a mitral bioprosthesis will be adequate in most patients.

Surgical indication for tricuspid annuloplasty
Tricuspid repair will be done concomitantly to the mitral procedure in case of severe tricuspid insufficiency defined as follows:
- Tricupid annular dilatation without structural involvement of the valve leaflets of subvalvular apparatus resulting in severe tricuspid regurgitation identified at the preoperative awake transthoracic echocardiogram (TTE) with normal filling pressures for age (systolic systemic blood pressure>90 mmHg, pulmonary diastolic pressure>10 mmHg): severe TR is defined by maximum jet area >10cm^2 or >66% of RA area. (Class IB recommendation in the presence of pulmonary hypertension mean pulmonary artery pressure>50 mmHg)
- Tricuspid repair for moderate functional TR (maximum jet area 6-10cm^2 or 33-66% of RA area) secondary to left heart lesion at the time of mitral valve surgery is a class IIa recommendation. A tricuspid procedure in these patients is left at the

surgeon's discretion and may be addressed as part of a substudy or separate protocol upon further reflection from the CTSN Steering Committee.

Surgical technique for tricuspid annuloplasty

A rigid ring (examples: Carpentier-Edwards annuloplasty ring or an Edwards MC3) tricuspid anuloplasty system must be used. The size of the prosthetic ring is based on the distance between the antero-septal and the postero-septal commissures and the surface area of the anterior leaflet of the tricuspid valve with commercial seizers. Usually a 30 - 32 ring is selected for men and a 28 – 30 for women.

Eight to ten U stitches are placed in the fibrous tricuspid annulus (2 mm from the leaflet hinge) except in the area of the bundle of His situated in front of the first half of the septal leaflet. Stitches are of 1 cm wide in the annulus and plication of the annulus is obtained with smaller distances applied to the ring in front of the anterior and the posterior leaflets. Upon lowering of the ring and tying of the sutures, the adequacy of the repair is tested by the saline infusion test. Replacement of the valve may be undertaken if repair seems unsatisfactory or if valve seems unrepairable according to surgeon's judgement.

Other Treatment

All patients are to receive standard medical management for their coronary artery, regurgitant mitral valvular disease and other co-morbid conditions in accordance with current medical practice guidelines when indicated. This includes, when clinically indicated and tolerated, but is not limited to, beta-blocker therapy, angiotensin converting enzyme inhibitors (ACE) or angiotensin receptor blockers (ARB), antiplatelet agents, statin therapy, aldosterone antagonists, implantable defibrillators and cardiac resynchronization therapy. A clinical management committee will update the guidelines for medical management, as necessary.

Management of postoperative atrial fibrillation

Controlling the ventricular response rate in postoperative atrial fibrillation

Beta-blockers should be used as first-line therapy for rate control. In patients with contraindications for beta-blocker use, nondihydropyridine calcium channel blockers are recommended as second-line agents.

Converting to normal sinus rhythm

Sotalol or class 1A antiarrhythmic drugs are recommended in patients with coronary artery disease who do not have congestive heart failure. Amiodarone therapy is recommended in patients with depressed left ventricular function.

Prevention of thromboembolism

If postoperative atrial fibrillation persists or is recurrent for more than 24 hours, anticoagulation with warfarin for 4 to 8 weeks, or at least 30 days after return of sinus rhythm is indicated.

Prophylaxis to prevent postoperative atrial fibrillation

Preoperative or early postoperative administration of beta-blockers in patients without contraindication should be used to reduce the incidence of atrial fibrillation. Preoperative administration of amiodarone can be used to reduce the incidence of postoperative atrial fibrillation in patients who have contraindications to beta-blockers.

POST-RANDOMIZATION DATA COLLECTION

Study Visits
- o 30 days post-op (+/- 3 days)
- o 6, 12 and 24 months post-op (+/- 14 days)

For patients who are unable to return to the clinical site for the *30 day, 6 and 24 month* assessments because of extreme geographic distance, the clinical coordinator will obtain the required data from a remote clinical site outside of the core CTSN sites. The remote clinical site *must* be identified in advance of discharge from the index hospitalization. All efforts must be made to acquire all follow-up at the CTSN clinical site. *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
Pulmonary artery pressures including central venous pressure, systolic, diastolic and mean pulmonary artery pressures (PA_S, PA_D, PA_M), pulmonary capillary wedge pressure (PCWP), trans-pulmonary gradient, cardiac output (CO), cardiac index (CI), systemic vascular resistance (SVR), pulmonary vascular resistance (PVR measured in Wood Units) and pulmonary artery oxygen saturation (PAO_2 sat) as determined by right heart catheterization.

Blood, Urine, and Tissue Sample Collection
Intra-operative and at 6 and 12 months post randomization
For those patients that consent to participate in the biological specimen collection and analysis program, blood, urine, and tissue specimens will be obtained and banked for future genetic, molecular, and biomarker analyses. In brief, the samples will be collected and banked by using the NHLBI Blood and Tissue Repository service (operated by SeraCare Bio Services, 217 Perry Parkway, Gaithersburg, Maryland 20877.). The repository only assists in the collection and storage of samples; it does not conduct assays nor analyze samples. The samples will be available to the Network Investigators during the "proprietary period" which starts when the samples are collected and banked, and continues up to three (3) years beyond the last clinic visit or two (2) years after the main results paper is published (whichever is first). The "open period" begins when the proprietary period ends; during this open period Limited Access Data Sets (LAD) and biospecimens are made available to the wider scientific community. By using the NHLBI repository, it is expected that Network Investigators will not exhaust samples during the proprietary period and that aliquots will be available to the wider community during the open period. The following table shows the sample type, quantity and time of collection:

Type of Sample	Collection Time Points			
	Baseline/Intra-op*	6 months	12 months	Total

				Blood
Cardiac tissue**	1cm2	--	--	
Urine	8mls	8mls	8mls	
Whole Blood for Plasma	24mls	24mls	24mls	72mls
Whole Blood for DNA***	10mls	--	--	10mls
Whole Blood for RNA	5mls	5mls	5mls	15mls
Total Whole Blood	39mls	29mls	29mls	97mls

*Venous blood prior to induction of anesthesia.
**Cardiac tissue (collected as available): 1cm^2 of left atrial tissue from the left atrial (LA) atriotomy. In subjects undergoing mitral valve replacement: $\geq$ 1cm^2 of excised mitral valve (MV) tissue from the A2 region will also be collected.
*** DNA may be collected at any time point if missed at baseline.

Detailed instructions on collection methods and procedures (such as sample collection, specific collection tubes, packing materials, coding labels and preaddressed shipping labels) will be provided in the Operations Manual.

Surgical Procedures
Initial surgical intervention and event driven
The initial surgical procedure (MV repair or replacement) and all subsequent 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.

> *Initial Surgical Procedure*
> In addition to the routine information collected on standard surgical procedure, the initial surgical procedure form will collect detailed information on the coronary artery bypass grafting performed.

> *Follow-up Surgical Procedure*
> Information about any surgical procedure(s) performed following the initial surgical procedure and during the follow-up period will be collected on this form.

Hospitalizations
Index Hospitalization and event driven
For all patients the index (baseline) hospitalization and all subsequent hospital admissions (for any reason) must be reported on the Hospitalization form. This form collects limited information about hospital procedures, length of stay, days in intensive care, and discharge if applicable as well as patient condition and disposition for each hospitalization.

Medications
At 30 days, 6, 12, and 24 months post randomization and event driven
All cardiovascular medications will be recorded at each study visit, and also as indicated at the time of associated adverse events.

Physical Examination
At 30 days, 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 30 days, 6, 12 and 24 months post randomization
The presence of heart failure will be assessed, and when present, classified according to the NYHA scale. NYHA classification will be determined by a clinical site coordinator not otherwise involved in this trial, blinded to the treatment assignment. The NYHA class will be documented on this form.

Angina Class - Canadian Cardiovascular Society Classification (CCSC)
At 30 days, 6, 12, and 24 months post randomization
The presence of angina will be assessed, and when present, classified according to the CCSC scale. The CCSC Classification will be determined by a clinical site coordinator not otherwise involved in this trial, blinded to the treatment assignment. The CCSC class will be documented on this form.

Echocardiogram
At 30 days, and 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 (Appendix I) at each of the designated time points. For patients who are unable to return to the clinical site for the *30 day, 6* and *24* month assessments because of extreme geographic distance, a limited echo will be obtained at a remote center (see Echocardiogram Image Acquisition section, Severe MR Trial Manual of Procedures). The remote echo center *must* be identified in advance of discharge from the index hospitalization. All efforts must be made to acquire all follow-up echocardiograms at the clinical site. *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.

Functional Status
At 6 and 12 months post randomization
Functional status as assessed by a cardiopulmonary stress test will be evaluated and the peak oxygen uptake will be recorded. (See Appendix III)

Neurocognitive Testing
At 12 months post randomization
Cognitive performance will be assessed 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. The testing will take a total of 45 minutes, will involve a trained technician but will not require a neurologist or neuro-psychologist and can be performed with a minimal amount of special equipment. Results from these tests will be independently scored by investigators from the CTSN Neurocognition Committee. All neurocognitive batteries will be tape recorded and the de-identified recordings sent to the Duke University neurocognitive core lab for quality assurance evaluation.

Quality of Life
At 30 days, 6, 12, and 24 months post randomization
The MLHQ, Duke Activity Status Index (DASI), SF 12 and EuroQol (Appendix VI) questionnaires will be used to assess quality of life. The patients themselves must complete these questionnaires.

Cost
Inpatient costs for all admissions (index hospitalization and all subsequent re-hospitalizations) will be measured from baseline to 24 months. Costing data will be obtained from UB-92 forms and hospital billing sheets for enrolled patients on a quarterly basis. For Medicare-eligible enrollees, we will also collect CMS billing data. All costing data will be cross-referenced against the clinical database to ensure that the available costing data are appropriate and complete.

Event Driven Data Collection

Follow-Up Surgical Procedures
All operations following the initial mitral valve surgery 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 adverse events will be recorded at the time an adverse event occurs. Investigators will be asked to make a judgment as to the seriousness and relationship of the event to the surgical intervention. All adverse events will be recorded until completion of the trial.

Missed Visit Assessment
Event Driven
If a patient is unable to return for follow-up before the closure of a study visit window, a missed visit assessment that captures the reason for missing the visit must be completed.

Mortality
Event Driven within 24 hours of knowledge of event
The investigator will record the date of death, immediate cause of death, primary underlying cause of death, notation of autopsy being performed, and clinical narrative of the event.

Study Completion/Early Termination
Event Driven
This form records the date and reason for study completion or early termination. The only anticipated reason for a patient to be withdrawn from this study is patient request, which should be detailed in the narrative section of the form.

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.

DATA MANAGEMENT
All study data will be entered in the web-based electronic data capture (EDC) system (specified in detail in the operations manual). Study personnel requiring access will have their own Login/Password. Access to clinical study information will be based on individuals' roles and responsibilities. The application provides hierarchical user permission for data entry, viewing, and reporting options. For optimum security, the system operates Secure Socket Layer (SSL) 128-bit encryption protocol over Virtual Private Networks. This application is designed to be in full compliance with International Conference on Harmonization and Good Clinical Practices (ICH-GCP), the FDA's Code of Federal Regulations (CFR) Number 21 Part 11 Electronic Record and Electronic Signatures, the FDA's "Guidance: Computerized Systems Used in Clinical Trials, and the Privacy Rule of the Health Insurance Portability and Accountability Act of 1996 (HIPAA).

Quality Assurance
The data quality assurance tool has been designed as an automatic feature of the EDC system. When a form is submitted the system conducts instantaneous validation and cross-form validation checks. A query is generated and sent to the site coordinator electronically so that data may be verified and corrected. All changes made to a form are stored in an audit log.

Monitoring
The primary objectives of the DCC in monitoring clinical sites are to educate, support, identify and resolve issues related to the clinical trial. The monitors will discuss the protocol in detail, and clarify any areas of uncertainty. At initiation of the study, the monitors will conduct a tutorial on the EDC system. The coordinators will practice entering data so that the monitors can confirm that the coordinators are proficient in all

aspects of data entry, query response, and communication with the data management team.

The DCC will conduct on-site monitoring visits after enrollment begins and at least once each year for every clinical site for the duration of the study. Copies of all source documents must be kept in the patient source binders at each site for review by the monitors.

The monitors will review the source documents to determine whether the data reported in the EDC system are complete and accurate. They will also verify that all serious and protocol-defined adverse events exist on the source documents, are consistent with the protocol and are documented in the appropriate format. Source documents include medical charts, initial hospital admission reports, operative procedure records, discharge and re-admission reports, consult notes, radiology reports, lab reports, clinic records, and other study-related notes. The study monitors reserve the right to copy de-identified records in support of all adverse events and outcomes.

The monitors will also confirm that the regulatory (administrative) binder is complete and that all associated documents are up to date. The regulatory binder should include all revisions of the protocol and informed consent, IRB roster, IRB approvals for all of the above documents, IRB correspondence, investigator's agreements, CVs of all study personnel, institutional HIPAA certificates, monitor site visit log, telephone contact log, and correspondence with the DCC.

If a problem is identified during the visit (i.e., poor communication with the DCC, inadequate or insufficient staff to conduct the study, missing study documents etc.), the monitor will assist the site in resolving the issues. Some issues may require input from the Steering Committee or the Principal Investigator, as well as the sponsor.

The combination of yearly on-site monitoring and ongoing monitoring using the EDC system that includes instantaneous electronic validation, and visual cross-validation to detect complex errors, it is anticipated that the best possible quality and most complete data will be collected.

The monitor will verify a minimum of the following variables for all patients: initials, date of birth, sex, signed informed consent, eligibility criteria, date of enrollment, anticoagulation, serious and protocol-defined adverse events, mortality, NYHA Classifications, and QoL. These data will be 100% source data verified. All other data collection will be monitored as indicated by the data completeness and accuracy at each clinical site.

ANALYTICAL PLAN
General Design Issues
This study is a prospective, multi-center, randomized clinical trial. Enrolled patients will have severe ischemic mitral regurgitation. The primary aim of the trial is to evaluate the impact of replacement versus repair on left ventricular remodeling. The primary

endpoint for the trial is the degree of left ventricular remodeling, as assessed by Left Ventricular End Systolic Volume Index (LVESVI) at 12 months post surgery. The nature of the treatments precludes masking of patients and their treating clinicians to treatment assignment; however, all echocardiograms will be analyzed by core laboratory personnel masked to treatment assignment. Investigators will also be blinded to all data from other clinical sites with the exception of serious, unexpected AEs for IRB reporting purposes.

Sample size
Sample size is based on previously published data, and on ensuring the ability to detect, with high probability, a clinically meaningful presumed benefit for patients undergoing mitral valve repair [23-25]. We assume that the mean baseline LVESVI in the target population is 100 ml/m^2. For patients randomized to receive mitral valve repair we anticipate a 20% reduction in LVESVI, or an absolute change of 20 ml/m^2. We believe a meaningful effect worth detecting is an additional 15% (15 ml/m^2), or a total reduction of 35% or 35 ml/m^2 for patients undergoing mitral valve replacement. Assuming that the standard deviation for the change in both arms is 35 ml/m^2, a total of 250 patients, randomized with equal probability to each arm, provides approximately 90% power to detect a difference of 15 ml/m^2 in LVESVI between patients randomized to mitral valve repair and patients randomized to mitral valve replacement.   Power is based on a 0.05 level two-tailed Wilcoxon Rank-Sum test. The sample size takes account of a single interim analyses to be performed in addition to the final analysis. Randomization will be implemented as described in the Randomization section.

Randomization Design and Procedure
Patients will be randomized using a 1:1 allocation to mitral valve repair or mitral valve replacement. The randomization will be stratified by clinical center (i.e., a separate randomization scheme will be employed in each center). A random permuted block design will be employed, with blocks of size 2, 4, or 6 randomly chosen. Randomization will be implemented as described in Randomization Section, as previously described.

Data Monitoring and Analysis

Methods of Analysis
The primary outcome of this trial is the degree of left ventricular remodeling at 12 months post surgical intervention, assessed by Left Ventricular End Systolic Volume Index (LVESVI). The null hypothesis is that there is no difference in the post surgical LVESVI between patients randomized to undergo mitral valve repair compared to patients randomized to undergo MV replacement. The primary null hypothesis will be tested in an intent-to-treat analysis using a 0.05 level two-tailed Wilcoxon Rank-Sum test.

The choice of the Wilcoxon Rank-Sum test for the primary analysis is motivated by the expectation of a relatively substantial amount of non-ignorable missing data, primarily due to patient death. One-year incidence of mortality is expected to range from 15-20%, and potentially differ between randomization arms. Some patients, expected to be few, may also be missing echocardiographic assessment for reasons directly related to the severity of their illness. These missing data cannot be considered ignorable, and we are

hesitant to impute such data using models whose assumptions would not be testable. Absent these concerns, the primary analysis would be by analysis of covariance.

The Wilcoxon Rank-Sum test allows a straightforward incorporation of patients with non-ignorable missing data into the analysis; thereby, avoiding the potential bias of relying on a complete case analysis or on an analysis that assumes the missing data mechanism is missing at random (MAR). For the analysis, patients who die will be assigned ranks lower than the lowest observed rank, in ascending order based on the time of death (earliest to latest). Patients whose missing data are determined by independent adjudicators to be due to severity of illness will be given the next lowest set of tied ranks. We expect relatively few patients to be missing 12 month LVESVI due to withdrawal or refusal. Patients with missing data not due to severity of illness or mortality will have their 12 month LVESVI imputed via multiple imputation (Rubin) assuming that the data are MAR, i.e., the missing nature of the variable is independent of the value of the variable given the observed data. The specific imputation model to be used will be determined prior to examination of any outcome data, but will include measured LVESVI at six months.

The main feature of the imputation approach is the creation of a set of clinically reasonable imputations for change in LVESVI for each patient with missing data. This will be accomplished using a set of repeated imputations created by predictive models based on the majority of participants with complete data. The imputation models will reflect uncertainty in the modeling process and inherent variability in patient outcomes, as reflected in the complete data.

After the imputations are completed, all of the data (complete and imputed) will be combined and the analysis performed for each imputed-and-completed dataset. Rubin's method of multiple (i.e., repeated) imputation will be used to estimate treatment effect. We propose to use 15 datasets (an odd number to allow use of one of the datasets to represent the median analytic result). An illustration of the use of this general imputation approach for rank based methods is provided in Mogg and Mehrotra (Statistics in Medicine, 2007). For simplicity our primary analysis will not be stratified by clinical center, although the randomization will stratify by clinical center. This should result in only a small loss of efficiency.

Estimating treatment effect
The treatment effect will be summarized by the median and interquartile range for each randomization group, by the point and interval estimates of the one-year incidence of mortality for each randomization group and associated relative risk, and by point and interval estimates of 12 month LVESVI for surviving patients.

Secondary analyses of the primary endpoint
Several analyses are planned to facilitate interpretation of the trial's results. These include repeating the primary analysis on the ranked differences of LVESVI from randomization to 12 months and extending the Wilcoxon Rank-Sum test to adjust for baseline LVESVI (a "non-parametric analysis of covariance", i.e., an analysis of covariance using ranked baseline and ranked outcome data). While this "nonparametric

analysis of covariance" may be slightly more efficient than our primary analysis, we use it secondarily as it is not commonly employed and has less straightforward interpretation than Wilcoxon Rank-Sum test. Since this is a randomized trial, no baseline differences are expected.

A secondary analysis of the primary endpoint will also be performed by jointly modeling LVESVI and time to death, using a model suggested by Xu and Zeger (Applied Statistics, 2001). This model uses a latent variable approach, whereby conditional on this latent variable LVESVI and time to death are assumed to be independent. The model is flexible and borrows information from mortality to assess differences in LVESVI between randomization arms, and borrows information from LVESVI to assess differences in mortality.

Interim Analysis
We plan to perform a single interim analysis with respect to the primary endpoint to give the option of stopping early should results strongly favor one arm or the other. The proposed timing of this analysis is at 0.5 on the information scale, i.e., after one-half of patients (125 reach the primary endpoint. The utility of performing this analysis will depend on the rate of accrual of patients into the trial. We assume an accrual rate of approximately sixteen to seventeen (16-17) patients per month, or slightly more than two (2) patients per center per month. As the decision to terminate early would likely occur after most, if not all, patients were randomized, the principal benefit of early termination would be prompt dissemination of results, and no further randomization into an inferior treatment. A group sequential procedure will be used to allow for flexibility in the number and timing of interim analyses should the DSMB choose to modify the proposed plan, or should accrual mitigate the usefulness of an interim look. We will use the Lan-DeMets approach, implementing an O'Brien-Fleming-type spending function that allots most of the type I error to the final look. The resulting critical values to be used for each analysis are 2.963 at the first interim analysis, 1.969 at the final analysis.
In addition to the ethical concern of continuing a trial that shows a clear benefit in favor of one treatment, there is also a corresponding ethical concern of continuing a trial that has little chance of ever showing a benefit of one treatment compared to the other. We propose that the trial's conditional power, under the original alternative hypothesis, be computed at the interim look and that the DSMB use this to determine whether randomization, if not completed, be halted for futility. We propose that consideration be given to halting the trial for futility if, given the data up to the point of the interim analysis, the probability of detecting a difference of 15 ml/m^2 in LVESVI between patients randomized to CABG plus mitral valve repair and patients randomized to CABG plus mitral valve replacement is less than 20%.

We do not propose any a priori stopping criteria based on adverse events. The treatments in this trial are not experimental, and have well known adverse event profiles. Moreover, we believe that incident rates of adverse events and mortality must be interpreted along with information about the consistency of related measures, consistency across centers, data completeness, and any external factors including scientific developments that might impact patient safety. In addition to considering the data generated by this trial, the DSMB will consider all relevant background knowledge about the treatment of mitral

regurgitation. The DSMB would be capable, and uniquely suited, to determine decisions for convening outside the schedule of meetings, and to determine decisions to suspend or terminate the trial. These decisions should be at the discretion of the DSMB alone. We therefore recommend that the DSMB should be responsible for defining its deliberative processes, including event triggers that would call for an unscheduled review.

Assessment of Balance of the Randomization
The success of the randomization procedure in balancing important covariates (e.g. age, baseline LVEF and NYHA Class, etc.) between randomization groups will be assessed at the interim analysis and at the final analysis. Continuous measures will be compared using t-tests, while chi-squared tests will be used to compare categorical variables. As 250 patients will be randomized, no substantial imbalances are expected. However, should any covariate differ significantly between treatment groups at the 0.01 level, and be substantively large, we will adjust for those covariates in all analyses.

Analyses of Secondary Endpoints

Mortality. All-cause mortality is a particularly important secondary endpoint. Given that this trial's primary endpoint is an echocardiographic assessment (LVESVI), it will be important to supplement the finding of a treatment effect (or lack of one) for the primary endpoint with a corresponding effect on a clinical endpoint such as all-cause mortality. As the trial is not powered to detect a mortality difference, a statistically significant difference in mortality between randomization arms is not expected; however, an observed difference in mortality, consistent in direction with that observed for LVESVI will serve to validate the trial's findings. No matter the result, the interpretation of the trial's results will necessarily consider the difference in mortality observed between randomization arms. The proportion of deaths between randomization groups, both at 12 and 24 months, will be compared by a by a chi-squared test. Time to death will be described by Kaplan-Meier curves and differences between randomization groups assessed via the log-rank test. One-year mortality is difficult to specify precisely for this patient population, but is expected to be in the range of 15-30% for patients randomized to CABG plus mitral valve replacement. With a total of 250 patients randomized with equal allocation to CABG plus mitral valve repair or to CABG plus mitral valve replacement, there is 80% power to detect an absolute decrease in mortality in the range of 11 to 15% for patients randomized to CABG plus mitral valve repair compared to CABG plus mitral valve replacement.

A number of additional secondary analyses are planned to supplement the primary analysis and aid interpretation of the trial's results. These secondary analyses will use a 0.01 level for significance.

MACE. The proportion of patients experiencing a major cardiac event will be compared between randomization groups, both at 12 and 24 months, by a chi-squared test.

NYHA classification and Angina class. The distribution of NYHA and Angina class will be presented for each randomization arm and compared using a chi-squared test.

Additional echo parameters: ERO, LVEF, LV sphericity will be analyzed analogously to the primary endpoint.

Quality of life. Quality of life will be measured using the Duke Activity Sataus Index (DASI), Minnesota Living with Heart Failure Score (MLHF), SF-12, and EuroQol. We will employ two approaches to the analysis of quality of life. The first will be to base the analysis on longitudinal mixed effects models. These models would predict outcome from treatment group and time. The mixed modeling approach requires an assumption that patient dropout is ignorable in that the probability of dropping out at any time is related only to previously observed data items. Of course, this assumption may not hold, and moreover it is impossible to test robustly from the data at hand. An alternative approach we will also use, not subject to this criticism, will be to separate the data into strata defined by the time of death or dropout. We will then estimate a separate linear model, including a treatment effect, for the data in each stratum. This method, known as pattern-mixture modeling is not sensitive to un-testable assumptions about the dropout mechanism because it models the data directly in strata defined by dropout time. The method of Wu and Bailey is an instance of pattern-mixture modeling.

Neurocognitive Outcomes. Neurocognitive outcomes for each test will be standardized using the means and standard deviations observed in the overall sample and combined within cognitive domains using weights, which are being defined by the Neurocognitive Committee. Differences in the scores for each domain at 12 months post-randomization will be compared between randomization arms based on an analysis of covariance that adjusts for important baseline values.

Peak VO$_2$. Peak VO$_2$ levels determined from cardiopulmonary exercise (CPX) testing will be used as the primary measure of a patient's functional status. While peak VO$_2$ is an objective measure, the nature of CPX testing combined with the severity of illness of this patient population patient may lead to a relatively large amount of missing data compared to other outcomes. Our analytic approach will ultimately depend upon the amount of missing data, but will likely focus on multiple imputation methods. These methods generally require the relatively strong assumption that missing data for a variable is independent of the value of the variable given observed data. While it is never possible to prove that data are missing at random, it is possible to detect, based on the pattern of missing data, when data are not missing at random. Absent evidence that the data are not missing at random, the multiple imputation method described by Rubin (2002) would likely be used. If the missing at random assumption is clearly violated by the data, other procedures including pattern mixture modeling will be considered.

Our focus will be on imputing the 12 month assessment as this is the time that the primary outcome will be assessed. For example, it is reasonable to assume a strong linear relationship between peak VO2 at 6 and 12 months. Based on this assumption, a regression imputation approach could be used in which the relationship between patients with both 6 and 12 month measures may be used to generate a distribution of potential values for patients with missing 12 month assessments. Values from this distribution would be sampled (imputed) and used for those patients with missing data. Several values (e.g., 15) would be imputed and the results using these different "complete" data sets

combined. Peak VO$_2$ values between randomization groups could be compared using a classical t-test.

For patients without 6 and 12 month assessments, "hot deck" imputation could be employed. Patients would be are grouped by selected characteristics determined by statistical models to be related to peak VO$_2$ at 12 months. Patients with missing data would have values imputed by randomly chosen values from other patients within their group. Patients whose missing values are due to death or inability to perform the test due to worsening condition could be given the lowest observed value for peak VO2.

Additionally, a complete case analysis could also be performed with adjustment for important variables using a propensity score. Whatever methods are used, a sensitivity analysis will be important for interpretation as any statistical analysis may produce biased results if the amount of missing data is large.

Adverse Events. Differences in the incidence of individual adverse events will be compared between randomization arms using Poisson regression. Exact 95% confidence intervals (based on the Poisson distribution) for the risk ratios for individual adverse events for treatment with replacement versus repair will be computed.

Peri-operative Measures. Operative time, cardiopulmonary bypass and cross clamp time will be summarized compared between treatment arms using a t-test.

Hospital length of stay and days in ICU. We will compare hospital length of stay and days spent in ICU for the index hospitalization between treatment groups using a Wilcoxon Rank-Sum test.

Readmissions. We will use a Poisson regression model to compare the frequency of readmissions between groups for any cause, and specifically for heart failure hospitalizations.

Days alive out of hospital. We will compare the total number of days alive out of hospital between treatment groups accounting for the total days alive. The analysis will be based on a Poisson regression model which will have the number of days alive out of hospital as a dependent variable, an indicator for treatment groups as an independent variable and the total days alive as an offset.

Hospital readmission. Rates of all-cause hospitalizations, and rates of cardiovascular and heart failure specific hospitalizations, both within 30 days and within one year will be compared using a chi-squared test.

Costs and Cost-Effectiveness.

Cost
Cost will be calculated by converting charges to cost using institution specific Ratio-of-Cost-to-Charges (RCCs). Institution-specific cost reports will be used to calculate RCCs for each major resource category. Costing data will be compared by Student's t test after

log transformation. Independent predictors of cost, including baseline factors, operative factors and postoperative events, will be determined by multivariate regression analysis.

Cost-Effectiveness
The primary objective of the CEA is to estimate the incremental CE ratio (ICER) of the intervention under investigation as compared to the study-defined alternative. This ratio measures the ratio of the difference in costs and outcomes between the two study arms, with outcomes measured as quality-adjusted life-years (QALYs). QALYs reflect an individual's preference for both quantity and quality of life in a single measure that facilitates comparisons across diverse treatment modalities. We will also compute net health benefits (NHB) as an alternative way of looking at cost-effectiveness.   This parameter compares the incremental effectiveness of an intervention with the minimum health effect that society would demand in return for the investment; i.e., with the health produced by investing at the societal ceiling cost-effectiveness ratio (CR).

Costs will be estimated as discounted incremental health care costs, and effectiveness will be measured as the discounted increment in quality-adjusted life years. A secondary objective will be to identify disease- and patient-related factors that predict high costs of care following the intervention. All CE ratios will be reported with probability intervals to reflect the level of uncertainty in the clinical estimates used in the model and the underlying economic assumptions. We anticipate that the distribution of costs will be skewed to the right. If this violates the assumption of normality, we will modify the method using the nonparametric Bayesian bootstrap. We will use standard discount rates for both QALYs and costs.

We will calculate the ICER based on actual trial data and also develop a model to project long-term cost-effectiveness. Sensitivity analyses will be performed to estimate several sources of uncertainty, including: (1) sampling variation; (2) variations in discount rates; and (3) changes in outcomes (e.g., survival, hospitalization costs, stroke rate) due to innovation and learning.

Crossovers
Crossovers (patients who after randomization switch from the allocated treatment to the non-allocated treatment) are expected to be few in this trial. Patients randomized to mitral valve repair who are converted to replacement can be considered crossovers. As the primary analysis is by intention to treat, crossovers will be analyzed as belonging to the group to which they were randomized. The pattern of crossovers will be examined, and if differential crossover rates between arms are noted, further analyses will be performed to determine the effect of on trial outcomes.

ORGANIZATION OF THE STUDY
This section describes the overall study organization. The study is to be conducted in the participating CT Surgery Network Centers. The following committees and institutions will be involved in the administration of the study.

Event Adjudication Committee
The charge of the Event Adjudication Committee (EAC) is to review source documents and adjudicate all adverse events and causes of mortality. The individuals who will serve on the committee are unaffiliated with the clinical sites and the DCC, and will be appointed by the DCC. The committee will consist, at least, of a cardiothoracic surgeon a cardiologist, and a neurologist. The EAC will meet every 6 months or as needed to review outcomes data for each subject enrolled.

Data and Safety Monitoring Board (DSMB)
To meet the study's ethical responsibility to its subjects, an independent data safety monitoring board (DSMB) will monitor results during the study. The board consists of physicians, biostatisticians, ethicists and bioengineers, who have no formal involvement or conflict of interest with the subjects, the investigators, the DCC or the clinical sites, and will be appointed by the NHLBI. The DSMB will act in a senior advisory capacity to the DCC and the NHLBI regarding data and safety matters throughout the duration of the study. In addition, the DSMB will review interim summary results of the accumulating data from the Event Adjudication Committee every 6 months. These data include adverse events (e.g., infection, bleeding, right heart failure) and mortality. They will communicate their findings directly with the DCC and the NHLBI. The clinical centers will have no contact with the members of DSMB and no voting member of the committee may participate in the study as an investigator.

Data Coordinating Center (DCC)
A university-based DCC (InCHOIR) will collaborate with the Network Investigators to develop protocols, and bears responsibility for monitoring interim data, and analyzing the study's results in conjunction with the investigators and the sponsor. The DCC will coordinate and monitor the trial, and will administrate the DSMB and EAC.

Echocardiography (Echo) Core Lab
All echocardiograms will be performed according to a standardized protocol (Appendix I) and will be centrally analyzed the Echo Core Lab at Massachusetts General Hospital, Boston, MA.

Cardiopulmonary Exercise Testing Core Lab
All exercise testing will be performed according to a standardized protocol (Appendix III) and will be centrally analyzed by the Network CPX Core Lab located at Henry Ford Hospital, Detroit MI.

Neurocognitive Core Lab
The Neurocognitive Core Lab, located at Duke University is directed by Joseph Mathew, MD. The core lab will be responsible for training the clinical site personnel in administration of the specific tests. All neurocognitive tests will be scored centrally by the core lab.

Executive Steering Committee
The Network Steering Committee (with the assistance of the protocol development committee) will provide the overall scientific direction for the study. The responsibilities

of the Steering Committee are to: (a) maintain contact with study investigators to ensure high quality data collection; (b) approve and implement major protocol changes in response to advice from the DSMB or to changes in clinical guidelines; (c) collaborate in data analysis, interpretation, and publication; (d) establish criteria for authorship on all manuscripts, publications and presentations that arise from the study.

Clinical Management Committee
The CMC will be comprised of cardiothoracic surgical and cardiology investigators with extensive expertise in the management of ischemic and valvular heart disease. The charge to the CMC is to update guidelines for the medical management group, and guidelines for management as needed. They will monitor the implementation of these guidelines for patients in the trial.

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APPENDIX I: Echocardiographic Image Acquisition Protocol

For the echocardiogram, the patient will be positioned in left lateral recumbency or in the position that permits optimal imaging. It is strongly recommended that a customized echocardiography bed be used with a standard cut-out mattress to expose the cardiac apex. With digital archiving, at least 3 and no more than 5 cardiac cycles are requested for two-dimensional imaging. At least 5 cardiac cycles are required for spectral pulsed wave (PW) and continuous wave (CW) Doppler. For patients in atrial fibrillation, a minimum of 2 captures of 5 consecutive cardiac cycles are required. Unless otherwise specified, depth should be adjusted to maximize the image while including all necessary structures. All images will be acquired at end-expiration held during quiet respiration. Harmonic imaging should be employed to optimize visualization of endocardial borders. All PW, CW Doppler and m-mode recordings will be performed at a sweep speed of 100 mm/sec. Color Doppler Nyquist limits will be adjusted to the range of 0.5 – 0.7 m/sec, unless otherwise specified. The following protocol is required however additional images should be obtained at the discretion of the sonographer/physician.

Protocol for Transthoracic Echocardiogram (TTE)
1. PLAX with and without magnification of the left ventricular outflow tract; with and without color flow Doppler interrogation of the aortic and mitral valves. Careful attention will be paid to identifying the vena contracta of the mitral regurgitant jet using zoom views.

2. An m-mode recording of the left ventricle just below the tips of the mitral leaflets.

3. Parasternal inflow view of the tricuspid valve; with and without color flow Doppler (CW if jet imaged parallel to beam).

4. Parasternal outflow view of the pulmonic valve; with and without color flow Doppler and PW and CW of the PV.

5. PSAX (ensure on-axis views)
   a. Apex
   b. Mid-papillary muscle level.
   c. Level of the mitral valve when both anterior and posterior leaflets are visualized. Position the Color Doppler scan box over the mitral orifice to visualize the regurgitant jet origin.
   d. Tips of the mitral valve leaflets (identity minimum diastolic orifice).

6. Basal PSAX (at the aortic valve level). Evaluation of PV and TV performed; with and without color flow Doppler. Pulsed Doppler sample of pulmonary flow at the level of the pulmonary valve to measure pulmonary velocity time interval (VTI) opening and closing transients of the pulmonary valve should be recorded. Optimize the pulmonary valve annulus for measurement of the pulmonary annular diameter.

7. Apical 4-chamber view
    a. Full sector and zoom/res of individual valves with and without color flow interrogation of mitral and tricuspid valves. The color flow Doppler interrogation should include the entire left atrium taking care to include wall-impinging eccentric jets in the region of interest. Gain should be adjusted to reduce excess noise. Spectral Doppler interrogation in this view includes:

    i. PW Doppler of mitral inflow at mitral leaflet tips.
    ii. PW Doppler of mitral inflow at the level of the mitral annulus at end diastole with a small sample volume.
    iii. CW of the mitral inflow signal.
    iv. CW of the mitral regurgitant jet with care to record a complete signal and maximize the peak velocity. Contrast should be used to enhance this signal when incomplete and when a peak velocity cannot be determined. NOTE: Occasionally eccentric CW jets may require interrogation of additional views (e.g., PLAX, Apical 2C view) to obtain the true maximal jet velocity.
    v. CW of tricuspid regurgitant jet for estimation of pulmonary artery systolic pressure. If jet is inadequate for measurement, this recording should be repeated following contrast injection (see below).
    vi. PW Doppler of right pulmonary vein flow. The sample volume should be placed at least 1 cm within the pulmonary vein, if possible. If jet is inadequate for measurement, this recording should be repeated following contrast injection (see below).
    vii. Color flow Doppler visualization of regurgitant jets (mitral and tricuspid).
    viii. PISA (proximal isovelocity surface area) using zoomed views for estimation of regurgitant orifice area.
        1. Mitral Regurgitation: the Nyquist limit will be lowered and the baseline shifted in the direction of flow (toward left atrium) to maximize the PISA signal. The PISA aliasing velocity should be set between 0.3 and 0.4 m/sec. Record 3-5 cycle (more for atrial fibrillation) clip of PISA as well as still frame of maximum PISA radius.
        2. Tricuspid regurgitation: : the Nyquist limit will be lowered and the baseline shifted in the direction of flow (toward left atrium) to maximize the PISA signal. The PISA aliasing velocity should be set as close to 0.28 m/sec as possible. Record 3-5 cycle clip of PISA as well as still frame of maximum PISA radius.
    ix. Tissue Doppler of the mitral annulus (lateral and septal) and the tricuspid annulus.
    x. Velocity of propagation across the mitral valve.

       b. Apical 4-chamber zoom/res image of the left atrium with mitral annulus in the middle of sector.
       c. Apical 4-chamber zoom/res images of the left ventricle (excluding most of LA but including all of the basal LV/annulus).

8. Anteriorly angulated 4-chamber view:
       a. Color flow Doppler to exclude aortic insufficiency. If present, aortic insufficiency jet will be optimized to permit measurement of the pressure half time using CW Doppler.
       b. PW Doppler in left ventricular outflow tract positioned such that closing artifact but not opening artifact of the valve is visible.
       c. CW Doppler through the aortic valve.

9. Apical 2-chamber view
       a. Mitral valve with and without color Doppler.
       b. Apical 2-chamber zoom/res images of the left ventricle (excluding most of LA but including all of the basal LV/annulus).

10. Apical 3-chamber view
       a. Mitral valve and aortic valve with and without color Doppler.
       b. Apical 2-chamber zoom/res images of the left ventricle (excluding most of LA but including all of the basal LV/annulus)

11. Subcostal imaging
       a. Inferior vena cava with and without a "sniff".
       b. Color Doppler of inter-atrial septum to interrogate presence of ASD.
       c. 4-chamber and SAX views (particularly if parasternal evaluation was limited).

12. Contrast will be used for endocardial border delineation when less than 80% of the endocardium can be visualized on the harmonic image. Contrast can also be employed for enhancement of the tricuspid regurgitant and pulmonary venous flow signals. During the contrast imaging, the mechanical index (MI) should be adjusted according to manufacturer recommendations.

Note: Addition of any non-standard imaging will be coordinated in collaboration with the selected Core Laboratory under a protocol amendment and should be obtained at the discretion of the sonographer/physician.

Protocol for Intra-operative Transesophageal Echocardiogram (TEE)
Intra-operative TEE imaging will be performed on all specified index operative procedures in the CTSN clinical trials, consistent with standard clinical care. For the purposes of the CTSN trials, the clinically indicated TEE's will be performed according to the standardized protocol below. The echos will be over-read by the echo core lab.

Valvular evaluation should always include Color Doppler and Pulsed/Continuous Wave Doppler as appropriate.

Pre-Procedure Imaging
A comprehensive intra-operative multiplane TEE as defined by the ASE/SCA Guidelines
(Shanewise JS et al. J Am Soc Echocardiogr 1999;12:884-900) should be performed.
The following checklist may be used with appropriate Doppler performed for valvular
assessment:

Mid and High esophageal views
o 4 Ch view (of entire LV/RV)
o Mitral Valve: (lower depth) with appropriate color Doppler and recording of
   CW in at least one plane
      o Transverse Plane (0°)
      o Commissural View (60°)
      o Two-chamber View (90°)
         ▪ Change depth to imaged entire LV as well
      o Three-chamber View (120-140°)
         ▪ Change depth to imaged entire LV as well
o LVOT/AV/Aorta
      o Long-axis view (120-140°) with color Doppler
      o Ascending aorta (mid to high esophageal view) (90°)
      o Ascending aorta SAX views (0°, high esophageal)
      o AV SAX (30°, mid esophageal) with color Doppler
o Main PA/PV
      o Bifurcation view (0-30°, high esophageal)
      o RVOT view (70°, mid esophageal)
o LA/LAA (0-180°)
o RA/TV/IAS:
      o 4 Ch view (all of RV then change depth for TV)
      o TV/IAS rotation (0-90°) with color Doppler
      o Bicaval view (90-110°)
      o Pulmonary veins (either at 90° or 0°)

Transgastric views
o Three horizontal 2D short axis views are requested
      o Mitral valve level
      o Mid papillary muscle
      o Apical level.
o Horizontal 2D images of the right ventricle and tricuspid valve.
o Deep Gastric views
      o 5Ch view Aortic valve (with color, PW and CW Doppler)

Aorta
o Thoracic aorta
o Aortic arch (SAX and LAX views)
o Pulmonic valve

Post-procedure Imaging
A full post-procedure TEE should be obtained if time permits. Otherwise, the study
should be tailored to the procedure performed, including a minimum of the following:

Mitral valve procedures
o Full rotation on mitral valve (with color, pulsed and continuous wave
  Doppler) with attention to:
    o MR jet area and vena contracta
    o PISA (time permitting)
    o Continuous wave Doppler to assess post-procedure gradients
o LVOT PW (deep gastric) to calculate MR volume or MVA by CE
o Deep gastric SAX views of LV requested
    o Base (MV level)
    o Mid (papillary muscle level)
    o Apex (no papillary muscles seen)

Echocardiographic Analysis
TTE will be performed using parasternal, apical, and subcostal views according to a
standardized echo study protocol (see below).

1. *Quantification of MR*
   Quantification of mitral regurgitation will be performed according to the
   recommendations of the American Society of Echocardiography
   Recommendations for evaluation of the severity of native valvular regurgitation[1].
   The primary measure of mitral regurgitation will be effective regurgitant orifice
   area (EROA)[2-4].

   Two methods will be used to calculate EROA:

   a. PISA (Proximal Isovelocity Surface Area) method.

$$EROA = \frac{6.28 \ x \ radius^2 \ _x \ aliasing \ velocity}{Peak \ MR \ velocity}$$

   Using this technique, flow convergence area proximal to mitral regurgitant
   orifice visualized on echocardiography can be used to calculate the rate of
   mitral regurgitant flow and effective regurgitant orifice area (EROA).
   Regurgitant flow converges to the regurgitant orifice with multiple
   isovelocity hemispheric configurations. Manipulation of the color flow
   map identifies a proximal isovelocity surface area (PISA) at a certain
   aliasing velocity which is equal to the velocity of the PISA. The region of
   interest centered on the regurgitant orifice and PISA needs to be zoomed
   with color-flow imaging and the zero baseline of the color flow map is
   shifted downward to increase the radius of the PISA. It is recommended

that the aliasing velocity be set at 25-40 cm/s. PISA is calculated as 2 л x radius^2. Therefore, flow rate at the PISA is calculated as 6.28 x radius^2 x aliasing velocities. It is divided by peak MR velocity to obtain the EROA. Peak MR velocity is obtained by continuous-wave Doppler from the apex. Mitral regurgitant volume (RVol) is calculated by multiplying MR TVI by EROA.

b. Quantitative Flow method. Flow rate and stroke volume can also be estimated using a combination of PW Doppler and two-dimensional measurements . The hydraulic orifice formula states that the volume of blood crossing any valve-annulus is the product of the cross-sectional area (CSA) and the velocity time integral (VTI) of flow at the annulus. In the presence of mitral regurgitation, the diastolic flow across the mitral annulus represents both the systolic forward stroke volume and systolic regurgitant volume. Subtracting the forward stroke volume (across a nonregurgitant aortic or pulmonic valve) from this diastolic volume, yields the mitral RVol. The EROA is subsequently derived by dividing the RVol by the MR VTI.

The EROA will be used as the measure of MR severity, because (1) it is objective, and (2) because it is less load dependent than regurgitant volume. MR shall be graded by the following scale:

- o   <20 mm^2 = mild MR
- o   20-40 mm^2 = moderate MR
- o   >40 mm^2 = severe MR

In using MR for statistical calculations, the PISA value will be treated as a continuous variable. PISA has significant limitations (e.g. non-spherical or multiple jets), but will not be 'overcalled' for the purpose of this study. Additional secondary TTE measures of MR will be recorded as follows:

- a) color flow width and area
- b) intensity of the continuous-wave Doppler signal
- c) pulmonary venous flow contour
- d) peak early mitral inflow velocity
- e) vena contracta width
- f) regurgitant volume

2. *Quantification of Mitral Valve Area*
   Given the possibility of excessive tightening of the mitral annulus with mitral repair, it is important to remember to include the continuous wave Doppler of the mitral inflow (see Protocol 7iii) and if possible, add images of color inflow with baseline shift toward the ventricle, in order to see a diastolic PISA. Mitral valve area will be calculated by at least one of the following methods:
   a. Continuity equation: Limited if there is any mitral regurgitation or significant pulmonic or aortic regurgitation

   b. Planimetry: from parasternal short-axis view
   c. Color Doppler jet width in orthogonal planes: use of 4-chamber color
       Doppler (diastolic flow) and 2 or 3-chamber color Doppler (diastolic flow)
   d. Diastolic PISA: validated for MV area even in the setting of MR
   e. Pressure Halftime method

3. *Quantification of Left Ventricular Size and Function*
   a. Short axis dimension using the parasternal long-axis view of the LV just
       distal to the mitral valve and left ventricular outflow.
   b. Long-axis dimension from the apical view.
   c. LV sphericity will be calculated as the ratio of the LV long-axis
       dimension and the maximum short-axis dimension.
   d. LVEF will be measured by the biplane Simpson's volumetric method (a
       combination of apical four- and two-chamber views). The LV endocardial
       border will be traced contiguously from one side of the mitral annulus to
       the other side excluding the papillary muscles and trabeculations. LVEF
       will be determined from LV volumes using the formula *LVEF = (EDV-
       ESV)/EDV* where EDV = end-diastolic volume and ESV = end-systolic
       volume.
   e. If the definition of the LV endocardial border is not satisfactory for
       digitization following image acquisition, LVEF will be determined
       visually.
   f. LV end-systolic volume index shall be calculated using the biplane
       volumetric method as above, adjusted for body surface area (ml/m^2). [4,5]
   g. Radial strain and twist at different levels of the myocardium will be
       assessed from apical SAX, mid-papillary SAX and basal SAX views of
       the left ventricle.

4. *Assessment of Regional Left Ventricular Function and Viability Assessment*
   a. Baseline assessment: Regional left ventricular function will be reassessed
       echocardiographically using the ASE/ACC/AHA approved 17 segment
       model. For each segment, function will be scored as normal = 2,
       hypokinetic = 1, akinetic = 0, dyskinetic = - 1. A wall motion score
       (WMS) will be calculated as the sum of the individual segment scores and
       the wall motion score index calculated as WMS/17.
   b. Post-revascularization: Regional left ventricular function will be
       reassessed echocardiographically using the ASE/ACC/AHA approved 17
       segment model. As on the baseline study, for each segment, function will
       be scored as normal = 2, hypokinetic = 1, akinetic = 0, dyskinetic = - 1. A
       wall motion score (WMS) will be calculated as the sum of the individual
       segment scores and the wall motion score index calculated as WMS/17.
       WMSI (post-revascularization) – WMSI (baseline) will be used as a
       surrogate for viability. This assumes complete revascularization of all
       viable segments.

5. *Quantification of Right Ventricular Size and Function*

    a. Tricuspid annular plane systolic excursion (TAPSE) will be measured from apical 4-chamber view of the right ventricle (either by M-mode recording of the annular excursion or two-dimensional estimation).

    b. Tissue Doppler of the tricuspid annulus will be recorded for measurement of peak systolic velocity as well as diastolic E' and A'.

    c. Fractional area change: Diastolic and systolic areas will be measured by tracing the endocardial right ventricular cavity from the 4-chamber view, in diastole and systole. The difference between systolic and diastolic area, divided by diastolic area and multiplied by 100, is the fractional area change (%).

6. *Quantification of Tricuspid Regurgitation*

    a. Jet Area will be measured from multiple planes however the accuracy of semi-quantitative measure of TR severity (mild, moderate and severe) is greatest with central jets.

    b. Vena Contracta will be measured from multiple views noting that only a binary classification can be used with this measure (severe and not severe).

    c. PISA: semi-quantitative measure of TR severity (mild, moderate and severe) according to the ASE recommendations[1]:

Table 8 Echocardiographic and Doppler parameters used in grading tricuspid regurgitation severity

Parameter	Mild	Moderate	Severe
Tricuspid valve	Usually normal	Normal or abnormal	Abnormal/Flail leaflet/Poor coaptation
RV/RA/IVC size	Normal*	Normal or dilated	Usually dilated**
Jet area-central jets (cm²)§	< 5	5-10	> 10
VC width (cm)⌀	Not defined	Not defined, but < 0.7	> 0.7
PISA radius (cm)ψ	≤ 0.5	0.6-0.9	> 0.9
Jet density and contour–CW	Soft and parabolic	Dense, variable contour	Dense, triangular with early peaking
Hepatic vein flow†	Systolic dominance	Systolic blunting	Systolic reversal

CW, Continuous wave Doppler; *IVC*, inferior vena cava; *RA*, right atrium; *RV*, right ventricle; *VC*, vena contracta width.

* Unless there are other reasons for RA or RV dilation. Normal 2D measurements from the apical 4-chamber view: RV medio-lateral end-diastolic dimension ≤ 4.3 cm, RV end-diastolic area ≤ 35.5 cm² , maximal RA medio-lateral and supero-inferior dimensions ≤ 4.6 cm and 4.9 cm respectively, maximal RA volume ≤ 33 ml/m²(35;89).

** Exception: acute TR.

§ At a Nyquist limit of 50-60 cm/s. Not valid in eccentric jets. Jet area is not recommended as the sole parameter of TR severity due to its dependence on hemodynamic and technical factors.

⌀ At a Nyquist limit of 50-60 cm/s.

ψ Baseline shift with Nyquist limit of 28 cm/s.

† Other conditions may cause systolic blunting (eg. atrial fibrillation, elevated RA pressure).

7. *Additional Chamber and Valve Measurements*

    a. Left atrial dimensions: AP dimension and volume by biplane Simpson's rule and/or biplane area-length method.

    b. Mitral valve: tethering length and area, tethering angle, papillary muscle position and separation.

8. *Doppler*

    a. Intracardiac pressures:

        i. Pulmonary Artery (PA): PA systolic, diastolic and mean pressures will be estimated from TR velocity, PR end-diastolic velocity and

PR peak diastolic velocity (if possible). Pulmonary vascular
resistance will be estimated from TR velocity and PV VTI.

   ii. PCWP: estimated from E/E' ratio or E/Vp ratio.

9. *TEE Measurements*
The intra-operative TEE protocol is designed to confirm left ventricular function
and severity of mitral regurgitation, understanding that these measures may differ
due to changes in loading conditions from the pre-operative TTE.

   a. Pre and Post-operative qualitative assessment of left ventricular function
(see 4 above).

   b. Severity of mitral valve disease:
      iii. Mitral regurgitation jet area, vena contracta and PISA
      iv. Mitral valve area (see 2 above) if possible with peak and mean
gradients recorded.

Baseline Transthoracic Echo Assessment of Degree of MR
The assessment of the degree of mitral regurgitation will be based on an integrated
method as outlined by ASE document on Valvular Regurgitation outlined below. This is
a semi-quantitative technique and would grade MR categorically as: Mild; Moderate; or
Severe. The integrated method will use all aspects of the color Doppler jet including jet
area/Left atrial area ratio; vena contracta and effective orifice area (EROA) base on the
PISA method. In addition, supportive data such as left atrial size, E wave peak, and
presence of pulmonary vein flow reversal will be incorporated into the assessment.

1. COLOR DOPPLER CRITERIA

	Mild	**Moderate**	**Severe**
Color Flow Jet Area	< 20% of LA area)	20% to 39% of LA area	Large central jet (usually > 10 cm$_2$ or > 40% of LA area) or variable size wall-Impinging jet swirling in LA
Quantitative Parameters			
VC width (cm)	< 0.3	0.3 – 0.69	≥ 0.7
EROA (cm$_2$)	< 0.20	0.20-0.29 0.30-0.39	≥ 0.40

2. SUPPORTIVE CRITERIA

	Mild	**Moderate**	**Severe**
Structural Doppler			

Parameters			
LA size	Normal	Normal or dilated	Usually dilated
LV size	Normal	Normal or dilated	Usually dilated
Mitral leaflets or support apparatus	Normal or abnormal	Normal or abnormal	Abnormal/ Flail leaflet/ Ruptured papillary muscle
Mitral inflow - PW	A wave dominant	Variable	E wave dominant (E usually 1.2 m/s)
Jet density - CW	Incomplete or faint	Dense	Dense
Jet contour – CW	Parabolic	Usually parabolic	Early peaking-triangular
Pulmonary vein flow	Systolic dominance§	Systolic blunting§	Systolic flow reversal†

Examples:

Jet Area
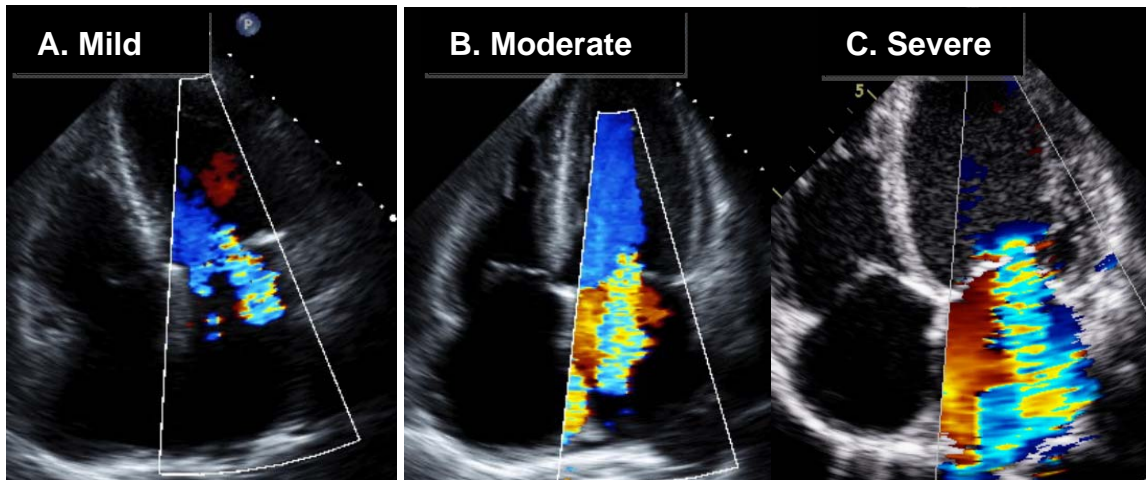
Measurement of Vena Contracta
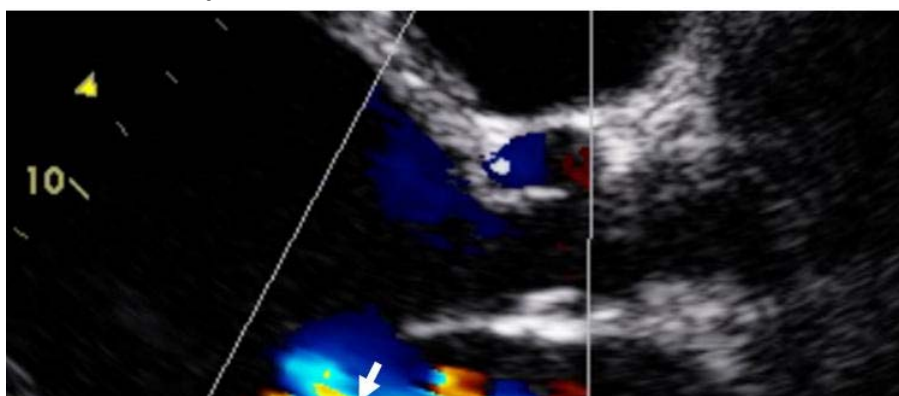
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APPENDIX II: NY HEART ASSOCIATION (NYHA) CLASSIFICATION

Class	Patient Symptoms
Class I (Asymptomatic)	No limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, or dyspnea (shortness of breath).
Class II (Mild)	Slight limitation of physical activity. Comfortable at rest, but ordinary physical activity results in fatigue, palpitation, or dyspnea.
Class III (Moderate)	Marked limitation of physical activity. Comfortable at rest, but less than ordinary activity causes fatigue, palpitation, or dyspnea.
Class IV (Severe)	Unable to carry out any physical activity without discomfort. Symptoms of cardiac insufficiency at rest. If any physical activity is undertaken, discomfort is increased.

APPENDIX III: CARDIOPULMONARY EXERCISE TESTING

Spirometric Cardiopulmonary Exercise Stress (CPX) Test: CPX presently provides the most accurate physiologic depiction of the response to aerobic exercise and quantitative measure of functional capacity. (1) CPX is also highly reliable and responsive to numerous interventions that positively impact physiologic systems involved in the response to physical stress (i.e. cardiovascular, pulmonary and skeletal muscle). Moreover, other variables exclusively obtained with ventilatory expired gas analysis, such as ventilatory efficiency and end tidal carbon dioxide, appear to provide clinically valuable information.(2-4) In the proposed cohort, changes in cardiac function are hypothesized to be significantly different between groups over time. Given the central role augmentation in cardiac output plays in the aerobic exercise response, the inclusion of CPX in this study is appropriate.

CPX testing will be conducted on a treadmill using a conservative ramping protocol, designed to be well tolerated by subjects with a low exercise capacity.(5) Patients will be asked not to eat for two hours prior to the test. Patients will, however, not discontinue their pharmacologic management. AHA/ACC absolute and relative contraindications to exercise testing will be used to guide CPX eligibility for each patient.(6;7) Patients will undergo identical CPX procedures at baseline and 6, 12 and 24 months post-intervention. Each individual subject will undergo serial CPX tests in the same laboratory utilizing the same equipment to decrease potential variability in the results. The ventilatory expired gas system will be calibrated prior to each test using known gas concentrations and a three-liter syringe. Unless the study is terminated for safety reasons, all studies will be performed until limited by symptoms (fatigue, dyspnea and/or angina). AHA/ACC relative and absolute exercise test termination criteria will be followed.(6;7) EKG, blood pressure, rating of subjective symptoms (exertion/dyspnea/angina), oxygen consumption (VO_2), and carbon dioxide production (VCO_2) will be monitored at rest, during exercise and into recovery. Maximal heart rate, heart rate recovery, peak VO_2 (in $mlO_2 \bullet kg^{-1} \bullet min^{-1}$), peak respiratory exchange ratio (RER-VCO_2/VO_2), ventilatory efficiency (VE/VCO_2 slope) and end-tidal CO_2 ($P_{ET}CO_2$) at rest, anaerobic threshold and maximal exercise will all be calculated. Anaerobic threshold will also calculated by the V-slope technique and confirmed by the ventilatory equivalents method.(1) Results will be interpreted by a CPX core lab.

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APPENDIX IV: CANADIAN CV SOCIETY CLASSIFICATION (CCSC)

Canadian Cardiovascular Society Classification

Overview:

The Canadian Cardiovascular Society Classification of angina pectoris separates patients with anginal symptoms into groups based on the severity of their symptoms. The classification uses the extent of limitation on daily activities and the kind of physical activity which precipitates the anginal episode.

Clinical Findings	Features	Grade
No limitation of ordinary activity	Ordinary physical activity (such as walking or climbing stairs) does not cause angina. Angina may occur with strenuous rapid or prolonged exertion at work or recreation.	I
Slight limitation of ordinary activity	Angina may occur with • walking or climbing stairs rapidly; • walking uphill; • walking or stair climbing after meals or in the cold in the wind or under emotional stress, or only during the few hours after awakening. • walking more than 2 blocks on the level at a normal pace and in normal conditions • climbing more than 1 flight of ordinary stairs at a normal pace and in normal conditions	II
Marked limitation of ordinary physical activity	Angina may occur after • walking 1-2 blocks on the level or • climbing 1 flight of stairs in normal conditions at a normal pace	III
Unable to carry on any physical activity without discomfort	Angina may be present at rest.	IV

Campeau L. Grading of angina pectoris (Letter to the Editor). Circulation. 1976; 54: 522-523.

APPENDIX V: CORONARY REVASCULARIZATION ASSESSMENT

Pre-operative evaluation and post-operative state for each coronary territory must be identified as defined.

Coronary Territory*	Pre-op Evaluation				Post-op		
	No CAD	Bypassable CAD	Non-Bypassable CAD		Not Bypassed	Bypassed, No Residual CAD	Bypassed, Residual CAD
LAD proximal							
LAD distal							
Proximal Diagonal							
Distal Diagonal							
Proximal Circumflex							
Distal Circumflex							
Distal Dominant Circumflex							
Right Posterolateral							
Right Posterior Descending							

*For Left Main indicate distal coronary territories intended to be grafted for treatment

Coronary territory revascularization status will be compared to regional wall motion assessed echocardiographically as defined schematically below.

FIGURE 1. *Diagram of regional wall segments and distribution of coronary perfusion. LAX, long axis; SAX PM, short axis at papillary muscle level; 4C, four chamber; 2C, two chamber; ANT, anterior; SEPT, septal; POST, posterior; LAT, lateral; INF, inferior.*
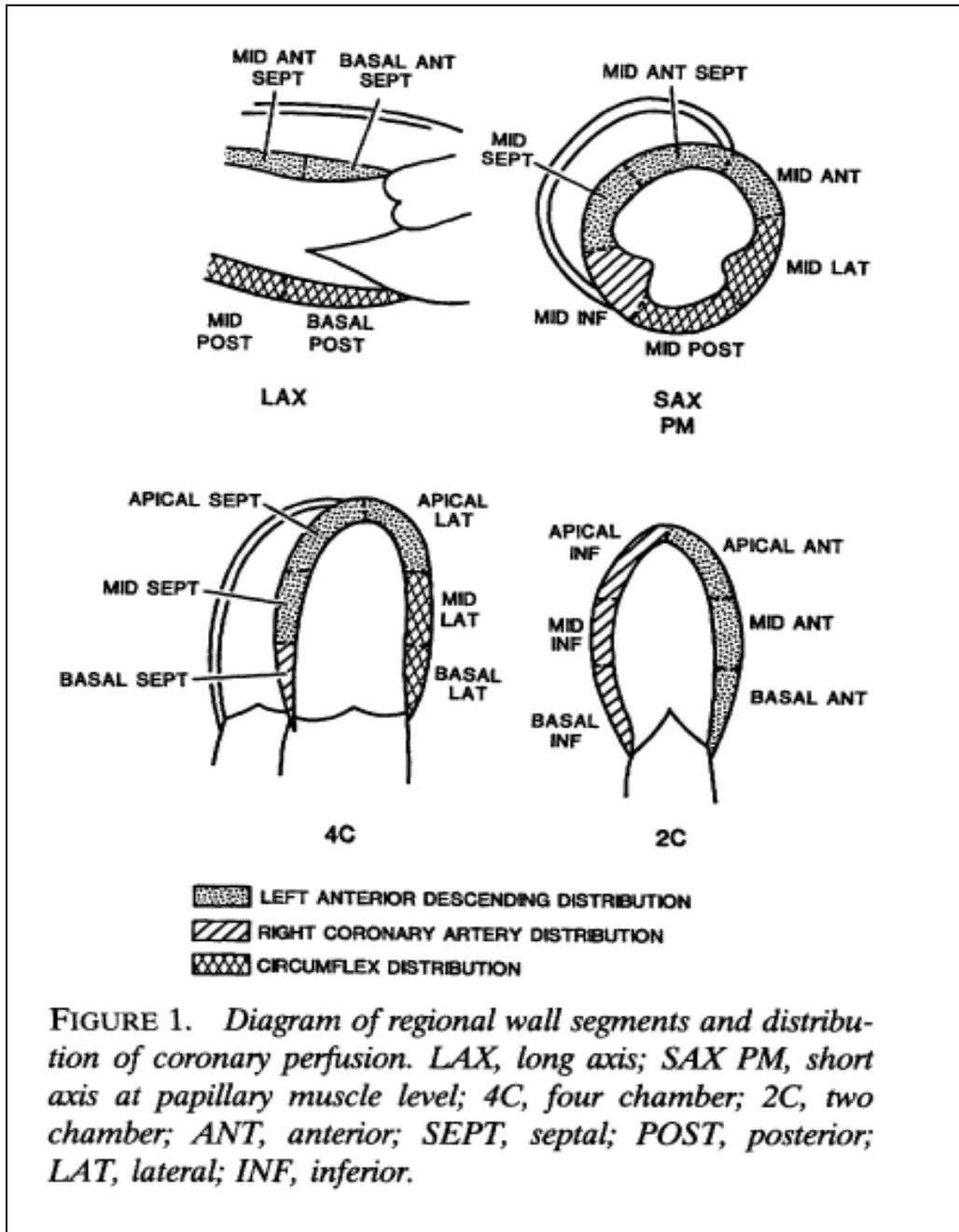
APPENDIX VI: QUALITY OF LIFE MEASURES

MINNESOTA LIVING WITH HEART FAILURE QUESTIONNAIRE

Instructions for Use

1) Patients should respond to the questionnaire prior to other assessments and interactions that may bias responses. You may tell the patient that you would like to get their opinion before doing other medical assessments.

2) Ample, uninterrupted time should be provided for the patient to complete the questionnaire

3) The following instructions should be given to the patient each time the questionnaire is completed.

   a) Read the introductory paragraph at the top of the questionnaire to the patient.

   b) Read the first question to the patient:

   "Did your heart failure prevent you from living as you wanted during the last month by causing swelling in your ankles or legs?"

   Tell the patient,

   "If you did not have any ankle or leg swelling during the past month, you should circle the zero after this question to indicate that swelling was not a problem during the past month."

   Explain to the patient that if he or she did have swelling that was caused by a sprained ankle or some other cause that was definitely not related to heart failure he or she should also circle the zero.

   Tell the patient,

   "If you are not sure why you had the swelling or think it was related to your heart condition, then rate how much the swelling prevented you from doing things you wanted to do and from feeling the way you would like to feel."

   In other words, how bothersome was the swelling?

   Show the patient how to use the 1 to 5 scale to indicate how much the swelling affected his or her life during the past month – from very little to very much.

4) Let the patient read and respond to the other questions. The entire questionnaire may be read directly to the patient if one is careful not to influence responses by verbal or physical cues.

5) Check to make sure the patient has responded to each question and that there is only one answer clearly marked for each question. If a patient elects not to answer a specific question(s) indicate so on the questionnaire.

6) Score the questionnaire by summating the responses to all 21 questions.

In addition, physical (items 2, 3, 4, 5, 6, 7, 12, and 13) and emotional (items 17, 18, 19, 20 and 21) dimensions of the questionnaire have been identified by factor analysis and may be examined to further characterize the effect of heart failure on a patients life.

Minnesota Living with Heart Failure® Questionnaire

The following questions ask how much your heart failure (heart condition) affected your life during the past month (4 weeks). After each question, circle the 0, 1, 2, 3, 4 or 5 to show how much your life was affected. If a question does not apply to you, mark the 0 after that question. Remember to think about ONLY THE LAST MONTH.

Did your heart failure prevent you from living as you wanted **during the past month (4 weeks)** by. . .

	No	Very Little				Very Much
MLHF1. causing swelling in your ankles, legs?	0 ☐	1 ☐	2 ☐	3 ☐	4 ☐	5 ☐
MLHF2. making you sit or lie down to rest during the day?	0 ☐	1 ☐	2 ☐	3 ☐	4 ☐	5 ☐
MLHF3. making your walking about or climbing stairs difficult?	0 ☐	1 ☐	2 ☐	3 ☐	4 ☐	5 ☐
MLHF4. making your working around the house or yard difficult?	0 ☐	1 ☐	2 ☐	3 ☐	4 ☐	5 ☐
MLHF5. making your going places away from home difficult?	0 ☐	1 ☐	2 ☐	3 ☐	4 ☐	5 ☐
MLHF6. making your sleeping well at night difficult?	0 ☐	1 ☐	2 ☐	3 ☐	4 ☐	5 ☐
MLHF7. making your relating to or doing things with your friends or family difficult?	0 ☐	1 ☐	2 ☐	3 ☐	4 ☐	5 ☐
MLHF8. making your working to earn a living difficult?	0 ☐	1 ☐	2 ☐	3 ☐	4 ☐	5 ☐
MLHF9. making your recreational pastimes, sports, or hobbies difficult?	0 ☐	1 ☐	2 ☐	3 ☐	4 ☐	5 ☐
MLHF10. making your sexual activities difficult?	0 ☐	1 ☐	2 ☐	3 ☐	4 ☐	5 ☐
MLHF11. making you eat less of the foods you like?	0 ☐	1 ☐	2 ☐	3 ☐	4 ☐	5 ☐
MLHF12. making you short of breath?	0 ☐	1 ☐	2 ☐	3 ☐	4 ☐	5 ☐
MLHF13. making you tired, fatigued, or low energy?	0 ☐	1 ☐	2 ☐	3 ☐	4 ☐	5 ☐
MLHF14. making you stay in a hospital?	0 ☐	1 ☐	2 ☐	3 ☐	4 ☐	5 ☐
MLHF15. costing you money for medical care?	0 ☐	1 ☐	2 ☐	3 ☐	4 ☐	5 ☐
MLHF16. giving you side effects from treatments?	0 ☐	1 ☐	2 ☐	3 ☐	4 ☐	5 ☐
MLHF17. making you feel you are a burden to your family or friends?	0 ☐	1 ☐	2 ☐	3 ☐	4 ☐	5 ☐
MLHF18. making you feel a loss of self-control in your life?	0 ☐	1 ☐	2 ☐	3 ☐	4 ☐	5 ☐
MLHF19. making you worry?	0 ☐	1 ☐	2 ☐	3 ☐	4 ☐	5 ☐
MLHF20. making it difficult for you to concentrate or remember things?	0 ☐	1 ☐	2 ☐	3 ☐	4 ☐	5 ☐
MLHF21. making you feel depressed?	0 ☐	1 ☐	2 ☐	3 ☐	4 ☐	5 ☐

DUKE ACTIVITY STATUS INDEX (DASI)

Administration

While the DASI was designed to be self-administered, consistency and reliability of answers and completeness of the data are enhanced when trained interviewers administer the questionnaire. As in all interviewing situations, interviewers should be blinded to relevant clinical patient information.

General Considerations

Items are scored in one of four categories: "Yes, with no difficulty," "Yes, but with some difficulty," "No, I couldn't do this," and "Don't do it for other reasons." If a person refuses to answer a particular question, use "Refuses to answer: RF." Remember, patients are being asked what they are able to do, not what they think they could do.

If a patient has had a sudden deterioration just prior to baseline administration of the DASI (e.g., unstable angina), then the responses should reflect what s/he could do in the (stable) period just before deterioration.

If a patient has had a stroke and cannot do certain activities (e.g., walk up a flight of stairs) then his/her answers should be coded "No, I couldn't do that," regardless of the cause of the physical impairment. However, if a patient is not doing activities because of doctor's orders, or if a patient does not know if s/he could do the activity, the answer should be coded "Don't do for other reasons."

Allow the patient to define "difficulty." If a patient responds that s/he could do something, ". . .but," that answer should be entered as "Yes, with difficulty."

Finally, watch for inconsistencies in a patient's responses and ask for clarification if needed. For example, if a patient answers that they could easily walk a block, but could not climb a flight of stairs, the interviewer can ask, "You stated that you would have no difficulty walking a block, but could not climb a flight of stairs. Is that what you meant to say?" However, never lead a patient to change an answer, and always enter his or her answer.

The Questions

Could you...	Yes, with no difficulty	Yes, but with some difficulty	No, I couldn't do this	Don't do it for other reasons
1. take care of yourself, that is, eating, dressing, bathing, and using the toilet?	1	2	3	4
2. walk indoors, such as around your house?	1	2	3	4
3. walk a block or two on level ground?.	1	2	3	4
4. climb a flight of stairs or walk up a hill?	1	2	3	4
5. run a short distance?	1	2	3	4
6. do light work around the house like dusting or washing dishes?	1	2	3	4
7. do moderate work around the house like vacuuming, sweeping floors, or carrying in groceries?	1	2	3	4
8. do heavy work around the house like scrubbing floors or lifting or moving heavy furniture?	1	2	3	4
9. do yard work like raking leaves, weeding, or pushing a power mower?	1	2	3	4
10. have sexual relations?	1	2	3	4
11. participate in moderate recreational activities like golf, bowling, dancing, doubles tennis, or throwing a baseball or football?	1	2	3	4
12. participate in strenuous sports like swimming, singles tennis, football, basketball, or skiing?	1	2	3	4

Notes for Particular Questions

Question 1: This question asks if the patient can do all the activities listed (eat, dress, bathe and use the toilet). If the patient is unable to do any of these activities, the question should be scored "No, I couldn't do it."

Questions 2-5: These questions deal with ambulation and increase in difficulty. In general, later items should present more difficulty to patients than earlier items.

Questions 6 through 9: These questions ask if the patient can do light/moderate/heavy housework. If the patient does not do housework or yardwork because someone else does it for him or her, but the patient knows that s/he could do similar activities, the answer should be "Yes." Unlike Question 1, a patient does not need to perform all the items listed in the questions; s/he need only perform one of the activities on the list or one closely related to it in effort.

Question 10: This question asks if the patient can have sexual relations. If the patient is widowed, divorced or separated, the answer should be coded, "Don't do for other reasons."

Questions 11 and 12: These questions ask if the patient participates in recreational activities. If the patient is fairly sedentary and has not participated in sports in several years, and has not done an activity of that difficulty prior to enrollment, the answer should be coded as "Don't do for other reasons." In rare cases, a patient may wonder if a related task, not on the list would count (e.g., a patient who plays rugby could answer "Yes" to Question 12). Sport hunting, fishing, brisk walking for 2 miles a day, lifting 20 pound weights without difficulty are examples of moderate activity in Question 11. A 10 minute mile pace of jogging or doing one arm pull-ups is a legitimate "strenuous sport" for Question 12. In such cases, the patient should judge whether the activity is "like/comparable" to those on the list. Unlike Question 1, a patient does not need to perform all the items listed in the questions; s/he need only perform one of the activities on the list or one closely related to it in effort.

SHORT FORM – 12 (SF-12)

INSTRUCTIONS: This survey asks for your views about your health. This information will help keep track of how you feel and how well you are able to do your usual activities.

Please answer every question by marking one box. If you are unsure about how to answer, please give the best answer you can.

1. In general, would you say your health is:

Excellent	Very good	Good	Fair	Poor
☐	☐	☐	☐	☐

The following items are about activities you might do during a typical day. Does <u>your health now limit you</u> in these activities? If so, how much?

		Yes, Limited A Lot	Yes, Limited A Little	No, Not Limited At All
2.	Moderate activities, such as moving a table, pushing a vacuum cleaner, bowling, or playing golf	☐	☐	☐
3.	Climbing several flights of stairs	☐	☐	☐

During the <u>past 4 weeks</u>, have you had any of the following problems with your work or other regular daily activities <u>as a result of your physical health</u>?

		YES	NO
4.	Accomplished less than you would like	☐	☐
5.	Were limited in the kind of work or other activities	☐	☐

During the <u>past 4 weeks</u>, have you had any of the following problems with your work or other regular daily activities <u>as a result of any emotional problems</u> (such as feeling depressed or anxious)?

		YES	NO
6.	Accomplished less than you would like	☐	☐
7.	Didn't do work or other activities as carefully as usual	☐	☐

8. During the <u>past 4 weeks</u>, how much did <u>pain</u> interfere with your normal work (including both work outside the home and housework)?

Not at all	A little bit	Moderately	Quite a bit	Extremely
☐	☐	☐	☐	☐

These questions are about how you feel and how things have been with you <u>during the past 4 weeks</u>. For each question, please give the one answer that comes closest to the way you have been feeling. How much of the time during the <u>past 4 weeks</u> -

		All of the Time	Most of the Time	A Good Bit of the Time	Some of the Time	A Little of the Time	None of the Time
9.	Have you felt calm and peaceful?	☐	☐	☐	☐	☐	☐
10.	Did you have a lot of energy?	☐	☐	☐	☐	☐	☐
11.	Have you felt downhearted and blue?	☐	☐	☐	☐	☐	☐

12. During the <u>past 4 weeks</u>, how much of the time has your <u>physical health or emotional problems</u> interfered with your social activities (like visiting with friends, relatives, etc.)?

All of the time	Most of the time	Some of the time	A little of the time	None of the time
☐	☐	☐	☐	☐

EUROQoL 5-D QUESTIONNAIRE

Check <u>one</u> box for each of the following six health dimensions.

Mobility
I have no problems in walking about ❑
I have some problems in walking about ❑
I am confined to bed ❑

Self-Care
I have no problems with self-care ❑
I have some problems washing or dressing myself ❑
I am unable to wash or dress myself ❑

Usual Activities (*e.g. work, study, housework, family or leisure activities*)
I have no problems with performing my usual activities ❑
I have some problems with performing my usual activities ❑
I am unable to perform my usual activities ❑

Pain/Discomfort
I have no pain or discomfort ❑
I have moderate pain or discomfort ❑
I have extreme pain or discomfort ❑

Anxiety/Depression
I am not anxious or depressed ❑
I am moderately anxious or depressed ❑
I am extremely anxious or depressed ❑

**Compared with my general level of health over the past 12 months,
my health state today is:**
Better ❑
Much the same ❑
Worse ❑

**Best
imaginable
health state**

To help people say how good or bad a health state is
we have drawn a scale (rather like a thermometer) on
which the best state you can imagine is marked by 100

and the worst state you can imagine is marked by 0.

We would like you to indicate on this scale how good or
bad is your own health today, in your opinion.
Please do this by drawing a line from the box below
to whichever point on the scale indicates how good or
bad your current health state is.

100

┌─────────────┐
│ **Your own**   │
│ **health state** │
│   **today**   │
│   │
└─────────────┘

**Worst
imaginable
health state**

APPENDIX VII: NEUROCOGNITIVE TESTING

HOPKINS VERBAL LEARNING TEST TRIAL INSTRUCTIONS

Trial 1

Say the following:

> **I am going to read a list of words to you. Listen carefully, because when I'm through, I'd like you to tell me as many of the words as you can remember. You can tell them to me in any order. Are you ready?**

- Repeat or paraphrase the instructions if necessary
- Read the words at the rate of approximately one word every 2 seconds
- If the individual does not spontaneously begin reporting words after the last word is read, say the following:

> **OK. Now tell me as many of those words as you can remember**

Record the responses verbatim (including repetitions and intrusions) in the Trial 1 column. When the individual indicates no more words can be recalled, proceed to Trial 2.

Trial 2

Say the following:

> **Now we are going to try it again. I am going to read the same list of words to you. Listen carefully, and tell me as many of the words as you can remember, in any order, including all the words you told me the first time.**

Use the same procedure as in Trial 1 to record the responses in the column for Trial 2. Then proceed to Trial 3.

Trial 3

Say the following:

I am going to read the list one more time. As before, I'd like you to tell me as many of the words as you can remember, in any order, including all the words you've already told me.

Record the responses in the column for Trial 3 using the same procedure as in the previous trials.

NOTE: *Do not tell the respondent that recall of the words will be tested later.*

Delayed Recall Trial Instructions

After the 20 –25 minute delay, say the following:

Do you remember that list of words you tried to learn before?

If the response is "No," remind the individual that you read the list three times and that he or she was asked to recall the words each time. Say the following:

Tell me as many of those words as you can remember.

Delayed Recognition Trial Instructions

The delayed recognition (forced choice) trial is administered immediately after the Delayed Recall trial. Say the following:

Now I am going to read a longer list of words to you. Some of them are words from the original list, and some are not. After I read each word, I'd like you to say "Yes" if it was on the original list, or "No" if it was not.

Read the words of the Delayed Recognition trial list in numerical order. Allow the individual as much time as needed to respond. You may use the prompt, **"Was horse on**

the list? Yes or no?" The individual must give you a response for every word. If the individual is not sure, ask for a guess.

TRAIL MAKING TEST INSTRUCTIONS

Part A:

Give the subject a pencil and the test page and say: *"On this page are some numbers."* Point to some numbers. *"Begin at number 1"* Point to number 1. "*and draw a line from 1 to 2, "* Point to number 2. *"2 to 3,"* Point to 3. *"3 to 4,"* Point to 4. "*and so on, in order, until you reach the end."* Point to the circle marked "end". *"Draw the lines as fast as you can. Ready ------- Begin!"* If the subject completes the sample item correctly demonstrating his/her understanding say: *"Good! Let's try the next one."* Turn the paper over and give Part A of the test. If the person makes a mistake on sample A, point out the error and explain it.

The following explanations of mistakes serve as illustrations.

1.   "You started with the wrong circle. This is where you start (point to number one)"

2.   *"You skipped this circle (point to the circle the subject omitted). You should go from number 1* (point) *to 2* (point)*, to 3* (point)*, and so on, until you reach the circle marked "end"* (point)*."*

If the subject cannot complete Sample A, take his/her hand and guide the pencil, <u>using the eraser end</u>, through the trail. Then say: *"Now you try it."*

Return the pencil to the subject with the point down and say: *"Remember, begin at number 1 (point) and draw a line from 1 to 2 (point to 2), 2 to 3 (point to 3), 3 to 4 (point to 4) and so on, in order, until you reach the circle marked "end" (point). Do not skip around, but go from one number to the next in the proper order. Remember to work as fast as you can. Ready --- Begin!"*

If the subject succeeds this time proceed to Part A. If the subject still has difficulty, repeat the above procedure until the task is completed successfully or it becomes evident that the subject cannot do the task.

After the subject has completed Sample A, turn the paper over to Part A and say: *"On the page are numbers. Do this the same way. Begin at number 1 (point 1) and draw a line from 1 to 2 (point to 2), 2 to 3 (point to 3), 3 to 4 (point to 4), and so on, in order, until you reach the end (point). Remember to work as fast as you can. Ready ---Begin!"*

Using a stopwatch, start timing as soon as the instruction is given to begin. The examiner must watch the subject closely in order to catch any errors as soon as they are made. If the subject makes an error, call it to his/her attention immediately, return the subject's pencil to the last correct circle, and continue the test from that point. Do not stop timing while correcting the subject's error.

After the subject completes Part A, take the test sheet and record the time in seconds. Errors contribute to evaluation of performance principally by increasing the total performance time.

Trails (Part B):

Next, tell the patient: *"That's fine. Now we'll try another one."* Place the <u>sample</u> side of Part B on the table in front of the subject, in the same position as the sheet for Part A was placed. Point to the sample and say:

"On this page are some numbers and letters. Begin at 1 (point) and draw a line from 1 to A" (Point to A *) "A to 2,"*(Point to 2), *"2 to B"* (point to B), *"B to 3"* (point to 3), *"3 to C"* (point to C)**,** *"and so on, in order, until you reach the end"* (point to the circle marked "end").

Then say: *"Remember, first you have a number"* (point to 1), *"then a letter"* (point to A), *"then a number"* (point to 2), *"then a letter"* (point to B), *"and so on. Draw the lines as fast as you can. Ready--- Begin!"*

If the subject completes the sample B correctly say: *"Good! Let's try the next one."*
Proceed immediately to Part B. If the subject makes a mistake on sample B, point out the error and explain why it is incorrect. The following explanations of mistakes serve as illustrations:

1.   *"You started with the wrong circle. This is where you start (point to number 1)"*

2.   *"You skipped this circle"* (point to the circle the subject omitted). *"You should go from 1"* (point to 1) *"to A"* (point to A), *"A to 2"* (point to 2), *"2 to B"* (point to B), *"B to 3"* (point to 3) *"and so on until you reach the circle marked 'end'.* (point)

If the subject cannot complete Sample B, take his/her hand and guide the pencil, <u>using the eraser end</u>, through the circles. Then say: *"Now you try it. Remember, you begin at number 1"* (point) *"and draw a line from 1 to A"* (point to A), *"A to 2"* (point to 2), *"2 to B"* (point to B), *"B to 3"* (point to 3), *"and so on until you reach the circle marked "end"* (point). *"Ready --- Begin!"*

If the subject succeeds this time, go on to Part B. If not repeat the procedure until the task is performed successfully or it becomes evident that the subject cannot do the task.

After the subject has completed the sample, turn the paper over to Part B and say:

"On this page are both numbers and letters. Do this the same way. Begin at number 1" (point to 1) *"and draw a line from 1 to A"* (point to A), *"A to 2"* (point to 2), *"2 to B"* (point to B), *"B to 3"* (point to 3), *"3 to C"* (point to C), *"and so on, in order, until you reach the end"* (point to the circle marked "end*"). "Remember, first you have a number"* (point to 1), *"then a letter"* (point to A), *"then a number"* (point to 2), *"then a letter"* (point to B), *"and so on. Do not skip around, but go from one circle to the next in the proper order. Draw the lines as fast as you can. Ready ---Begin!"*

Using the stopwatch, start timing as soon as the subject is told to begin. Remember to be alert for mistakes. If the subject makes an error, point it out immediately, return the subject to the last correct circle, and continue the test from that point. Do not stop timing.

After the subject completes Part B, take the test sheet and record the time in seconds. Errors contribute to the evaluation of the performance principally by increasing the total performance time.

Scoring

Part A and Part B are scored separately. The score for each part is the number of seconds required to complete the task.

DIGIT SPAN INSTRUCTIONS

Digit Span (Wechsler Adult Intelligence Scale - Third Edition)

Administration Rules:

Administer Digits Backward even if participant scores a 0 on Digits Forward.

Read digits at a rate of 1 per second in a loud, even voice, dropping the tone of your voice at the end of the string of digits, as if you were ending a sentence.

Write down the numbers that the participant says, in the order he/she repeats them. Do not let the participant know whether or not the responses are correct.

The participant is allowed to change his/her response. If the participant changes the response on one of the items, write 'participant changed mind' next to the correction.

Digits Forward: State to the participant:

"I am going to say some numbers. Listen carefully, and when I stop, say them right after me."

Digits Backward: State to the participant:

"Now I am going to say some numbers, and this time when I stop I want you to say them

backward. For example, if I say 7-1-9 what would you say?"

If participant says 9-1-7, say *"That's right."* and continue with test

If participant is incorrect, **say** *"No, you would say 9-1-7. I said 7-1-9, so to say it backward,*

you would say 9-1-7. Now try these numbers. Remember, you are to say them

backward. 3-4-8." Do not provide any assistance on this example or any of the items.

Whether or not the participant responds correct (i.e., 8 – 4 – 3), proceed to Trial 1 of Item 1.

Scoring:

Each item is scored 0, 1, or 2 points as follows:

- o 2 points if the participant passes both trials
- o 1 point if the participant passes only one trial
- o 0 points if the participant fails both trials

Discontinuation Rule:

Digits Forward and Digits Backward

Discontinue test when participant obtains a trial score of 0 on both trials of any item.

DIGIT SYMBOL SUBSTITUTION TEST INSTRUCTIONS

DIGIT SYMBOL SUBSTITUTION TEST (Wechsler Adult Intelligence Scale - Third Edition)

- o A smooth drawing surface must be provided. If the table has a rough surface, the Record Form should be placed on a clipboard, a piece of cardboard, or another flat surface.
- o To introduce the subtest, say:

  In this section, I'm going to ask you to copy some symbols.

- o If examinees ask what they should do if they make a mistake, encourage them to continue to work as fast as they can. However, do not discourage examinees from making spontaneous corrections unless they do so repeatedly and it impedes their performance.
- o If, after completing a row, an examinee to start at the beginning of the row and not to skip any.

Item Instructions

Turn to the Digit Symbol-Coding page. Hand the examinee a pencil without an eraser, point to the key above the test items, and say:

Look at these boxes. Notice that each has a number in the upper part and a special mark in the lower part. Each number has its own mark.

Point to 1 and its mark in the key, then 2 and its mark. Then point to the seven squares located to the left of the heavy black line and say:

Now look down here where the squares have numbers in the top part but the squares at the bottom are empty. In each of the empty squares, put the mark that should go there. Like this:

Point to the first Sample Item, then point back to the key to show its corresponding mark, and say:

Here is a 2; the 2 has this mark. So I put it in this empty square, like this:

Write in the symbol. Point to the second Sample Item and say:

Here is a 1; the 1 has this mark (point to the second Sample Item, then to the mark below the 1 in the key)**, so I put it in this square.**

Write in the symbol.

Point to the third Sample Item and say:

This number is a 3; the 3 has this mark (point to the third square and to the mark below the 3 in the key)**. So I put in the square** (write in the symbol)**.**

After marking the first three Sample Items, say:

Now you fill in the squares up to this heavy line.

If the examinee makes an error on any of the Sample Items, correct the error immediately and review the use of the key. Continue to provide help if needed. Do not proceed with the subtest until the examinee clearly understands the task.

When the examinee completes a Sample Item correctly, offer encouragement by saying **Yes** or **Right.** When all the Sample Items have been completed, say:

Now you know how to do them. When I tell you to start, you do the rest of them.

Point to the first square to the right of the heavy line and say:

Begin here and fill in as many squares as you can, one after the other without skipping any. Keep working until I tell you to stop. Work as quickly as you can without making any mistakes.

Sweep across the first row with your finger and say:

When you finish this line, go on to this one.

Point to first square in the second row. Then point to the heavy black line and say:

Go ahead.

***Begin timing.

If the examinee omits an item or starts to do only one type (e.g., only the 1's), say:

Do them in order. Don't skip any.

Point to the first item omitted and say:

Do this one next.

Provide no further assistance except to remind the examinee to continue until instructed

to stop.

At the end of 120 seconds, say: **Stop**

MEDICAL COLLEGE OF GEORGIA (MCG) COMPLEX FIGURES TEST

INSTRUCTIONS

MCG Complex Figures (A compendium of neuropsychological tests (3rd Edition).

Strauss E, Sherman EMS, Spreen O. New York, USA: Oxford University Press, 2006:

1216)

Present figure to participant and ask participant to replicate it as precisely as possible on

an 8.5 in. by 11 in. sheet of paper. Once completed, remove the figure. Ask the

participant to reproduce the figure following a 3 minute delay (immediate recall) and a 30

minute delay (delayed recall). There are no time limits for all figural reproductions.

SCORING:

Consider each of the eighteen units separately. Appraise accuracy of each unit and

relative position within the thole of the design. For each unit count as follows:

|	
Correct, placed properly	2 points
Correct, placed poorly	1 point
Distorted or incomplete but recognizable, placed properly	1 point
Distorted or incomplete but recognizable, placed poorly	1/2 point
Absent or not recognizable	0 points
Maximum total points	36 points

FIGURE 1:
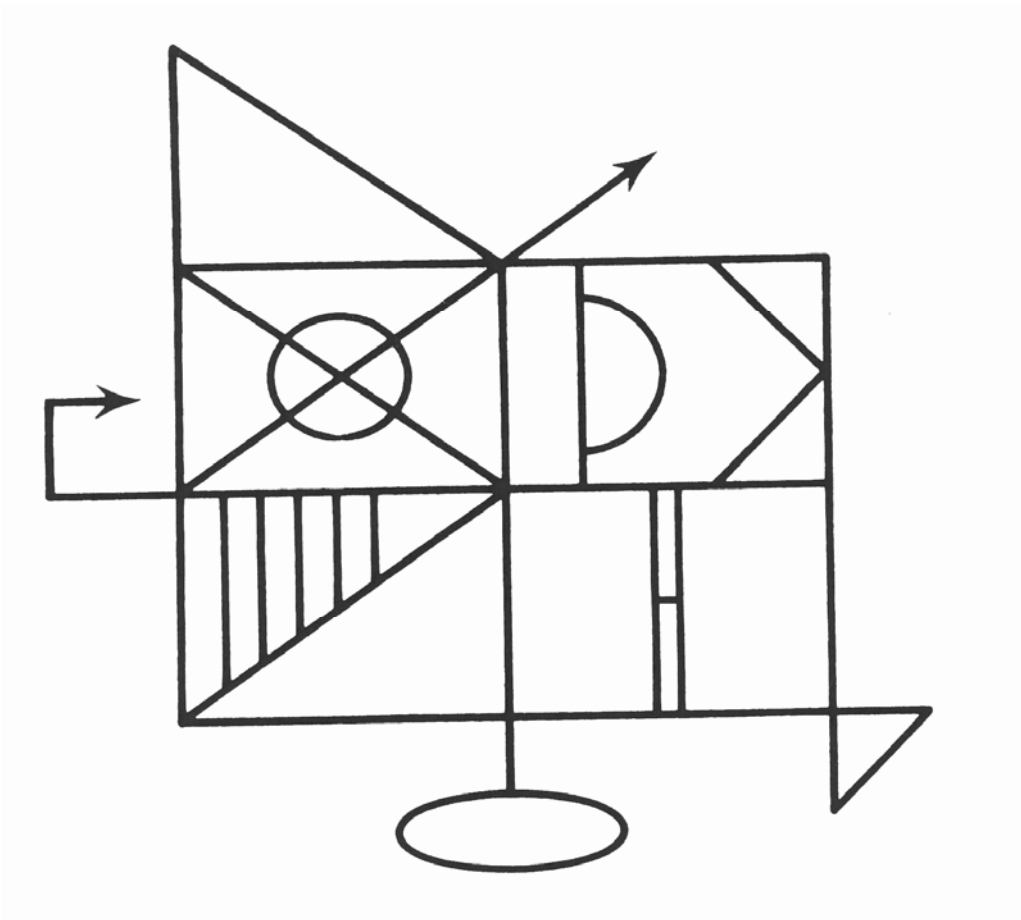
1. Large rectangle
2. Vertical midline of 1
3. Horizontal midline of 1
4. Small triangle on right hand corner of 1
5. Oval and attaching line at the bottom of 1
6. Bent arrow to the left of 1
7. Triangle above left upper quadrant of 1
8. Tilted arrow at top of 1
9. Diagonal in upper left quadrant of 1
10. Second diagonal in left quadrant of 1
11. Circle in upper left quadrant of 1
12. Diagonal in lower left quadrant of 1
13. Five vertical lines extending above 12
14. Vertical lines and horizontal connection ("H") in lower right quadrant of 1
15. Vertical line in right upper quadrant of 1
16. Semicircle attached to the right of 15
17. Diagonal line at upper right corner of 1
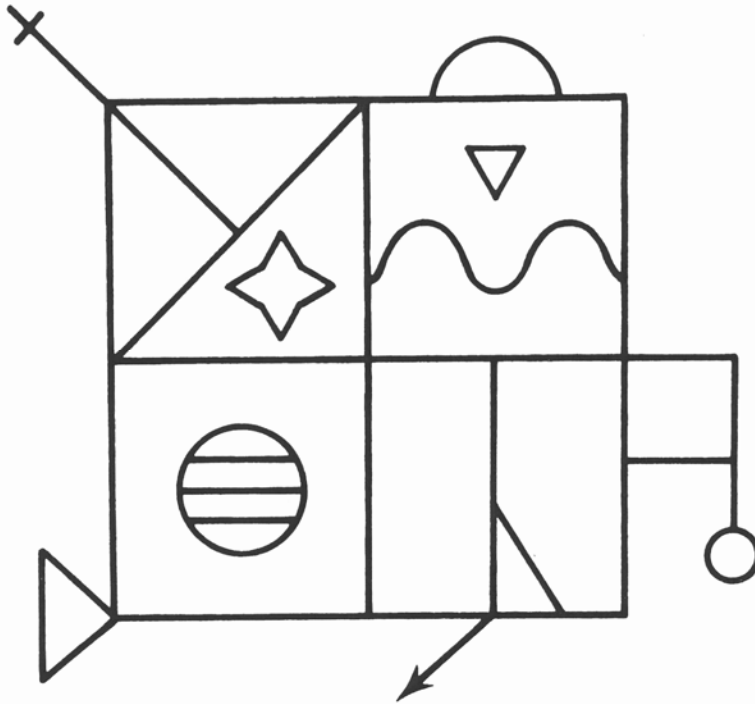18. Diagonal line extending from 17 to 3

FIGURE 2:
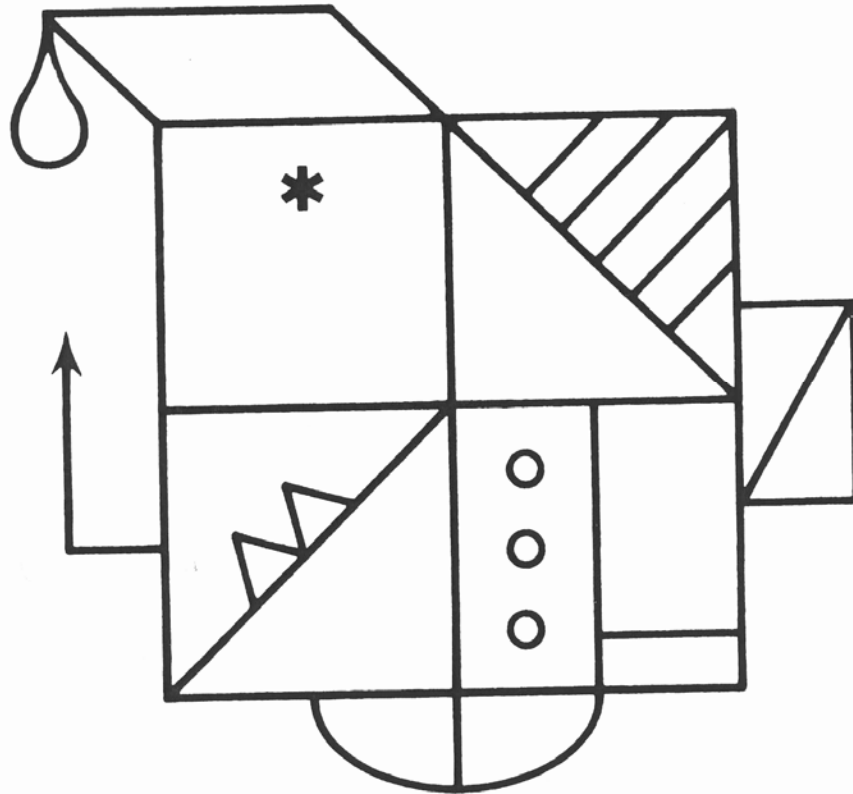
1. Large square
2. Vertical midline for 1
3. Horizontal midline for 1
4. Asterisk in the upper left quadrant of 1
5. Diagonal in the lower left quadrant of 1
6. Two triangles attached to 5
7. Three circles in the lower right quadrant of 1
8. Vertical midline in the lower right quadrant of 1
9. Horizontal line to the right of 8
10. Diagonal line in the upper right quadrant of 1
11. Five diagonal lines perpendicular to 10
12. Small rectangle to the right of 1
13. Diagonal line in 12
14. Semicircle at the base of 1
15. Vertical line in 14
16. Angled arrow to the left of 1
17. Parallelogram above 1
18. Teardrop attached to 17

FIGURE 3:
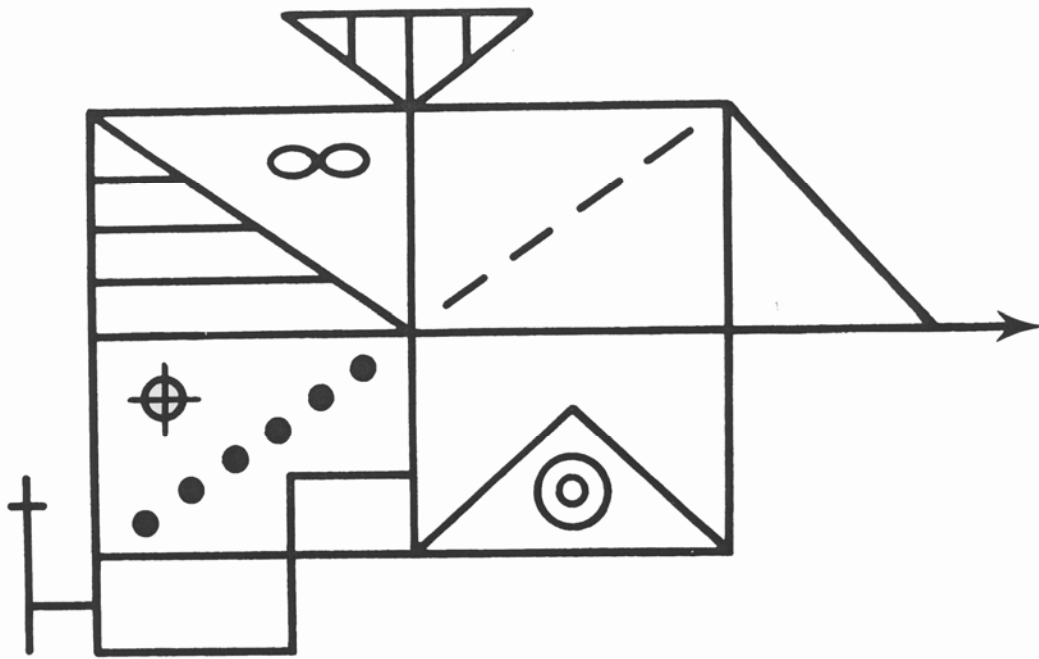
1. Large rectangle
2. Vertical midline of 1
3. Horizontal midline of 1
4. Diagonal line in left upper quadrant of 1
5. Three horizontal lines extending to 4
6. Infinity sign in left upper quadrant of 1
7. Circle and cross in lower left quadrant of 1
8. Six diagonal dots in lower left quadrant of 1
9. Small rectangle in lower left quadrant of 1
10. Small rectangle extending from bottom of 1
11. Cross attached to 10
12. Right angle in lower right quadrant of 1
13. Two concentric circles places under 12
14. Four dashed lines in upper right quadrant of 1
15. Triangle atop 1
16. Three vertical lines in 15
17. Triangle to the right of 1
18. Arrow attached to the right of 17

FIGURE 4:

1. Large square
2. Vertical midline of 1
3. Horizontal midline of 1
4. Rectangle to the right of 1
5. Circle with stem attached to 4
6. Angled arrow at bottom of 1
7. Small triangle outside lower left corner of 1
8. Cross outside of upper left corner of 1
9. Semicircle on top of 1
10. Diagonal line in the upper left quadrant of 1
11. Perpendicular line to 10
12. Star in the upper left quadrant of 1
13. Circle in the lower left quadrant of 1
14. Three horizontal lines inside of 13
15. Small triangle in upper right quadrant of 1
16. Sine wave in upper right quadrant of 1
17. Vertical midline of the lower right quadrant
18. Diagonal line extending to the right of 17