



Published in final edited form as:

*J Thorac Cardiovasc Surg.* 2012 June ; 143(6): 1396–1403. doi:10.1016/j.jtcvs.2011.05.030.

## Optimal Surgical Management of Severe Ischemic Mitral Regurgitation: To Repair or to Replace?

Louis P. Perrault, MD, PhD<sup>a</sup>, Alan J. Moskowitz, MD<sup>b</sup>, Irving L. Kron, MD<sup>c</sup>, Michael A. Acker, MD<sup>d</sup>, Marissa A. Miller, DVM, MPH<sup>e</sup>, Keith A. Horvath, MD<sup>f</sup>, Vinod H. Thourani, MD<sup>g</sup>, Michael Argenziano, MD<sup>h</sup>, David A. D'Alessandro, MD<sup>i</sup>, Eugene H. Blackstone, MD<sup>j</sup>, Claudia S. Moy, PhD<sup>k</sup>, Joseph P. Mathew, MD, MHSc<sup>l</sup>, Judy Hung, MD<sup>m</sup>, Timothy J. Gardner, MD<sup>n</sup>, and Michael K. Parides, PhD<sup>b</sup>

<sup>a</sup>Department of Surgery, Montreal Heart Institute, University of Montréal, Montréal, Québec, Canada

<sup>b</sup>International Center for Health Outcomes and Innovation Research (InCHOIR) in the Department of Health Evidence and Policy, Mount Sinai School of Medicine, New York, NY

<sup>c</sup>Division of Thoracic and Cardiovascular Surgery, University of Virginia School of Medicine, Charlottesville, VA

<sup>d</sup>Division of Cardiovascular Surgery, University of Pennsylvania, Philadelphia, PA

<sup>e</sup>Division of Cardiovascular Sciences, National Heart, Lung, and Blood Institute, Bethesda, MD;

<sup>f</sup>NIH Heart Center at Suburban Hospital, Bethesda, MD

<sup>g</sup>Division of Cardiothoracic Surgery, Emory University Hospital Midtown, Atlanta, GA

<sup>h</sup>Division of Cardiothoracic Surgery, Columbia University Medical Center, New York, NY

<sup>i</sup>Department of Cardiovascular and Thoracic Surgery, Montefiore-Einstein Heart Center, New York, NY

<sup>j</sup>Department of Thoracic and Cardiovascular Surgery, Cleveland Clinic, Cleveland, OH

<sup>k</sup>National Institute of Neurological Disorders and Stroke, Bethesda, MD

<sup>l</sup>Department of Anesthesiology, Duke University Medical Center, Durham, NC

<sup>m</sup>Division of Cardiology, Massachusetts General Hospital, Boston, MA

<sup>n</sup>Center for Heart & Vascular Health, Christiana Care Health System, Newark, DE

### Abstract

---

© 2011 Published by Mosby, Inc on behalf of The American Association For Thoracic Surgery.

Corresponding author: Michael K. Parides, PhD InCHOIR, Department of Health Evidence and Policy Mount Sinai School of Medicine New York.

**Publisher's Disclaimer:** This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

**Background**—Ischemic mitral regurgitation (MR), a complication of myocardial infarction and coronary artery disease more generally, is associated with a high mortality rate and estimated to affect 2.8 million Americans. With 1-year mortality rates as high as 40%, recent practice guidelines of professional societies recommend repair or replacement, but there remains a lack of conclusive evidence supporting either intervention. The choice between therapeutic options is characterized by the trade-off between reduced operative morbidity and mortality with repair versus a better long-term correction of mitral insufficiency with replacement. The long-term benefits of repair versus replacement remain unknown, which has led to significant variation in surgical practice.

**Methods and Results**—This paper describes the design of a prospective randomized clinical trial to evaluate the safety and effectiveness of mitral valve repair and replacement in patients with severe ischemic mitral regurgitation. This trial is being conducted as part of the Cardiothoracic (CT) Surgical Trials Network. This paper addresses challenges in selecting a feasible primary endpoint, characterizing the target population (including the degree of MR), and analytical challenges in this high mortality disease.

**Conclusions**—The paper concludes by discussing the importance of information on functional status, survival, neurocognition, quality of life and cardiac physiology in therapeutic decision-making.

---

## Introduction

Ischemic mitral regurgitation (MR), especially severe ischemic MR, has long been associated with poor health outcomes in cardiac patients. Also known as functional MR, ischemic 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 following MI increases, so will the number of people with ischemic MR (2). Ischemic MR is associated with a shortened survival. Even mild ischemic MR post MI dramatically increases cardiovascular mortality, with a 17% increase at 3.5 years compared to patients with similar degrees of ischemia but without MR (29% versus 12%,  $p < 0.001$ ) (3). In a population with mixed levels of severity of ischemic MR, overall mortality was 62% versus 39% in patients without MR ( $p < 0.001$ ) at 5 years (4). When the ischemic MR was severe, the 1-year mortality rate has been reported as being as high as 40% (5).

Post-infarction changes in ventricular structure and function can produce mitral regurgitation through two distinct processes. Locally, inferior and posterior remodeling can cause displacement of the papillary muscles away from the mitral valve annulus, producing leaflet tethering and restriction of motion. This inhibits the leaflets' ability to close effectively at the level of the annulus. Globally, annular enlargement due 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 (1,6,7).

Revascularization does not often significantly reduce moderate to severe MR; one study reported that moderate to severe MR persisted in 77% of patients (8). Mitral valve replacement was the preferred approach in early studies. However, suboptimal results were

demonstrated, in part because the subvalvular apparatus was not being preserved. Although repair and replacement both appear to eliminate MR immediately post-operatively, large retrospective studies have suggested that repair has lower perioperative mortality (9, 10).

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% (11, 12). The long-term recurrence rates are in the 72% range (11). Significant mitral annulus undersizing has been attempted; however, these long-term results are still not optimal (13). There are several new rings available that attempt to reshape the annulus. 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 (14); external infarct plication sutures (15); reduction of leaflet tethering by cutting a limited number of secondary chordae (16, 17); edge-to-edge suture creating a double orifice valve (18); LV restoration procedure with improvement of papillary muscle orientation (19); and suture relocation of the posterior papillary (20).

Several studies, thus, 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 (i.e., risk factors) 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. Consequently, recent practice guidelines of professional societies recommend (Class I) surgical treatment of patients with symptomatic severe MR, but do not indicate whether to repair or replace the mitral valve as the long-term benefits of these alternative procedures are unknown (21,22). The choice between therapeutic options is characterized by a perceived trade-off between reduced operative morbidity and mortality with repair versus a potentially better long-term correction of mitral insufficiency with replacement. This uncertainty 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 in patients with severe ischemic MR could have a significant impact on patient management and health outcomes.

This paper describes the design of such a trial that is currently being conducted as part of the Cardiothoracic Surgical Trials Network (CTSN) and funded by the National Heart Lung and Blood Institute (NHLBI), the National Institute for Neurological Diseases and Stroke (NINDS), and the Canadian Institute for Health Research (CIHR). In particular, the paper addresses challenges in selecting a feasible primary endpoint, characterizing the target population (including the degree of MR), and analytical challenges in this high mortality disease. This paper concludes by discussing important insights that are expected to emerge from this trial, which has already accrued over 50% of required sample size.

## Study Design

The primary aim of the trial is to evaluate the impact of replacement versus repair on left ventricular remodeling, as assessed by left ventricular end systolic volume index (LVESVI) at 12 months post surgery. This is a parallel design, prospective, multi-center, randomized (1:1) clinical trial comparing mitral valve repair to mitral valve replacement (figure 1). The trial is conducted in highly experienced clinical centers participating in the CT Surgery Clinical Trials Network.

The randomization procedure is being performed intra-operatively, following first incision and before cannulation of aorta. Following verification of entry criteria, random treatment assignment is generated by the trial's electronic data capture (EDC) system. The randomization is stratified by clinical center and uses a random permuted block design with blocks of size 2, 4, and 6 to ensure balance in the number of patients assigned to each treatment.

For the purpose of the primary analysis, patients are considered enrolled in the study once they are randomized and an identification code is generated. All patients are to be followed for 24 months post-randomization, and endpoints are measured at 30 days, 6, 12, and 24 months. The nature of the treatments precludes masking of patients and their treating clinicians to treatment assignment; however, all echocardiograms are being analyzed by a core laboratory masked to treatment assignment, although it will be evident whether the valve was replaced or repaired. Investigators will also be blinded to all data from other clinical sites with the exception of serious, unexpected adverse events for IRB reporting purposes. Trial oversight is provided by an independent data safety and monitoring board (DSMB).

## Characterization of Patient Population

The patient population for this trial consists of patients with severe ischemic MR (often with tethering as a major mechanism) with and without the need for concomitant coronary artery bypass surgery (see table 1). The degree of MR is assessed by transthoracic echocardiogram, in the judgment of the clinical site echocardiographer. Subsequently, all echocardiograms are over read by the echocardiography core laboratory. If site investigators have questions about the degree or etiology of MR (i.e., the presence and contribution of structural valve disease), echocardiograms can be transmitted, via a secure web-based system, for feedback from the core laboratory prior to patient randomization.

Initially, the entry criteria established the degree of MR based on assessment of effective regurgitant orifice area (EROa) alone with severe MR defined as an EROa  $\geq$  0.4 cm sq. However, screening efforts identified patients with multiple quantitative echocardiographic indicators of severe MR, who had an EROa  $<$  0.4 cm sq, who were unable to be enrolled. In this ischemic population, this was primarily observed in patients with eccentricity of MR jets. As a result, the assessment of mitral regurgitation was modified to the integrative method. If the EROa in a patient is found to be  $<$  0.4 cm sq, then additional assessments of the degree of mitral regurgitation are guided by other color Doppler quantitative methods

(jet area/left atrial area ratio, vena contracta), and supportive criteria in an integrated fashion (see appendix 1).

Because patients with mitral regurgitation due to structural disease have a different prognosis than those who have ischemic mitral regurgitation, such patients are excluded from entry. In addition, patients with poor operative risk due to pulmonary hypertension, severe renal disease and hepatic disease are also excluded from randomization. Selected exclusion criteria are depicted in table 2.

## Primary Endpoint and Analysis

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 intervention by transthoracic echocardiogram. 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 was motivated by the expectation of a relatively substantial amount of non-ignorable missing data, primarily due to patient mortality. 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 imputation requires strong untestable assumptions.

A number of additional secondary analyses are planned to supplement the primary analysis and aid 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 (i.e., a “non-parametric analysis of covariance”). Because 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 (23). This model uses a latent variable approach, whereby conditional on this latent variable LVESVI and time to death are assumed to be independent.

## Sample Size Estimation

Sample size estimates to ensure the ability to detect, with high probability, a clinically meaningful presumed benefit for patients undergoing mitral valve repair were based on data derived from the clinical literature (24-26). We assume that the mean baseline LVESVI in the target population is 100 ml/m<sup>2</sup>. For patients randomized to receive mitral valve repair we anticipate a 20% reduction in LVESVI, or an absolute change of 20 ml/m<sup>2</sup>. We believe a meaningful effect worth detecting is an additional 15% (15 ml/m<sup>2</sup>), or a total reduction of 35% or 35 ml/m<sup>2</sup> for patients undergoing mitral valve replacement. Assuming that baseline and 12 month LVESVI in both arms follows a gamma distribution with common standard deviation of 35 ml/m<sup>2</sup>, a total of 250 patients, randomized with equal probability to each

arm, provides approximately 90% power to detect a difference of 15 ml/m<sup>2</sup>. Power is based on a 0.05 level two-tailed Wilcoxon Rank-Sum test. The sample size takes account of a single interim analysis to be performed in addition to the final analysis.

## Interim Analysis

We will 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. 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, and 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. The trial's conditional power, under the original alternative hypothesis, will be computed at the interim look, which will allow the DSMB to use this to determine whether randomization, if not completed, should be halted for futility.

## Characterization of Treatment Interventions

In designing this trial, the investigators spent considerable time specifying the guidelines that define the surgical technique. These specifications include designation that all procedures must be performed with full or partial sternotomy, or a right thoracotomy with cardiopulmonary bypass according to local standards. Exposure of the mitral valve is accomplished by either the left atrial (Waterston's groove) or biatrial approach. *Mitral Valve replacement* is accomplished with complete chordal-sparing. The technique for subvalvular preservation, the type of prosthesis (mechanical or bioprosthesis), and technique of suture placement are selected by the surgeon, at their preference. *Mitral valve repair* is accomplished using an undersized annuloplasty ring. The ring size is determined by the surface area of the anterior mitral leaflet as measured by the intertrigonal distance and anterior leaflet height. A subvalvular procedure can be performed if tethering is present. Secondary mitral valve replacement can be performed at the surgeon's discretion if residual MR is significant after left ventricular saline infusion testing or at post CPB TEE. *Coronary artery bypass grafting* is performed using standard techniques and two-stage venous cannulation. Conduit selection and harvesting methods are not prescribed, although utilization of the LIMA is recommended when an LAD graft is indicated. Complete revascularization should be accomplished, within the judgment of the surgical investigator.

## 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. The trial is not

powered to detect small mortality differences; however, an observed difference in mortality, consistent in direction with that observed for LVESVI will serve to validate the trial's findings. 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.

### **Quality of Life, Functional Status and Neurocognition**

Several measures of quality of life will be used, to capture both overall quality of life and disease specific quality of life. Overall quality of life will be captured with the SF-12 and EuroQol, while disease specific quality of life will be measured with the Minnesota Living with Heart Failure Score and the Duke Activity Status Index. Measurements with these instruments will occur at 30 days, and at 6, 12 and 24 months. Functional status will be captured through measurement of cardiopulmonary stress testing, as clinically tolerated, NYHA heart failure class and the Canadian Cardiovascular Society Angina class at 6 and 12 months post randomization. Neurocognitive performance at 12 months will be assessed using the following battery of tests: Hopkins Verbal Learning Test, Trailmaking Tests A and B, MCG Complex Figures, Boston Naming Test, Digit Span and Digit Symbol Substitution Test.

### **Adverse Events, Hospitalization and Economic Endpoints**

Serious and protocol-defined adverse events are measured prospectively and differences between treatment groups will be assessed using Poisson regression. In addition, major adverse cardiac events (MACE) are being assessed, which is a non-weighted composite endpoint comprised of death, stroke, worsening heart failure (+ 1 NYHA Class), CHF hospitalization, and mitral valve re-intervention. The proportion of patients experiencing a major cardiac event will be compared by chi-squared test at 12 and 24 months. Economic endpoints are important as well. Hospital resource use will be captured by measuring overall length of stay and ICU days during the index hospitalization, as well as readmission rates for all causes and specifically for heart failure. Days alive out of the hospital will be compared between treatment groups accounting as a percent of survival. Hospital costs will be calculated from hospital charges using the institution-specific ratio of cost to charges. The incremental cost-effectiveness ratio in units of dollars per quality-adjusted life years will be calculated when the differences in health outcomes are associated with a difference in cost.

### **Discussion**

Patients with severe ischemic MR constitute a large and growing population with a dismal prognosis. Both mitral valve repair and replacement procedures are widely used to treat this problem. Yet, there is considerable controversy over the relative benefits of these two treatment approaches and no definitive trials to guide treatment decisions. The Cardiothoracic Surgical Trials Network identified this as a high priority concern and chose to address it as one of its first randomized trials. The Network's severe mitral regurgitation trial, which is in essence a comparative effectiveness trial, is designed to provide insights into a range of outcomes that are relevant to clinicians and patients for making treatment decisions, and should expand the methodology for conducting surgical trials.

Ideally, clinical trials should be powered to make definitive statements about all of the relevant clinical endpoints. However, providing adequate power for all of the relevant clinical endpoints, including mortality, in the SMR trial, would have required a sample size in the range of several thousand patients. It would not have been feasible to enroll and complete follow-up for all patients, and analyze and disseminate the results of such a trial within the 5-year term of the Network. As such, the Network investigators chose left ventricular remodeling as the primary endpoint. Specific guidelines were created for ensuring rigorous and standardized measurement of this endpoint, and an independent core lab was established to over-read all echocardiograms in this trial, and provide real time consultation to investigators during the enrollment process. Mortality is the most important secondary endpoint and will provide corroborating evidence needed to interpret the differences observed in ventricular remodeling.

A critical dimension for making treatment decisions is information about the expectations for quality of life post-surgery. Particularly relevant to this target population are the impact of treatment on congestive heart failure and angina pectoris symptoms. To measure treatment effects on congestive heart failure symptoms and functional status, the trial is measuring NYHA classification, Minnesota Living with Heart Failure Score, the Duke Activity Status index, and peak  $\dot{V}O_2$ . Given that one of the concerns about mitral valve repair is that it might not be as effective as replacement in controlling mitral regurgitation, it is important that the impact of heart failure on quality of life and functional status be measured longitudinally throughout the follow up period of the trial. The fact that the trial includes general measures of quality of life (i.e., the SF12 and EuroQol) will allow us to interpret the observed disease-specific symptoms in the broader context of physical and mental quality of life experienced by patients. These health status measures will also be used to calculate quality adjusted life years for the cost-effectiveness analysis.

Another critical concern of patients undergoing cardiac surgery is the impact of surgery on brain functioning. This trial, therefore, has been designed to carefully measure cognitive functioning and neurological events over the two year time period. An independent neurocognitive core laboratory was established to train investigators in neurocognitive testing, score all test results, and provide quality assurance relative to this measure throughout the trial. The investigators are also exploring alternative methods for analyzing neurocognitive data, which have the potential to address some of the controversies regarding analysis in this field.

The severe ischemic mitral regurgitation trial has already enrolled over half of the required patient population. The enrollment rate has increased substantially over time and completion of enrollment is clearly within sight. The broad spectrum of endpoints being captured in this trial should address the current dilemmas in choosing an optimal surgical approach for this patient group, and provide invaluable information for clinicians and patients alike making this treatment decision.

## Appendix 1

### Cardiothoracic Surgical Trials Network (CTSN)

#### National Heart, Lung and Blood Institute

Marissa A. Miller, Wendy C. Taddei-Peters, Dennis Buxton, Ron Caulder, Nancy L. Geller, David Gordon, Neal O. Jeffries, Albert Lee **National Institute of Neurological Disorders and Stroke:** Claudia S. Moy **Canadian Institutes of Health Research:** Ilana Kogan Gombos, Jennifer Ralph

#### Network Chairs

*Christiana Care Health System*, Timothy J. Gardner, (Chair); *Brigham and Women's Hospital*, Patrick T. O'Gara, (Co-Chair)

#### Data Coordinating Center

International Center for Health Outcomes and Innovation Research (InCHOIR) in the Department of Health Evidence and Policy, Mount Sinai School of Medicine, New York, NY, Annetine C. Gelijns, Michael K. Parides, Deborah D. Ascheim, Alan J. Moskowitz, Ellen Moquete, Eric A. Rose, Melissa Chase, Yingchun Chen, Rosemarie Gagliardi, Alejandra Guerchicoff, Lopa Gupta, Alexander Iribarne, Edlira Kumbarce, Ron Levitan, Karen O'Sullivan, Mark J. Russo, Milerva Santos, William Slavik, Alan Weinberg, Martin Wells, Paula Williams, Carrie Wood, Xia Ye

#### Core Clinical Site Investigators

*Cleveland Clinic Foundation*, Eugene H. Blackstone (PI), A. Marc Gillinov, Tomislav Mihaljevic, Richard A. Grimm, Ben Barzilai, Bruce D. Lindsay, Christine Whitman, Denise Kosty Sweeney, Roberta Palumbo; *NHLBI Clinical Research Scholars:* Gregory Pattakos, Pamela A. Clarke;

*Columbia University Medical Center*, Michael Argenziano (PI), Mathew Williams, Lyn Goldsmith, Rebecca T. Hahn, Linda Gillam, Craig R. Smith, Yoshifumi Naka, Allan Stewart, Allan Schwartz;

*Duke University*, Peter K. Smith (PI), Stacey Welsh, John H. Alexander, Carmelo A. Milano, Donald D. Glower, Joseph P. Mathew, J. Kevin Harrison; *NHLBI Clinical Research Scholars:* Mark F. Berry, Cyrus J. Parsa, Betty C. Tong, Judson B. Williams;

*East Carolina Heart Institute*, T. Bruce Ferguson (PI), Alan P. Kypson, Evelio Rodriguez, Malissa Harris, Brenda Akers, Allison O'Neal;

*Emory University*, John D. Puskas (PI), Vinod H. Thourani, Robert Guyton, Jefferson Baer, Kim Baio, Alexis Neill;

*Montefiore-Einstein Heart Center, New York, NY*, Robert E. Michler (PI), Ricardo Bello, David A. D'Alessandro, Joseph J. DeRose, Jr., Daniel J. Goldstein, Cynthia Taub, Daniel Spevak, Roger Swayze;

*Montreal Heart Institute*, Louis P. Perrault (PI), Arsène-Joseph Basmadjian, Denis Bouchard, Michel Carrier, Philippe Demers, Michel Pellerin, Sophie Robichaud;

*NIH Heart Center at Suburban Hospital*, Keith A. Horvath (PI), Philip C. Corcoran, Michael P. Siegenthaler, Mandy Murphy, Margaret Iraola, Ann Greenberg;

*University of Pennsylvania*, Michael A. Acker (PI), Y. Joseph Woo, Wilson Y. Szeto, Mary Lou Mayer;

*University of Virginia*, Irving L. Kron (PI), Gorav Ailawadi, Karen Johnston, John M. Dent, Sandra Burks, Kim Gahring

### **Affiliate/Ancillary Sites**

*Hôpital du Sacré-Cœur de Montréal*, Pierre Pagé (PI), Hugues Jeanmart, Philippe Demers, Claude Sauvé, Carole Sirois;

*Institut Universitaire de Cardiologie et de Pneumologie de Québec*, Pierre Voisine (PI), François Dagenais, Eric Dumont, Gladys Dussault;

*Inova Fairfax Hospital*, Alan M. Speir (PI), Niv Ad, Minh Dang;

*The Ohio State University Medical Center*, Chittoor B. Sai-Sudhakar (PI), Danielle Jones;

*WellStar Health System, Kennestone Hospital*, William A. Cooper (PI), Rajnish Prasad, Richard J. Myung, Jennifer LaCorte, Melinda Mock;

### **Satellite Sites**

*Baylor Research Institute*, Michael J. Mack (PI), Robert Smith, William Ryan, Jennifer Withers;

*Brigham and Women's Hospital*, Frederick Y. Chen (PI), R. Morton Bolman III, Anne M. Burgess, Debra Conboy;

*Jewish and St. Mary's Hospital*, Mark S. Slaughter (PI), Matthew Williams, Marcus Stoddard, Heather Moody;

*Mission Hospital*, Mark A. Groh (PI), Ben Trichon, Todd Hansen, Claudine Cuento;

*University of Southern California*, Vaughn A. Starnes (PI), Michael Bowdish, Becky Lopez;

*University of Maryland*, James S. Gammie (PI), Mandeep Mehra, Bartley Griffith, Dana Beach;

*Washington University*, Ralph J. Damiano, Jr. (PI), Scott Silvestry, Marc Moon, Jennifer Lawton

### **Cardiopulmonary Exercise Core Laboratory**

*Henry Ford Hospital*, Steven J. Keteyian, Clinton A. Brawner

**Echo Core Laboratory**

Massachusetts General Hospital, Judy Hung, Xin Zeng

**Electrophysiology Core Laboratory**

University of Rochester Medical Center, Jean-Philippe Couderc

**Neurocognitive Core Laboratories**

*Duke University*, Joseph P. Mathew

**Protocol Review Committee**

David A. Bull (Chair); Patrice Desvigne-Nickens, Executive Secretary; Dennis O. Dixon, Mark Haigney, Richard Holubkov, Alice Jacobs, Frank Miller, John M. Murkin, John Spertus, Andrew S. Wechsler

**Data and Safety Monitoring Board**

Frank Selke (Chair); Cheryl L. McDonald, Executive Secretary; Robert Byington, Neal Dickert, Dennis O. Dixon, John S. Ikonomidis, David O. Williams, Clyde W. Yancy

**Medical Monitors**

James C. Fang, Wayne Richenbacher

**Overall Event Adjudication Committee**

Vivek Rao (Chair); Karen L. Furie, Rachel Miller, Sean Pinney, William C. Roberts

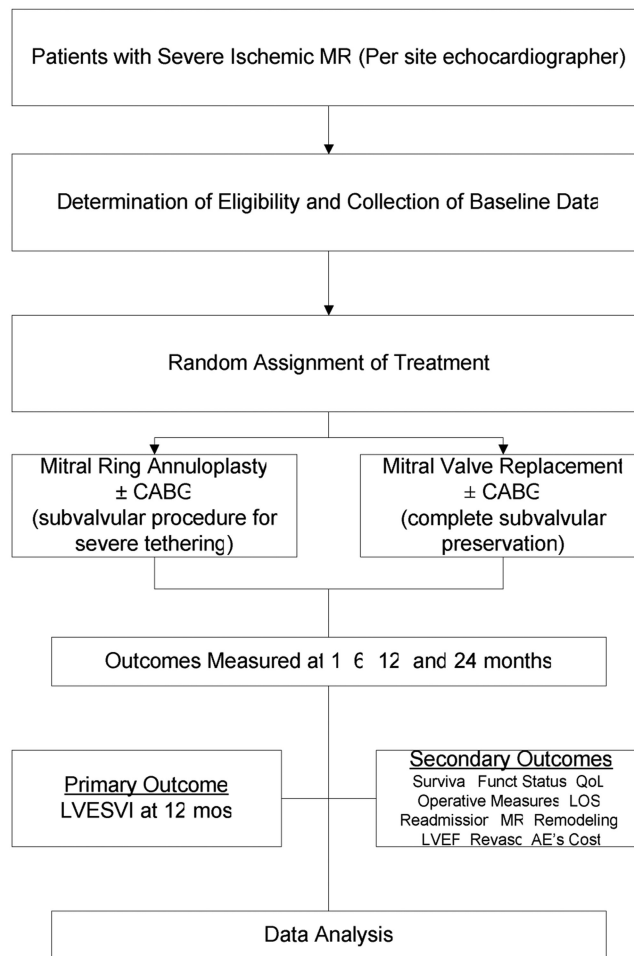
**Infection Event Adjudication Committee**

Rachel Miller (Chair); Shirish Huprikar, Marilyn Levi

**References**

1. Borger MA, Alam A, Murphy PM, et al. Chronic ischemic mitral regurgitation: Repair, replace or rethink? *Ann Thorac Surg.* 2006; 81:1153–1161. [PubMed: 16488757]
2. Gorman, RC.; Gorman, JI.; Edmunds, LH, Jr. Ischemic mitral regurgitation. In: Cohn, LH.; Edmunds, LH., Jr, editors. *Cardiac Surgery in the Adult*. New York: McGraw-Hill; 2003. p. 751-769.
3. Lamas GA, Mitchell GF, Flaker GC, et al. Clinical significance of mitral regurgitation after acute myocardial infarction. *Circulation.* 1997; 96:827–833. [PubMed: 9264489]
4. Grigioni F, Enriquez-Serrano M, Zehr KJ, et al. Ischemic mitral regurgitation: Long-term outcome and prognostic implications with quantitative doppler assessment. *Circulation.* 2001; 103:1759–1764. [PubMed: 11282907]
5. Hickey MS, Smith LR, Muhlbaier LH, et al. Current prognosis of ischemic mitral regurgitation: Implications for future management. *Circulation.* 1988; 78(Suppl):I51–9. [PubMed: 2970346]
6. Dent JM, Spotnitz WD, Nolan SP, et al. Mechanism of mitral leaflet excursion. *Am J Physiol.* 1995; 269:H2100–8. [PubMed: 8594922]
7. Levine RA, Schwammenthal E. Ischemic mitral regurgitation on the threshold of a solution: from paradoxes to unifying concepts. *Circulation.* 2005; 112:745–758. [PubMed: 16061756]
8. Aklog L, Filsoufi F, Flores KQ, et al. Does coronary artery bypass grafting alone correct moderate ischemic mitral regurgitation? *Circulation.* 2001; 104(Suppl 1):I68–75. [PubMed: 11568033]

9. Gillinov AM, Wierup PN, Blackstone EH, et al. Is repair preferable to replacement for ischemic mitral regurgitation? *J Thorac Cardiovasc Surg.* 2001; 122:1125–1141. [PubMed: 11726887]
10. Grossi EA, Goldberg JD, LaPietra A, et al. Ischemic mitral valve reconstruction and replacement: Comparison of long-term survival and complications. *J Thorac Cardiovasc Surg.* 2001; 122:1107–24. [PubMed: 11726886]
11. Hung J, Papakostas L, Tahta SA, et al. Mechanisms of recurrent mitral regurgitation after annuloplasty: Continued LV remodeling as a moving target. *Circulation.* 2004; 110:II-85–II-90. [PubMed: 15364844]
12. McGee EC, Gillinov AM, Blackstone EH, et al. Recurrent mitral regurgitation after annuloplasty for functional ischemic mitral regurgitation. *J Thorac Cardiovasc Surg.* 2004; 128:916–24. [PubMed: 15573077]
13. Wu AH, Aaronson KD, Bolling SF, et al. Impact of mitral valve annuloplasty on mortality risk in patients with mitral regurgitation and left ventricular systolic dysfunction. *J Am Coll Cardiol.* 2005; 45:381–7. [PubMed: 15680716]
14. Hung J, Guerrero JL, Handschumacher MD, et al. Reverse ventricular remodeling reduces ischemic mitral regurgitation: Echo-guided device application in the beating heart. *Circulation.* 2002; 106:2594–2600. [PubMed: 12427657]
15. Liel-Cohen N, Guerrero JL, Otsuji Y, et al. Design of a new surgical approach for ventricular remodeling to relieve ischemic mitral regurgitation: Insights from 3-Dimensional echocardiography. *Circulation.* 2000; 101:2756–2763. [PubMed: 10851215]
16. Messas E, Guerrero JL, Handschumacher MD, et al. Chordal cutting: A new therapeutic approach for ischemic mitral regurgitation. *Circulation.* 2001; 104:1958–1963. [PubMed: 11602501]
17. Messas E, Pouzet B, Touchot B, et al. Efficacy of chordal cutting to relieve chronic persistent ischemic mitral regurgitation. *Circulation.* 2003; 108(1):II 111–5.
18. Alfieri O, Maisano F, De Bonis M, et al. The Double-Orifice technique in mitral valve repair: a simple solution for complex problems. *J Thorac Cardiovasc Surg.* 2001; 122:674–681. [PubMed: 11581597]
19. Menticanti L, Di Donato A, Frigiola A, et al. Ischemic mitral regurgitation: Intraventricular papillary muscle imbrication Without mitral ring during left ventricular restoration. *J Thorac Cardiovasc Surg.* 2002; 123:1041–50. [PubMed: 12063449]
20. Kron IL, Green GR, Cope JT. Surgical relocation of the posterior papillary muscle in chronic ischemic mitral regurgitation. *Ann Thorac Surg.* 2002; 74:600–601. [PubMed: 12173864]
21. Bonow RO, Carabello BA, Kanu C. ACC/AHA 2006 guidelines for the management of patients with valvular heart disease: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (writing committee to revise the 1998 Guidelines for the Management of Patients with valvular Heart Disease): developed in collaboration with the Society of Cardiovascular Anesthesiologists: endorsed by the Society for Cardiovascular Angiography and Interventions and the Society of Thoracic Surgeons. *Circulation.* 2006; 114:e84–231. [PubMed: 16880336]
22. Jamieson WR, Cartier PC, Allard M, et al. Surgical management of valvular heart disease 2004. *Can J Cardiol.* 2004; 20(E):7E–120E.
23. Xu J, Zeger SL. Joint analysis of longitudinal data compromising repeated measures and time to events. *Applied Statistics.* 2001; 50:375–387.
24. Bax JJ, Braun J, Somer ST, et al. Restrictive annuloplasty and coronary revascularization in ischemic mitral regurgitation results in reverse left ventricular remodeling. *Circulation.* 2004; 110(Suppl 1):II-103–II-108. [PubMed: 15364847]
25. Yiu SF, Enriquez-Sarano M, Tribouilloy C, et al. Determinants of the degree of functional mitral regurgitation in patients with systolic left ventricular dysfunction: A quantitative clinical study. *Circulation.* 2000; 102:1400–6. [PubMed: 10993859]
26. Kang DH, Kim MJ, Kang SJ, et al. Mitral valve repair versus revascularization Alone in the treatment of ischemic mitral regurgitation. *Circulation.* 2006; 114(1 Suppl):I499–503. [PubMed: 16820626]



**Figure 1. SMR Trial Design Schematic**

**Table 1**  
**Selected Inclusion Criteria**

<b>1</b>	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.
<b>2</b>	Eligible for surgical repair and replacement of mitral valve
<b>3</b>	Coronary artery disease with or without the need for coronary revascularization

**Table 2**  
**Selected Exclusion Criteria**

Selected Exclusion Criteria	
1	Any evidence of structural mitral valve disease or ruptured papillary muscle
2	Inability to derive ERO and ESVI by transthoracic echocardiography
3	Planned concomitant intra-operative procedures (except tricuspid valve repair, patent foramen ovale closure, atrial septal defect closure or Maze procedure)
4	Prior mitral valve repair
5	Contraindications to CPB
6	Clinical signs of cardiogenic shock at the time of randomization
7	Treatment with chronic intravenous inotropic therapy at the time of randomization
8	Severe irreversible pulmonary hypertension in the judgment of the investigator
9	ST segment elevation MI requiring intervention within 7 days prior to randomization
10	Congenital heart disease (except PFO or ASD)
11	Chronic renal insufficiency defined by Cr $\geq$ 2.5 or chronic renal replacement therapy
12	Evidence of cirrhosis or hepatic synthetic failure
13	Excessive surgical risk (in the judgment of the surgical investigator)