Protocol

Protocol for: Gammie JS, Chu MWA, Falk V, et al. Concomitant tricuspid repair in patients with degenerative mitral regurgitation. N Engl J Med. DOI: 10.1056/NEJMoa2115961

This trial protocol has been provided by the authors to give readers additional information about the work.

SUPPLEMENTARY DOCUMENTS

Evaluating the Benefit of Concurrent Tricuspid Valve Repair During Mitral Surgery

This supplement contains the following items:

1. Original protocol Version 1.0
2. Final protocol, Version 2.2, with summary of changes pgs 5-8 within document.
3. Original statistical analysis plan (SAP) Version 1.0 (only version used during trial), with signature page omitted.

Cardiothoracic Surgical Trials Network

Protocol

EVALUATING THE BENEFIT OF CONCURRENT TRICUSPID VALVE REPAIR DURING MITRAL SURGERY

Sponsored By NHLBI, NINDS & CIHR

CT Surgery Network Research Group

Data Coordinating Center
InCHOIR
Icahn School of Medicine at Mount Sinai
New York

November 2015

CONFIDENTIAL

Cardiothoracic Surgical Trials Network

Core Clinical Centers
Baylor Research Institute (Michael Mack, MD)
Cleveland Clinical Foundation (Marc Gillinov, MD)
Duke University (Peter Smith, MD)
Institut Universitaire de Cardiologie de Québec (Hôpital Laval) (Pierre Voisine, MD)
Montefiore Medical Center - Albert Einstein College of Medicine (Robert Michler, MD)
Montreal Heart Institute (Louis Perrault, MD)
    Centre Hospitalier de l'Université de Montréal (Louis-Mathieu Stevens, MD)
    Hôpital du Sacré-Cœur de Montréal (Hugues Jeanmart, MD)
NIH Heart Center at Suburban Hospital (Keith Horvath, MD)
University of Pennsylvania (Michael Acker, MD)
University of Southern California (Michael Bowdish, MD)
University of Virginia Health Systems (Irving L. Kron, MD)

Consortium Centers
Columbia University Medical Center (Michael Argenziano, MD)
Dartmouth-Hitchcock Medical Center (Jock McCullough, MD)
Emory University (Vinod Thourani, MD)
Mission Hospital (Mark Groh, MD)
Ohio State University Medical Center (Bryan Whitson, MD)
Toronto General Hospital (Terry Yau, MD)
University of Alberta (John Mullen, MD)
University of Maryland Medical Center (James Gammie, MD)
University of Michigan (Steve Bolling, MD)

Universitäts-Herzzentrum Freiburg (Friedhelm Beyersdorf, MD)
Universitätsklinikum Schleswig-Holstein, Kiel (Jochen Cremer, MD)
Herz- und Gefäß-Klinik, Bad Neustadt / Saale (Anno Diegeler, MD)
Deutsches Herzzentrum Berlin, (Volkmar Falk, MD)
Klinikum Braunschweig, Braunschweig (Wolfgang Harringer, MD)
Herzzentrum, Leipzig (Friedrich Mohr, MD)
Kerckhoff Klinik, Bad Nauheim (Thomas Walther, MD)
Universitätsklinikum Bonn (Armin Welz, MD)

Data Coordinating Center
International Center for Health Outcomes and Innovation Research, Icahn School of Medicine at Mount Sinai (InCHOIR), (Annetine Gelijns, PhD; Alan J. Moskowitz, MD; Michael K. Parides, PhD Emilia Bagiella, PhD; Ellen Moquete, RN; Karen O'Sullivan, MPH; Anu Lala, MD)

Study Chair, Co-Chair, Vice-Chair
Richard Weisel, MD; University of Toronto
Patrick T. O'Gara, MD; Brigham and Women's Hospital
Eric Rose, MD; Icahn School of Medicine at Mount Sinai

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

Protocol Development Committee

James S. Gammie, MD (U Maryland)
Steven Bolling, MD (U Michigan)
Michael Parides, PhD (InCHOIR)
Gorav Ailawadi, MD (UVA)
Michael Argenziano, MD (Columbia)
Emilia Bagiella, PhD (InCHOIR)
Eugene Blackstone, MD (CCF)
Denis Bouchard, MD (Montreal)
Michael Bowdish, MD (USC)
Helena L Chang, MS (InCHOIR)
Julia Collins, CRC (U Maryland)
Francois Dagenais, MD (Laval)
Stephanie Deasey, PhD (U Maryland)
Annetine Gelijns, PhD (InCHOIR)
Nancy L Geller, PhD (NIH/NHLBI)
Marc Gillinov, MD (CCF)
Judy Hung, MD (MGH)
Katherine Kirkwood, MS
Irving L. Kron, MD (UVA)
Anu Lala, MD (InCHOIR)
Albert Lee, PhD (NHLBI)
Michael Mack, MD (Baylor)
Marissa Miller, DVM (NHLBI)
Ellen Moquete, RN, BSN (InCHOIR)
Alan Moskowitz, MD (InCHOIR)
Patrick O'Gara, MD (Brigham and Women's)
Karen O'Sullivan, MPH (InCHOIR)
Jessica Overbey, MS (InCHOIR)
Vivek Rao, MD (Toronto)
Eric Rose, MD (Mount Sinai)
Peter K. Smith, MD (Duke)
Robert Smith, MD (Baylor)
Wendy C. Taddei-Peters, PhD (NHLBI)
Vinod Thourani, MD (Emory)
Robert Villanueva, MPA (U Maryland)
Bryan Whitson, MD (OSU)
Markus Heinemann, MD (Germany)
Friedhelm Beyersdorf, MD (Freiburg, Germany)
Jochen Cremer, MD (Kiel, Germany)
Anno Diegeler, MD (Bad Neustadt, Germany)
Volkmar Falk, MD (Berlin, Germany)
Wolfgang Harringer, MD (Braunschweig, Germany)
Friedrich Mohr, MD (Leipzig, Germany)
Thomas Walther, MD (Bad Nauheim, Germany)
Armin Welz, MD (Bonn, Germany)
Richard Weisel, MD (Toronto)

TABLE OF CONTENTS

Table of Changes

Revision	Section	Change	Reason	Page

DEFINITIONS, ACRONYMS & ABBREVIATIONS

ACE	Angiotensin converting enzyme antagonist
AE	Adverse event
AICD	Automatic implantable cardioverter defibrillator
ARB	Angiotensin receptor blocker
ASD	Atrial septal defect
AV	Atrioventricular
CABG	Coronary artery bypass grafting
CHF	Congestive heart failure
CIHR	Canadian Institutes of Health Research
CSA	Cross sectional area
CTA	Clinical Trial Agreement
CW	Continuous wave
DCC	Data coordinating center
DSMB	Data and Safety Monitoring Board
EAC	Event Adjudication Committee
EC	Ethics Committee
EDC	Electronic data capture system
EDV	End diastolic volume
EROa	Effective Regurgitant Orifice area
EQ-5D	EuroQoL
ESV	End systolic volume
ESVI	End systolic volume index
GCP	Good Clinical Practice
HIPAA	Health Insurance Portability and Accountability Act
InCHOIR	International Center for Health Outcomes & Innovation Research
IRB	Institutional Review Board
KCCQ	Kansas City Cardiomyopathy Questionnaire
LA	Left atrium
LAA	Left atrial appendage
LBBB	Left bundle branch block
LOS	Length of stay
LV	Left ventricle
LVEDP	Left ventricular end diastolic pressure
LVEF	Left ventricular ejection fraction
LVESVI	Left ventricular end systolic volume index
MACCE	Major adverse cardiac and cerebrovascular event
MI	Myocardial infarction
MR	Mitral regurgitation
mRS	modified Rankin scale
MV	Mitral valve
MVR	Mitral valve repair
MVRR	Mitral valve repair/replacement
MVS	Mitral valve surgery

NHLBI	National Heart, Lung, and Blood Institute
NIHSS	National Institutes of Health Stroke Scale
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-operative day
PR	Pulmonic regurgitation
PV	Pulmonic valve
PVI	Pulmonary vein isolation
PW	Pulsed wave
QOL	Quality of Life
REB	Research Ethics Board
RV	Right Ventricle
RVFAC	Right ventricular fractional area change
RVol	Regurgitant volume
SAE	Serious adverse event
SAX	Short axis
SF-12	Short Form 12
STEMI	ST segment elevation myocardial infarction
6MWT	Six Minute Walk Test
TAPSE	Tricuspid annular plane systolic excursion
TEE	Trans-esophageal echocardiography
TIA	Transient ischemic attack
TR	Tricuspid regurgitation
TTE	Transthoracic echocardiography
TV	Tricuspid valve
TVI	Tissue velocity imaging
VTI	Velocity time integral

ABSTRACT

Objectives	The *primary objective* of this trial is to evaluate the efficacy and safety of performing tricuspid valve (TV) repair in patients with either moderate tricuspid regurgitation (TR) or less than moderate TR with tricuspid annular dilation undergoing mitral valve surgery (MVS).
Study Design	Prospective, multi-center, randomized, controlled trial
Target Population	Patients undergoing MVS (*repair or replacement)* for degenerative mitral regurgitation (MR) who have *either* (a) moderate TR OR (b) tricuspid annular dimension ≥ 40 mm (index: ≥21mm/M^2 BSA) *and* trace/mild TR, determined by echocardiography.
Rx arms	(a) TV annuloplasty using a rigid, nonplanar, undersized (nominal 26, 28, or 30 mm) annuloplasty ring at the time of MVS (b) MVS alone Randomization will be stratified based on TR severity (i.e. moderate or trace/mild TR) and by clinical center.
Sample Size	400 patients provides 90% power to detect a decrease in "failure" from 25% without tricuspid valve repair to 12% in patients with repair.
Duration	60 months following randomization
1° Endpoints	• Composite of death, reoperation for TR, or progression of TR from baseline by two grades *or* the presence of severe TR at 24 months Degree of TV regurgitation will be categorized according to American Society of Echocardiography guidelines as none/mild/moderate/severe
2° Endpoints	*Clinical and Functional Outcomes* • Composite of major adverse cardiac and cerebrovascular events (MACCE), including stroke, death, and serious heart failure events • NYHA classification and diuretic requirements • Six-minute walk test (6MWT) *Echocardiography* • Degree of TR at index hospital discharge • Degree of TR at 12 and 24 months • Right ventricular size at 12 and 24 months • Right ventricular function [normal, mildly impaired, moderately impaired, severely impaired, peak tricuspid annular velocity, tricuspid annular plane systolic excursion (TAPSE), right ventricular fractional area change (RVFAC)] at 12 and 24 months • Pulmonary artery pressure at 12 and 24 months • Right ventricular volume at 12 and 24 months *Quality of Life* • SF-12 • Kansas City Cardiomyopathy Questionnaire (KCCQ) • EuroQoL (EQ-5D) *Survival* • Perioperative mortality (greater in-hospital or 30 day mortality)

	• Mortality *Serious Adverse Events* • Frequency of serious adverse events (SAEs) • Atrioventricular (AV)-Block requiring pacemaker implantation • New-onset atrial fibrillation *Hospitalizations* • Index hospitalization length of stay (LOS) and intensive care unit (ICU) days • All-cause readmissions, and readmissions for heart failure and TR reoperations *Economic Outcomes* • Cost • Cost-effectiveness
Selected Inclusion Criteria	1. Age $\geq$ 18 years 2. Undergoing MVS for degenerative MR 3. (a) moderate TR as determined by echocardiography, or (b) trace/mild TR *and* tricuspid annular dimension $\geq$ 40 mm
Selected Exclusion Criteria	1. Functional MR 2. Evidence of sub-optimal fluid management (e.g., lack of diuretics, weight in excess of dry weight) in the eyes of the cardiology investigator 3. Structural/organic TV disease 4. Severe TV regurgitation as determined by echocardiography 5. Implanted pacemaker or defibrillator, where the leads cross the TV from the right atrium into the right ventricle 6. Concomitant cardiac surgery other than atrial fibrillation correction surgery [pulmonary vein isolation (PVI), Maze, left atrial appendage (LAA) closure], closure of patent foramen ovale (PFO) or atrial septal defect (ASD), or coronary artery bypass grafting (CABG) 7. Cardiogenic shock at the time of randomization 8. ST segment elevation myocardial infarction (STEMI) requiring intervention within 7 days prior to randomization 9. Evidence of cirrhosis or hepatic synthetic failure 10. Severe, irreversible pulmonary hypertension in the judgment of the investigator 11. Pregnancy 12. Unable or unwilling to provide informed consent 13. Unable or unwilling to comply with study follow up in the opinion of the investigator

DATA COLLECTION SCHEDULE

Assessment	Screening/ Baseline	Intra-Operative	Pre-discharge	30 Days (± 7 days)	6 Mos (± 14 days)	12 Mos (± 14 days)	18 Mos (± 14 days)	24 Mos (± 30 days)	36, 48 & 60 Mos (± 30 days)	Event Driven
General										
Eligibility Criteria	X									
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									X
Screening Outcome	X									
Hospitalization	X									X
Vital Status Check									X	
Cardiac										
Surgical Procedure		X								X
TEE		X								
NYHA Heart Failure Class	X			X	X	X		X		
TTE	X		X		X	X		X		
Six Minute Walk Test (6MWT)	X				X	X		X		
3D Echo (TTE)	X					X		X		
Quality of Life (QOL)										
KCCQ	X				X	X	X	X		
SF-12	X				X	X	X	X		
EQ-5D	X				X	X	X	X		
Event Driven Data										
Adverse Events										X
Missed Visit										X
Protocol Deviation										X
Mortality										X
Study Completion/Early Termination										X
End of Study/Investigator Statement										X
Cost										
UB-92 Forms & Hospital Bills										X
UHC Data										X

OBJECTIVES

The overall objective of this study is to evaluate the safety and efficacy of tricuspid valve (TV) repair in the setting of mitral valve surgery (MVS) for degenerative mitral valve (MV) disease. Specifically, this study compares the surgical approach of combining TV annuloplasty with clinically indicated MVS to performing MVS alone.

- The primary aim of this trial is to evaluate the impact of these two surgical approaches on the composite endpoint of death and reoperation for tricuspid regurgitation (TR), or progression of TR, either by two grades from baseline *or* by the presence of severe TR at 2 year follow-up.

- Secondary aims of this trial include assessment of the impact of these two surgical approaches on right heart performance and function, mortality, adverse events (AEs), quality of life (QOL), functional status, presence and severity of TR, and health resource use.

BACKGROUND AND SIGNIFICANCE

Etiology & Prognosis

The presence of moderate or severe TR is commonly encountered, affecting over 1.6 million people in the United States alone (Taramasso, Vanermen et al. 2012). Intrinsic pathology of the TV is rare resulting in most TR being functional, which is defined as regurgitation in the presence of anatomically normal leaflets and chords. TR produces fewer observable symptoms compared with other valvular pathology, and its assessment by physical exam can be challenging. As a result, the presence and severity of TR is often appreciated solely on echocardiography.

The precise mechanism by which functional TR develops is thought to be due to tricuspid annular dilation, as well as right ventricular (RV) enlargement and dysfunction associated with left heart disease and/or significant pulmonary hypertension (Dreyfus, Randolph et al. 2015). Left heart disease in this context mainly refers to MV pathology in the presence of systolic and/or diastolic dysfunction. Up to one third of patients with mitral stenosis have moderate or greater TR. However reports of the prevalence of TR and/or annular dilation in patients undergoing surgery for mitral regurgitation (MR) vary, ranging from 8-65% (Sagie, Freitas et al.1997; Dreyfus, Corbi et al. 2005; McCarthy 2007; Chan, Burwash et al. 2009; Chikwe, Itagaki et al. 2015; TM Koelling, Aaronson et al. 2002).

In 1967, Braunwald and colleagues demonstrated that correction of left-sided disease allowed for resolution of TR (Morrow, Oldham et al. 1967). In more recent years however this philosophy has been challenged by some, on account of observations that TR may in fact resolve only in a minority of cases. Overall data on the postoperative course and clinical sequelae of TR are conflicting, largely due to heterogeneous surgical management and MV pathologies. Dreyfus et al, for example, have reported that up to 48% of patients have an increase of up to 2 grades of TR (Raja and Dreyfus 2009), whereas other investigators have demonstrated only small increases in mean TR over a 5-year postoperative period.

Although the clinical context in which TR occurs may influence prognosis, there are numerous reports that demonstrate the presence of TR being associated with increased mortality. Nath and colleagues showed that moderate or more severe TR conferred inferior survival even after adjusting for age, left ventricular and RV function in a cohort of over 5000 male Veteran patients (Nath, Foster and Heidenreich 2004). These findings were supported by a study by Lee et al, who reported a 74% 5-year survival for patients with moderate or severe TR who were medically managed (Lee, Song et al. 2010; Nishimura, Otto et al. 2014). Importantly, TR may influence the quality of survival as well. Decreased exercise tolerance has been reported in patients with TR after MV replacement, and patients who go on to develop more severe TR are more likely to develop New York Heart Association class III-IV symptoms (Groves, Lewis et al. 1991; Ruel, Rubens et al. 2004).

Rationale for the Trial

Medical therapy for TR is limited only to diuretics and potential treatment of elevated pulmonary pressures. Echocardiographic assessment of severity can be dynamic in that degree of TR is highly dependent on preload, afterload and RV function. Though functional TR is a result of annular dilation, routine measurement on echocardiography is not common in clinical practice.

In patients with severe TR already undergoing surgery for left valvular pathology, surgical correction is recommended by the AHA/ACC and ESC guidelines (Nishimura, Otto et al. 2014). Significant equipoise exists, however, as to the optimal approach for patients with only moderate TR or mild TR with annular dilation. Some centers argue that performing a TV annuloplasty at the time of MVS influences the incidence of right heart failure and improves long term survival, yet others believe the risk of an additional surgical procedure outweighs the potential benefit (Yilmaz, Suri et al. 2011). According to the STS database, among 46,500 isolated primary MV operations performed between 2011 and 2014, TV repair was performed in 4% of patients with none or mild TR, 35% of patients with moderate TR, and 79% of patients with severe TR. These practice patterns serve to reflect an uncertainty of benefit of concomitant TV repair for moderate TR as well as variability in practice.

Establishing whether or not definitive benefit is conferred by performing TV repair at the time of MVS for degenerative MV disease should provide the level of evidence needed to provide rigorous recommendations for the management of this significant patient population. As such, the Network has designed a trial to evaluate the efficacy and safety of concomitant TR annuloplasty at the time of MVS.

Justification of Primary Endpoint Selection

Ideally, the effectiveness of TR repair should be measured by the degree to which it reduces relevant clinical events. However, the combination of the relatively low expected two-year event rate in the target population of degenerative MR with moderate or less TR, and logistical constraints on the sample size for the trial, precludes using an

endpoint defined in terms of clinical events alone. Instead, we propose a composite endpoint of death from any cause, progression of TR (measured echocardiographically) or TV reoperation. There is evidence that the presence of severe TR is independently correlated with decreased late survival (Nath, Foster et al. 2004) and that the presence of significant TR after MV operations is correlated with RV dysfunction and decreased RV reverse remodeling (Goldstone, Howard et al. 2014; Van de Veire, Braun et al. 2011; Benedetto, Melina et al. 2012; Bertrand, Koppers et al. 2014; Vargas Abello, Klein et al. 2013). Among patients with systolic heart failure, the presence of significant TR is associated with an increased risk of hospital admission for congestive heart failure, and TR in combination with RV dysfunction is associated with renal dysfunction and excess mortality (Agricola, Marini et al. 2015).

We also considered cardiac MRI for the primary evaluation modality but thought the test onerous and likely to constrain enrollment and increase missing data. While MRI is the gold standard for determination of RV structure and function, compliance with initial (preoperative) MRI in a pilot study has been obtained in only 67 % (N=40) of patients due to contraindications or patient refusal, with follow-up compliance and acquisition rates significantly lower. RV volume as measured by 3D echocardiography is a potential alternative to MRI. However, this promising but emerging modality still presents technical limitations. In addition, established longitudinal data on 3D echo assessment of RV remodeling after TR annuloplasty do not exist as of yet. We, therefore, felt that RV volume by 3D echo was not appropriate as the primary endpoint, but did include it as a secondary endpoint.

ENDPOINTS

Primary

Composite of death, reoperation for TR, or progression of TR from baseline by two grades or the presence of severe TR at 2 years.

Degree of TV regurgitation will be categorized according to American Society of Echocardiography guidelines as none/mild/moderate/severe. Trace regurgitation is also used in the event that regurgitation is barely detected.

Secondary

Clinical and Functional Outcomes

- Composite of major adverse cardiac and cerebrovascular events (MACCE), including stroke, death, and serious heart failure events
- NYHA classification
- 6MWT

Echocardiography

- Degree of TR at index hospital discharge
- Degree of TR at 12 and 24 months
- RV size at 12 and 24 months

- RV function (normal, mildly impaired, moderately impaired, severely impaired, peak tricuspid annular velocity, TAPSE, RVFAC) at 12 and 24 months
- Pulmonary artery pressure at 12 and 24 months
- RV volume at 12 and 24 months

Quality of Life

- SF-12
- KCCQ
- EQ-5D

Survival

- Perioperative mortality (greater in-hospital or 30-day mortality)
- Mortality

Serious Adverse Events

- Frequency of SAEs
- AV-Block requiring pacemaker implantation
- New-onset atrial fibrillation

Hospitalizations

- Index hospitalization LOS and ICU days
- All-cause readmissions and readmissions for heart failure and TR re-operation

Economic Outcomes

- Cost
- Cost-effectiveness

STUDY DESIGN

This is a multi-center randomized clinical trial. The trial will be conducted in highly experienced clinical centers participating in the NIH/CIHR supported Cardiothoracic Surgical Trials Network (CTSN) and the German Society for Thoracic and Cardiovascular Surgery. The estimated enrollment period is 24 months (n = 400), and all patients will be followed for 60 months post-randomization. Endpoints will be measured at 30 days, 6 months, 12 months, and 24 months. Survival will continue to be measured after the 24-month visit via vital sign checks at 36, 48 and 60 months.

RANDOMIZATION

Patients will be randomly assigned (1:1) to MVS + TV annuloplasty or MVS alone. Patient randomization will be stratified by TR severity and by clinical center. The randomization procedure will be performed intra-operatively, following sternotomy or thoracotomy, in order to minimize the likelihood of enrolling patients in the study with unexpected surgical contra-indications to TV repair. Randomization will be performed centrally through a Web-based data collection system that automates the delivery of the

randomization assignments. The treatment assignment will be viewed by 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

Neither patients nor investigators will be blinded to treatment assignment due to the nature of the treatment intervention. Investigators will, however, be blinded to all data from other clinical sites, except serious unexpected AEs that are possibly or probably related to the investigational procedure for IRB/REB/EC reporting purposes. All echocardiograms will be analyzed by echocardiography core laboratory (Echo Core Lab) personnel who will be blinded to clinical outcomes. Adverse events (AEs) will be adjudicated by an Event Adjudication Committee (EAC) and trial oversight will be provided by an independent Data and Safety Monitoring Board (DSMB).

STUDY POPULATION

The patient population for this trial consists of adult patients undergoing MVS via full or minimal-access sternotomy or right thoracotomy for degenerative MV disease using legally marketed devices. Specific inclusion and exclusion criteria are listed below. All patients who meet the eligibility criteria may be included in the study regardless of gender, race, or ethnicity.

Inclusion Criteria

1. Undergoing MVS for degenerative MR with

   (a) Moderate TR as determined by transthoracic 2D echocardiography, or

   (b) Tricuspid annular dimension ≥ 40 mm (index: ≥21mm/M^2 BSA) and trace/mild TR, determined by echocardiography.

2. Age ≥ 18 years

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

Exclusion Criteria

1. Functional MR

2. Evidence of sub-optimal fluid management (e.g., lack of diuretics, weight in excess of dry weight) in the opinion of the cardiology investigator

3. Structural / organic TV disease

4. Severe TV regurgitation as determined by preoperative transthoracic echocardiography (TTE)

5. Implanted pacemaker or defibrillator, where the leads cross the TV from the right atrium into the right ventricle

6. Concomitant cardiac surgery other than atrial fibrillation correction surgery (PVI, Maze, LAA closure), closure of PFO or ASD, or CABG

7. Cardiogenic shock at the time of randomization

8. STEMI requiring intervention within 7 days prior to randomization

9. Evidence of cirrhosis or hepatic synthetic failure

10. Severe, irreversible pulmonary hypertension in the judgment of the investigator

11. Pregnancy at the time of randomization

12. 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

13. Any concurrent disease with life expectancy < 2 years

14. Unable or unwilling to provide informed consent

15. Unable or unwilling to comply with study follow up in the opinion of the investigator

Recruitment Strategies

Based on a survey of the clinical sites, it is estimated that approximately 150-200 patients could be enrolled annually through active screening and recruitment by the participating CTSN and German 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 Data Coordinating Center (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, and social reasons, and for the generalizability of trial results. The CTSN is strongly committed to ensuring a balanced recruitment of patients regardless of sex or ethnicity. The North American clinical sites 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

Patients will be randomly assigned to the following treatment groups:

Mitral Valve Surgery + Tricuspid Valve Annuloplasty

Mitral Valve Surgery Alone

DEFINITIONS AND MEASUREMENT OF ENDPOINTS

Primary Endpoint

The primary endpoint for the trial is the composite of death, reoperation for TR, or progression of TR from baseline by two grades *or* the presence of severe TR at 24 months.

Secondary Endpoints

Clinical and Functional Outcomes

MACCE (Major Adverse Cardiac and Cerebrovascular Events)

MACCE is defined as a non-weighted composite score comprised of the following components:

- Death
- Stroke
- Serious heart failure events

NYHA Classification and Diuretic Use

Functional status will be assessed by the NYHA Classification scale. Complete NYHA classification guidelines can be found in Appendix II. The diuretic requirements of patients will be assessed.

Six Minute Walk Test

The total distance walked in six minutes will be assessed.

Physiologic

Echocardiographic Parameters (Appendix I)

- Degree of TR at Index Hospital Discharge
- Degree of TR at 12 and 24 months

- RV Size at 12 and 24 months
- RV Function (normal, mildly impaired, moderately impaired, severely impaired, peak tricuspid annular velocity, TAPSE, RVFAC) at 12 and 24 months
- Pulmonary Artery Pressure at 12 and 24 months
- RV volume at 12 and 24 months as measured by transthoracic 3D echocardiography

Quality of Life

The change in QOL from baseline will be measured, using the disease-specific KCCQ score, the SF-12 general health status index, and EQ-5D measures of health state preference from the individual and societal perspective. The KCCQ is a widely used tool in heart failure populations. 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 EQ-5D 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.

For this trial, the SF-12, EQ-5D, and KCCQ are available in English, Spanish, French and German. 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).

Survival

Perioperative and all-cause mortality over 60 months will be assessed

Hospitalizations

Length of 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). LOS will be measured as time from index surgery to discharge. In addition, we will capture discharge location.

Readmission and Reoperations

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 cardiovascular and heart failure readmissions and readmissions for TR operation. Classification of a readmission as heart failure related requires *at least 2* out of the following signs and symptoms of acute decompensated heart failure:

- Dyspnea felt related to heart failure
- Treatment with intravenous diuretic, vasodilator or inotropic therapy

- X-ray evidence of pulmonary edema or pulmonary vascular congestion
- Rales on physical exam
- PCWP or LVEDP > 18 mmHg

All readmissions will be classified by the investigator and adjudicated by the EAC.

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

Economic Measures

Inpatient costs will be measured through the collection of hospital billing and resource utilization information. 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 visit if they have been hospitalized at another hospital and if yes for how long.

For those institutions who participate in the University Healthsystems Consortium (UHC), hospital costs and resource utilization data will be collected. UHC works with academic medical centers around the country to collect and warehouse clinical, safety, operational and financial data. These data are used to compare performance among peer hospitals and identify best practice patterns. Participating centers will provide unique trial information and the dates of participation in the trial to UHC who will provide a de-identified data set of the financial data for the trial to the investigators for analysis.

For institutions who do not participate in the UHC, hospital billing data in UB-92 will be collected in a de-identified manner from the institutional billing departments. As hospitalization practices differ substantially and detailed accounting data are unavailable for the participating German centers, the cost and cost-effectiveness analysis will be restricted to North American centers only.

Safety

Adverse Events

Please refer to the CTSN Clinical and Adverse Event Reporting and Adjudication Procedures guidance document for general reporting procedures and guidance on the determination of intervention-expected AEs.

Specific Adverse Event Definitions

AV Conduction Block leading to Permanent Pacemaker Placement

See “Cardiac Arrhythmias” below

New-onset Post-Operative Atrial Fibrillation

See “Cardiac Arrhythmias” below

Bleeding

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

- Transfusion of > 5 units RBC within the first 24 hours following surgery
- Death due to hemorrhage
- 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 follows:

- Cardiac arrest
- Sustained ventricular arrhythmia requiring defibrillation or cardioversion.
- Sustained supraventricular arrhythmia requiring drug treatment or cardioversion
- Cardiac conduction abnormalities or sustained bradycardia requiring permanent pacemaker placement (includes all PPMs whether associated with a serious AE or not)

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

Liver injury **and** impaired liver function defined as:

- ALT ≥ 3xURL *and* total bilirubin* ≥ 2xURL (>35% direct), **or**
- ALT ≥ 3xURL *and* INR** > 1.5.

* Serum bilirubin fractionation should be performed if testing is available; if unavailable, measure urinary bilirubin via dipstick. If fractionation is

unavailable and ALT ≥ 3xURL and total bilirubin ≥ 2xURL, then the event is still to be reported as an SAE.

** INR testing not required per protocol and the threshold value does not apply to subjects receiving anticoagulants. If INR measurement is obtained, the value is to be recorded on the SAE form.

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 ≥ 38.0^{o} C, positive blood cultures, new regurgitant murmurs or heart failure, evidence of embolic events (e.g., focal neurologic impairment, glomerulonephritis, renal and splenic infarcts, and septic pulmonary infarcts), and peripheral cutaneous or mucocutaneous lesions (e.g., petechiae, conjunctival or splinter hemorrhages, Janeway lesions, Osler's nodes, and Roth spots). Echocardiographic evidence of 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]:

[1] Joint ESC/ACCF/AHA/WHF Task for the Redefinition of Myocardial Infarction, *Circulation*. 2007; 116:0-0.

Myocardial Infarction (Non-Procedure Related)

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:

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

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.

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 indicative of peri-procedural myocardial necrosis. By convention, increases in biomarkers > 3 x 99th percentile URL have been designated as defining PCI-related MI. A subtype related to a documented stent thrombosis is recognized.

Note: 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) that is not classified as a clinical stroke. 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 on neuroimaging). The NIH Stroke Scale (NIHSS) and Modified Rankin Scale (mRS) must be administered within 24 hours following the event if the event is not captured at a protocol-defined assessment time point to document the presence and severity of neurological deficits.

Each neurological event must be subcategorized as:

- TIA defined as an acute event that resolves completely within 24 hours with no imaging evidence of infarction.
- Hemorrhagic stroke
- Ischemic stroke
- Toxic Metabolic Encephalopathy, defined as a disorder of the brain function that arises from abnormal systemic metabolism, infection, or exogenous substances, altering awareness and/or consciousness, in which there is a non-focal neurological examination and a negative brain image.
- Seizure, defined as an abnormal paroxysmal cerebral neuronal discharge that results in alteration of sensation, motor function, behavior, or consciousness
- Other

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 ventilator support within 48 hours post-surgical intervention. This excludes 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

- intravenous therapy (diuretics, inotropic support, or vasodilators) *and* prolongs hospital stay in the judgment of the investigator, ***or***
- introduction of intravenous therapy (diuretics, inotropic support, or vasodilators) at any point following discharge from the index hospitalization, ***or***
- 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:

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

This definition excludes 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

All other SAEs (events that cause 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 30 clinical centers participating in the NIH/CIHR supported Cardiothoracic Surgery Network and the German Society for Thoracic and Cardiovascular Surgery. Each clinical center will be required to obtain IRB/REB/EC approval for the protocol and consent revisions in a timely fashion, to recruit patients, to collect data and enter it accurately into the electronic data capture (EDC) system, to faithfully follow the protocol and adhere to the standards of Good Clinical Practice (GCP) and HIPAA regulations (US sites), the Personal Information Protection and Electronic Documents Act (PIPEDA) regulations (Canadian sites) or the European Union's Privacy Directive (German sites). In addition, centers will be required to provide the 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.

INVESTIGATORS

All surgeons, cardiologists, coordinators and other investigators involved in the trial must complete the Investigator Contact Form with their hospital affiliation, address, contact numbers (phone, fax, cell, pager), and email address. All investigators must send their CV, Clinical Study Agreement/Conflict of Interest Statement, Good Clinical Practice Certificates, and HIPAA or other Privacy Protection certification as required by the local institution to the DCC.

Qualifications and Training

Clinical investigators will be cardiothoracic surgeons with expertise in surgical management of the mitral and tricuspid valves. To qualify as a surgeon participating in this trial, the surgical investigator must have performed at least 10 MV and 5 TV procedures annually (averaged over a 2-year period). 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 (PI) will be responsible for overseeing the ongoing performance of the other participating surgical investigators at that site over the course of the study.

All clinical site investigators and coordinators will be trained by the DCC in the specifics of the protocol during site initiation in advance of patient enrollment. In addition, the investigators and coordinators will undergo a separate training session to gain familiarity with the EDC.

Echocardiography Qualification

Each clinical site echocardiography lab involved in image acquisition for this trial will be certified by the Echocardiography Core Lab to perform the protocol defined TTE and the intra-operative transesophageal echo (TEE). Importantly, the TTE assessments will be used to determine eligibility in terms of patients having moderate TR or a tricuspid annular dimension ≥ 40 mm (index: ≥21mm/M^2 BSA) and trace/mild TR.

The site certification for the TTE and TEE will happen in two steps:

1. Prior to being open to enrollment, the site will send a sample TEE and TTE which follows the acquisition protocol. The site must receive Echo Core Lab approval for both the TEE and TTE in advance of performing any study related images.

2. Once open to enrollment, the site will acquire and adjudicate the degree of TR on the research TTE images for consented patients. Prior to the scheduled surgical procedure, the site will upload the de-identified images along with the adjudication of the TR to the EDC for review and over-reading by the Echo Core Lab to confirm eligibility. Once the Echo Core Lab has confirmed that the site has successfully adjudicated the degree of TR for eligibility inclusion in the trial for 3 patients, the site will be certified to continue eligibility determination independently.

The clinical sites will upload all echoes to the EDC website as they are acquired. The Echo Core Lab will read these echoes as they are uploaded. The Core Lab will carefully monitor compliance of site acquisition and interpretation of the TTE images used for eligibility determination. If the Core Lab determines that eligibility TTE did not meet the protocol defined criteria, the Core Lab will provide immediate feedback to the site echocardiography site investigator and create a corrective action plan which will include re-training of site echocardiography investigators.

Delegation of Authority and PI Oversight

Principal Investigators are responsible for all study activities at their sites. They may delegate study tasks to qualified staff members while continuing to oversee all study activities. The Delegation of Authority Log will list each staff member's title and responsibilities for the study. The PI is responsible for careful review of each staff member's qualifications which includes training for the tasks to which each staff member is delegated. Each task should be assigned to more than one staff member to ensure proper coverage. Only staff members delegated for each task on the Delegation of Authority Log may conduct study-specific assessments. The Delegation Log will also contain the signature of each staff member. The PI will initial any additions to the Delegation of Authority Log that occur during the course of the study. The PI should document oversight of study activities throughout the life of the trial by indicating review of key elements such as eligibility, abnormal laboratory values and AEs via signature and date on appropriate source documentation.

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

Site Approval
The following documents must be collected prior to site approval:

- Fully executed Clinical Trial Agreement (CTA) with the CTSN DCC: InCHOIR, Department of Population Health Science & Policy, Icahn School of Medicine at Mount Sinai
- Curricula vitae
- IRB/REB/EC roster
- IRB/REB/EC approval, version and date for protocol and consent
- HIPAA/PIPEDA/Privacy Directive compliance approval
- Surgical Investigator Certification
- Echo Core Lab Certification
- National Institutes of Health Stroke Scale (NIHSS) Training Certification
- Modified Rankin Scale (mRS) Certification
- Delegation of Authority Log
- Clinical Center Laboratory Certification(s)
- Laboratory normal ranges

Other regulatory and training documentation may be required prior to site initiation. Prior to enrolling a patient, representatives from the DCC will conduct a site initiation for all investigators, coordinators and any other health care professionals who may be involved in the study.

Patient Confidentiality
All patients' records will be kept confidential according to privacy regulations. Study Investigators, site IRBs/REBs/ECs, the DCC, EAC, medical monitors and NHLBI personnel may review source documentation as necessary but all unique patient and hospital identifiers will be removed from source documents which are sent to the DCC. The aggregate data from this study may be published as per publication policy documented in the CTA; however, no data with patient identifiers will be published.

SCREENING AND BASELINE
Screening Registration 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 on the top portion of the screening registration form. The data collected is compliant with privacy regulations 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 IRB/REB/EC 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 and monitors.

Demographics Form

At initiation of screening

A screened patient is defined as a consented subject 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, date of birth, ethnic origin, and sex will be captured on the registration form. The EDC will generate a unique 5-digit identification code that will identify the patient throughout the course of the study.

Echocardiogram

Within 30 days prior to randomization

A complete TTE will be performed according to the specifications defined in the Echocardiographic Image Acquisition Protocol (Appendix I) within 30 days prior to randomization. ***The pre-randomization 2D echo will be read by the clinical site echocardiography investigator to assess the degree of TR which will determine echocardiographic eligibility for participation in the trial.*** (See Echocardiography Qualification above) 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. In addition, the sites will perform a 3D TTE to assess RV volume.

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 RV or biventricular pacemaker, stroke and other comorbidities such as diabetes and peripheral vascular disease.

Six Minute Walk Test
Within 7 days of randomization
This form captures the distance in feet walked on a level hallway in six minutes (See Appendix III). A research clinician trained on the protocol and designated by the PI will oversee the 6MWT.

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 delegated to perform this assessment and documented on either the New York Heart Association Classification form or in the body of the medical record. The NYHA classification scheme is detailed in Appendix II.

Medications
Within 7 days prior to randomization
This form captures current medications at one pre-operative time point.

Physical Examination
Within 30 days prior to randomization
This form captures the comprehensive physical examination including vital signs cardiopulmonary examination, abdominal examination, and anthropometrics (height, weight).

Quality of Life
Within 30 days prior to randomization
The KCCQ, SF-12, and EQ-5D questionnaires will be completed by the patient to assess QOL. Data regarding completeness of QOL data collection and reasons for missing responses to questionnaires will be collected on the QOL Checklist.

Laboratory Assessment
Within 30 days prior to randomization
- Hematology, including white blood cell *($10^3/\mu L$),* Hemoglobin *(g/dL),* Hematocrit *(%),* Platelet count *($10^3/\mu L$)*
- Coagulation profile, including 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 *(*BUN, *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).*

At time of randomization

- Urine or serum beta HCG *(IU/L)* is required for women who have the potential to become pregnant

Randomization Eligibility
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 Randomization Eligibility Form. The degree of TR will also be recorded for stratification purposes. 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 compliant with privacy regulations and includes reason for not being randomized.

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

RANDOMIZATION
The randomization procedure will be performed intra-operatively, following sternotomy or thoracotomy. Randomization to the study assignment will be generated by the EDC 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.

PROCEDURE
Surgical Procedure
Patients will be randomized to either (a) TV repair using a legally marketed annuloplasty ring in addition to the MVS (b) MVS alone.

After induction of anesthesia, all patients will undergo TEE. The TEE will be performed under loading conditions as close as possible to the patient's baseline. Intra-operative TEEs will be performed according to standardized acquisition protocol developed by the Echo Core Lab (Appendix I). A laminated copy of this acquisition protocol will be provided to the site and affixed to the operating room echo machine.

All procedures will be performed using cardiopulmonary bypass support and cardioplegic arrest. The management of cardiopulmonary bypass and myocardial protection will be at the discretion of the surgeon, using standard techniques. MV repair or replacement will be performed using standard techniques.

Tricuspid valve surgery
Patients randomly assigned to receive TV repair in addition to MVS will undergo concomitant TV repair.

It is recognized that surgical techniques for TV surgery may need to be adjusted at the discretion of the surgeon based on intra-operative findings that may not be previously

recognized in the preoperative evaluation. The common elements for tricuspid annuloplasty planned as part of this study are listed below:

- All procedures will be performed with cardiopulmonary bypass and with bicaval cannulation
- Both trans-septal and bi-atriatomies are acceptable as the approach to the TV
- Performance of TV repair on the arrested or the beating heart will be at the discretion of the surgeon
- TV repair will be performed with a rigid, incomplete, nonplanar, undersized annuloplasty ring
- Nominal annuloplasty ring sizes 26, 28, or 30 mm will be used. It is anticipated that normal tricuspid annular dimensions will be restored in most cases with a size 26 or 28 mm annuloplasty ring
- Commercially available rigid incomplete nonplanar tricuspid annuloplasty rings include:

    - Edwards MC3 tricuspid annuloplasty ring (model 4900)
    - Medtronic Contour 3D tricuspid annuloplasty ring (model 690R)
    - Medtronic Tri-Ad tricuspid annuloplasty ring (model 900SFC)
    - Carpentier-Edwards Classic tricuspid annuloplasty ring (model 4500)[1]
      Carpentier-Edwards Physio Tricuspid ring (model 6200)

- Interrupted non-pledgeted mattress sutures will be placed from 9:00 o'clock to 6:00 o'clock (the mid-point of the septal leaflet) around the tricuspid annulus. In general, 10 to 12 sutures will be required to assure reliable seating of the tricuspid annuloplasty ring.

Peri-operative Management

Peri-operative hemodynamic support may be necessary. A variety of strategies may be utilized to optimize postoperative ventricular function. These strategies may include pacing, infusions of vasopressors or positive inotropic agents including both beta receptor agonists and/or phosphodiesterase inhibitors such as milrinone. Occasional patients may require mechanical support, either intra-aortic balloon pumping or ventricular assist devices.

Other Treatment

All patients enrolled in this trial are to receive standard medical management for their regurgitant mitral / tricuspid valvular disease and other co-morbid conditions in accordance with current medical practice guidelines. This includes when clinically indicated and tolerated, but is not limited to, beta-blockade, angiotensin converting enzyme inhibitors (ACE) or angiotensin receptor blockers (ARB), antiplatelet agents, statin therapy (or alternative lipid lowering agent), aldosterone antagonists, antiarrhythmic therapy, implantable defibrillators and cardiac resynchronization therapy.

[1]needs to be manually bent into nonplanar shape similar to other commercially available annuloplasty rings

POST-RANDOMIZATION DATA COLLECTION

Study Visits

- Post-Randomization Day 30 *(±7days)*
- 6 *(±14 days*), 12 *(± 14 days*) and 24 months *(± 30 days*) post-randomization
- 36, 48 and 60 months vital status check *(± 30 days*)

For patients who are unable to return to the clinical site for the *6- and 12-month* assessments because of extreme geographic distance, the clinical coordinator will obtain the required data from a remote clinical site outside of the 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 24-month (Primary Endpoint) assessments must be performed at a CTSN clinical site.* The 36-, 48- and 60-month vital status check may be conducted via telephone or via a search of medical records.

Surgical Procedures

Initial surgical intervention and event driven

The initial surgical procedure (MV surgery ± TV repair) will be reported on the initial surgical Procedure form and all subsequent operations must be reported on the follow up 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 AE report.

Initial Surgical Procedure

Routine information will be collected on the standard surgical procedure, the MV procedure, TV procedure and any concomitant procedures.

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

For all patients, the index (baseline) hospitalization must be reported on the Hospitalization form. This form collects limited information about LOS, days in ICU, and disposition at time of discharge (home, skilled nursing facility, rehabilitation facility, death).

Medications

At 30 days (±7 days), 6 (±14days), 12(±14 days), and 24 months (± 30 days) post randomization and event driven

All cardiovascular medications will be recorded at each study visit, and also as indicated at the time of associated AEs.

Physical Examination
At 30 days (±7 days), 6 (±14days), 12 (±14 days), and 24 months (± 30 days) post randomization
In this limited physical examination, vital signs, weight and cardiopulmonary examination will be captured.

New York Heart Association Classification
At 30 days (±7 days), 6(±14 days), 12(±14 days), and 24 months (± 30 days) post randomization
The presence of heart failure will be assessed, and when present, classified according to the NYHA scale. We will assess diuretic requirements of patients as well.

Six Minute Walk Test
At 30 days (±7), 6 (±14days), 12 (±14 days), and 24 months (± 30 days) post randomization
This form captures the distance in feet walked on a level hallway in six minutes (See Appendix III). A research clinician trained on the protocol and designated by the PI will oversee the 6MWT.

Echocardiogram
At Pre-discharge, 6(±14days), 12(±14 days), and 24 months (± 30 days) post randomization
A complete TTE 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. **All patients must be euvolemic, (i.e., optimal fluid management in the judgment of the cardiology investigator) at all follow up echos.** For patients who are unable to return to the clinical site for the *6*- and *12*-month assessments because of extreme geographic distance, a limited echo will be obtained at a remote center (see Echocardiogram Image Acquisition section). 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 24-month (Primary Endpoint) assessments must be performed at a CTSN clinical site.* All study echos will be sent to the Echo Core Lab for centralized reading by a blinded investigator. In addition, a 3D TTE will be performed to measure RV volume at 12 and 24 months.

Quality of Life
At 6(±14 days), 12(±14 days), 18 (±14 days) and 24 months (± 30 days) post randomization
The KCCQ, SF-12, and EQ-5D Questionnaires will be completed by the patient to assess QOL. Data regarding completeness of QOL data collection and reasons for missing responses to questionnaires will be collected on the QOL Case Report Form.

Vital Status Check
At 36, 48 and 60 months (± 30 days) post randomization
The patient's vital status will be collected via telephone or a review of medical records.

Cost
Direct costing data for all randomized patients (from North American sites) will be obtained by the DCC at the conclusion of the trial.

Event Driven Data Collection

Follow-Up Surgical Procedures
Event Driven
All operations following the initial study defined surgical intervention 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 AE report. All intra-operative transfusion requirements must be documented.

Adverse Events
Event Driven
Detailed information regarding AEs will be recorded at the time an AE occurs. Investigators will be asked to make a judgment as to the seriousness and relationship of the event to the surgical intervention. All AEs will be recorded through month 24.

Re-Hospitalizations
Event driven
All ED visits (of any duration) and re-hospitalizations (>24 hours for any reason) must be reported on the Re-Hospitalization Form. This form collects limited information about hospital procedures, LOS, days in ICU, and discharge if applicable, as well as patient condition and disposition for each hospitalization.

Outpatient Intervention
Event driven within 48 hours of knowledge of event
All outpatient procedures following the index hospitalization must be reported on the surgical procedure form within 48 hours of the knowledge of the event. If the intervention is to address a complication, the coordinator must also complete an AE report.

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 recorded on the protocol deviation form.

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 anticipated reasons for a patient to be withdrawn from this study, is either the patient's request or at the physician's discretion, details of which will also be documented on this 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 EDC (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 (VPN). 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. 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.

Additional external cross-form checks for data consistency and validation will be made by the DCC's data management team. Data will be monitored remotely at the DCC on an ongoing basis to check for inconsistencies in information across forms and for data outliers (typically values that fall in the highest or lowest 10% of the accumulated data and/or values that are outside the range of what is typically considered to be physiologically possible). Monitors will enter these queries through the EDC for site coordinators to either correct or verify.

Monitoring

The DCC monitoring team employs a risk-based approach to centralized and on-site monitoring. This approach focuses efforts on the most crucial data and process elements

to allow for more efficient monitoring practices while maintaining the quality of the overall study conduct. Through the combination of centralized and on-site monitoring, instantaneous electronic validation via the EDC, and visual cross-validation by the InCHOIR monitors to detect complex errors, it is anticipated that the best possible quality and most complete data will be collected.

The centralized, or remote, monitoring of clinical trial data via the EDC is performed with a focus on safety, study endpoints, data completion and data outliers. DCC monitors will remotely monitor source documentation, study logs including the Informed Consent Log, the Protocol Violation/Deviation Log and the Serious Adverse Event/Safety Report Log periodically to ensure that the sites are adhering to the study protocol and procedures. In collaboration with the DCC data management team, the monitors will create and utilize reports outlining data completeness and timeliness, missing and outlier values as well as cross form consistency validations to generate queries and optimize reconciliation of data. This process significantly increases the efficiency of monitoring both remotely and while on site.

The DCC may conduct on-site monitoring visits after enrollment begins approximately once each year for every clinical site depending on site enrollment and other data quality metrics 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 are complete and accurate. They will also verify that all AEs 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 AEs and outcomes.

The monitors will also confirm that the regulatory 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/REB/EC roster, IRB/REB/EC approvals for all of the above documents, IRB/REB/EC correspondence, investigator's agreements, delegation of authority log, CVs of all study personnel, Human Subjects Protection training certificates, institutional HIPAA or other privacy training certificates, monitor site visit log, telephone contact log, and correspondence with the DCC.

Given the combination of approximately yearly on-site monitoring and ongoing monitoring using the EDC 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.

ANALYTICAL PLAN

General Design Issues

This study is a prospective, multi-center, randomized clinical trial. Enrolled patients will have degenerative MV disease with a clinical indication for MVS. This trial will compare the surgical approach of combining TV annuloplasty with clinically indicated MVS to performing the MVS alone.

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 TV repair (Goldstone, Howard et al. 2014; Nath, Foster and Heidenreich 2004; Koelling, Aaronson et al. 2002).

For computing sample size, we assume that at two years post randomization, 25% of patients treated with only MVS will experience the primary composite endpoint. We believe a meaningful effect worth detecting is at least a 50% relative reduction to 12%, for patients undergoing TV annuloplasty in addition to MVS. A total of 400 patients, randomized with equal probability to each arm, provides approximately 90% power to detect such a difference. For simplicity, power is based on a 0.05 level two-tailed chi-squared test. The sample size takes account of a single interim analysis to be performed in addition to the final analysis, and a minimal (less than 3%) rate of crossover.

Randomization Design and Procedure

Patients will be randomized using a 1:1 allocation to TV annuloplasty plus MVS or to MVS alone. The randomization will be stratified by clinical center (i.e., a separate randomization scheme will be employed in each center) and by whether severity of TR is moderate or not. 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.

Data Monitoring and Analysis

Methods of Analysis

The primary outcome of this trial is treatment failure defined as the composite of (1) death from any cause, (2) reoperation for TR, (3) presence of severe TR at two years post randomization or, for patients enrolled with less than moderate TR, the progression by two grades. The null hypothesis is that there is no difference in the probability of treatment failures at two years post randomization between patients randomized to undergo TV repair during MVS compared to patients randomized to undergo MVS alone. The primary null hypothesis will be tested in an intent-to-treat analysis using a 0.05 level two-tailed normal approximation (Wald) test.

A log binomial regression model will be used to estimate and test differences in treatment failure between randomization groups. Similar to the logistic regression model, the log-binomial model is a generalized linear model. The models differ only in the link function used for the "success" probability p; logit (log odds) for logistic regression and log (log p) for log-binomial. The different links parameterize the model differently, with

parameters of the log-binomial model yielding log relative risks rather than the log odds ratios of the logistic model.

The basic form of the log binomial models is:

$$\log P[Y_i = 1|X_{1i}, X_{2i}] = \beta_0 + \beta_1 X_{1i} + \beta_2 X_{2i} \ ,$$

where Y_i is a binary indicator of treatment failure for the i^{th} patient, X_{1i} is a binary indicator of randomization assignment for the i^{th} patient and X_{2i} is an indicator of moderate or less TR at baseline, a factor by which randomization will be stratified. While randomization will also be stratified by randomizing center, the analysis will not adjust for center due to their relatively large number compared to the proposed sample size. The exponentiated estimate of β_1 ($e^{\widehat{\beta}_1}$) in this model is the risk ratio for the composite endpoint for patients randomized to TV repair compared to patients randomized to no TV repair. The risk ratio and its associated 95% confidence interval will be used to quantify the relative risk of the composite endpoint. Differences between randomization groups in the risk of the composite endpoint will be determined by testing the null hypothesis H_0:β_1= 0 versus a two-sided alternative (H_1:$\beta_1 \neq 0$) using a 0.05 level intention-to-treat normal approximation test (i.e., the Wald test).

Imputation of missing data

We expect relatively few patients to be missing the primary endpoint due to withdrawal or refusal. Patients with missing data that are deemed by independent adjudicators to be due to severity of illness will be considered as treatment failures. Patients with missing data not due to severity of illness will have their 24 month status imputed via multiple imputation 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 and will be included in an accompanying statistical analysis plan.

The main feature of the imputation approach is the creation of a set of clinically reasonable imputations for treatment failure 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 5 datasets (an odd number to allow use of one of the datasets to represent the median result). 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.

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 (200) reach the primary endpoint. The utility of performing this analysis will depend on the rate of accrual of patients into the trial. 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 to 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 relative 52% reduction (from 25% to 12%) in the incidence of treatment failure for patients receiving TV annuloplasty in addition to MVS and patients randomized to MVS alone is less than 20%.

We do not propose any a priori stopping criteria based on AEs. The treatments in this trial are not experimental, and have well known AE profiles. Moreover, we believe that incident rates of AEs 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 MR. 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, based on all relevant information reported by the DCC and the Medical Monitors. We therefore recommend that the DSMB should be responsible for defining its deliberative processes, including event triggers that would call for an unscheduled review.

Sample Size Re-estimation

We propose considering increasing sample size should the observed primary endpoint event rate among patients randomized to no repair of the TV be appreciably less than the assumed rate of 25%. The planned sample size of 400 patients has been determined to ensure that power is at least 90% to detect a 52% relative reduction of "failure" for

patients randomized to tricuspid repair compared to no repair. Should the "failure" rate among controls be 20%, 400 patients provides approximately 83% to detect a 52% relative reduction; for a 15% "failure" rate among controls there is approximately 70% power to detect a 52% relative reduction. Therefore, we suggest that the primary endpoint event rate be examined in control patients, using the same analysis set to be used for the interim analysis, and that the sample size be increased by up to 100 additional patients in order to maintain 80% power under the original alternative hypothesis for control rates as low as 15%.

Assessment of Balance of the Randomization
The success of the randomization procedure in balancing important covariates 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 400 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 a secondary analysis of the primary endpoint.

Additional analysis of the primary endpoint
A subgroup analysis of the primary endpoint will be performed with subgroups defined by whether or not patients received a CABG procedure during the initial surgery. This analysis will be performed in the same manner as that described for the primary analysis.

Analyses of Secondary Endpoints
Individual components of the primary endpoint
Mortality: Differences in the rate of mortality between randomization groups over the planned 60 months of follow-up will be assessed using Cox proportional hazards regression.

Reoperation for TR: The difference in the probability of requiring subsequent TV annuloplasty after the initial MVS will be compared between randomization groups using a Cox proportional hazards regression model.

Degree of TR: Between group differences in the presence of severe TR at two years post randomization or, for patients enrolled with less than moderate TR, the progression by two grades will be compared using a two-tailed 0.05 level chi-squared test of the equality of two proportions.

MACCE: The proportion of patients experiencing major adverse cerebrovascular and cardiac events, defined as the composite event of death, stroke, and the serious heart failure events, is of particular interest. Given that this trial's primary endpoint is likely to be determined by echocardiographic assessments, 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 more clinical endpoint such as MACCE (and its component elements). As the trial is not powered to detect a difference in MACCE, a statistically significant treatment difference in MACCE is not expected; however, an observed

difference in MACCE, consistent in direction with that observed for the primary endpoint 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 MACCE observed between treatment groups. The proportion of patients experiencing a major cerebrovascular or cardiac event will be compared between randomization groups at 24 months by a two-tailed 0.05 level chi-squared test. We expect MACCE two-year event rates to be approximately 15% for patients randomized to MVS alone. With a total of 400 patients randomized with equal allocation to MVS alone or to TR repair plus MVS, there is 90% power to detect an absolute decrease in MACCE to approximately 9-10% for patients randomized to TR plus MVS compared to MV surgery alone.

Six Minute Walk Test: Differences between groups in the distances travelled during the 6MWT will be compared using the Wilcoxon Rank-Sum test.

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 two-tailed 0.01 level for significance.

Additional echo parameters: RV function (normal, mildly impaired, moderately impaired, severely impaired, peak tricuspid annular velocity, TAPSE, RVFAC) at 12 and 24 months and pulmonary artery pressure at 12 and 24 months will be compared between groups. RV volume as assessed by 3D TTE at 12 and 24 months will be compared between groups. Continuous variables will be compared for between group differences using the Wilcoxon Rank Sum test, and the level of function by chi-squared test.

Quality of life: QOL will be measured using the KCCQ SF-12, and EQ-5D. We will employ two approaches to the analysis of QOL. 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. 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.

Adverse Events: Differences in the incidence of individual AEs will be compared between randomization arms using Poisson regression. Exact 95% confidence intervals (based on the Poisson distribution) for the risk ratios for individual AEs for treatment with MVS and TV annuloplasty versus MVS alone.

NYHA classification: The distribution of NYHA at 12 and 24 months will be presented for each randomization arm and compared using a chi-squared test.

Hospital length of stay and days in Intensive Care: We will compare hospital LOS and days spent in ICU between treatment groups, separately by region (North America and Germany). A Wilcoxon Rank-Sum test will be used to test for differences within each geographic subgroup.

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

Hospital readmission: Rates of all-cause hospitalizations and rates of cardiovascular and heart failure specific hospitalizations, both within 30 days and within two years 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. Cost data will only be collected in the North American sites. 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 QOL 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 sampling variation and variations in discount rates.

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 TV annuloplasty who do not receive it during the trial can be considered crossovers. In addition, patients who are randomized to no annuloplasty but receive it during the index procedure are considered to have crossed over. As the primary analysis is by intention to treat, crossovers will be analyzed as belonging to the group to which they were randomized. Given the short duration between randomization and surgery, crossovers are assumed to be rare (no more than 3%).

ORGANIZATION OF THE STUDY

This section describes the overall study organization. The study will be conducted at up to 30 sites in the Cardiothoracic Surgical Trials Network sponsored by NHLBI, in collaboration with NINDS and CIHR, and the German Society for Thoracic and Cardiovascular Surgery. The following committees and institutions will be involved in the administration of the study.

Event Adjudication Committee

The charge of the EAC is to review source documents and adjudicate all AEs, causes of mortality and cardiovascular and heart failure related readmissions. The individuals who will serve on the committee are unaffiliated with the conduct of the clinical trial or the DCC. The committee will consist of experienced clinicians with expertise in cardiothoracic surgery, cardiology, infectious disease and neurology. Additional specialty clinicians can be added as deemed The EAC will meet every 2-4 months or as needed to review outcomes data for each subject enrolled.

Data and Safety Monitoring Board

To meet the study's ethical responsibility to its subjects, an independent DSMB will monitor results during the study. The board consists of physicians, biostatisticians, ethicists, neurologists 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 EAC every 6 months. These data include AEs 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

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

Echocardiography Core Laboratory

All echocardiograms will be performed according to a standardized protocol (Appendix I) and will be centrally analyzed by the Network Echo Core Lab directed by Judy W. Hung, MD, located at the Massachusetts General Hospital, Boston, MA.

Network 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; (c) collaborate in data analysis, interpretation, and publication; (d) establish criteria for authorship on all manuscripts, publications and presentations that arise from the study.

REFERENCES

Agricola E, Marini C, Stella S, et al. Effects of functional tricuspid regurgitation on renal function and long-term prognosis in patients with heart failure. J Cardiovasc Med (Hagerstown). 2015 Aug 7. [Epub ahead of print]

Benedetto U, Melina G, Angeloni E, Refice S, Roscitano A, Comito C, Sinatra R. Prophylactic tricuspid annuloplasty in patients with dilated tricuspid annulus undergoing mitral valve surgery. J Thorac Cardiovasc Surg. 2012 Mar;143(3):632-8.

Bertrand PB, Koppers G, Verbrugge FH, et al. Tricuspid annuloplasty concomitant with mitral valve surgery: effects on right ventricular remodeling. J Thorac Cardiovasc Surg. 2014 Apr;147(4):1256-64.

Chan V, Burwash IG, Lam BK, Auyeung T, Tran A, Mesana TG, Ruel M. Clinical and echocardiographic impact of functional tricuspid regurgitation repair at the time of mitral valve replacement. Ann Thorac Surg. 2009 Oct;88(4):1209-15.

Chikwe J, Itagaki S, Anyanwu A, Adams DH. Impact of Concomitant Tricuspid Annuloplasty on Tricuspid Regurgitation, Right Ventricular Function, and Pulmonary Artery Hypertension After Repair of Mitral Valve Prolapse. J Am Coll Cardiol. 2015 May 12;65(18):1931-8.

Dreyfus GD, Corbi PJ, Chan KM, Bahrami T. Secondary tricuspid regurgitation or dilatation: which should be the criteria for surgical repair? Ann Thorac Surg. 2005 Jan;79(1):127-32.

Dreyfus, GD, Martin, RP, Chan, KMJ, Dulguerov, F, Alexandrescu, C. Functional Tricuspid Regurgitation: A Need to Revise our Understanding. J Am Coll Cardiol. 2015;65(21):2331-2336.

Goldstone AB, Howard JL, Cohen JE, et al. Natural history of coexistent tricuspid regurgitation in patients with degenerative mitral valve disease: implications for future guidelines. J Thorac Cardiovasc Surg. 2014 Dec;148(6):2802-9.

Groves PH, Lewis NP, Ikram S, Maire R, Hall RJ. Reduced exercise capacity in patients with tricuspid regurgitation after successful mitral valve replacement for rheumatic mitral valve disease. Br Heart J. 1991 Oct; 66(4):295-301.

Koelling TM, Aaronson KD, Cody RJ, Bach DS, Armstrong WF. Prognostic significance of mitral regurgitation and tricuspid regurgitation in patients with left ventricular systolic dysfunction. Am Heart J. 2002 Sep; 144(3):524-9.

Lee JW, Song JM, Park JP, Lee JW, Kang DH, Song JK. Long-term prognosis of isolated significant tricuspid regurgitation. Circ J. 2010 Feb; 74(2):375-80. Epub 2009 Dec 14.

McCarthy PM. Adjunctive procedures in degenerative mitral valve repair: tricuspid valve and atrial fibrillation surgery. Semin Thorac Cardiovasc Surg. 2007 Summer;19(2):121-6.

Morrow AG, Oldham HN, Elkins RS, Braunwald E. Prosthetic replacement of the mitral valve. Preoperative and postoperative clinical and hemodynamic assessments in 100 patients. Circulation. 1967 May; 35(5):962-79.

Nath J, Foster E, Heidenreich PA. Impact of tricuspid regurgitation on long-term survival. J Am Coll Cardiol. 2004 Feb 4; 43(3):405-9.

Nishimura RA, Otto CM, Bonow RO, Carabello BA, Erwin JP 3rd, Guyton RA, O'Gara PT, Ruiz CE, Skubas NJ, Sorajja P, Sundt TM 3rd, Thomas JD; American College of Cardiology/American Heart Association Task Force on Practice Guidelines. 2014 AHA/ACC guideline for the management of patients with valvular heart disease: executive summary: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol. 2014 Jun 10;63(22):2438-88.

Pinney SP. The role of tricuspid valve repair and replacement in right heart failure. Curr Opin Cardiol. 2012 May;27(3):288-95.

Raja SG, Dreyfus GD Surgery for functional tricuspid regurgitation: current techniques, outcomes and emerging concepts. Expert Rev Cardiovasc Ther. 2009 Jan;7(1):73-84.

Ruel M, Rubens FD, Masters RG, Pipe AL, Bédard P, Mesana TG. Late incidence and predictors of persistent or recurrent heart failure in patients with mitral prosthetic valves. J Thorac Cardiovasc Surg. 2004 Aug; 128(2):278-83.

Sagie A, Freitas N, Chen MH, Marshall JE, Weyman AE, Levine RA. Echocardiographic assessment of mitral stenosis and its associated valvular lesions in 205 patients and lack of association with mitral valve prolapse. Am Soc Echocardiogr. 1997 Mar;10(2):141-8.

Taramasso M, Vanermen H, Maisano F, Guidotti A, La Canna G, Alfieri O. The growing clinical importance of secondary tricuspid regurgitation. J Am Coll Cardiol. 2012 Feb 21;59(8):703-10.

Van de Veire NR, Braun J, Delgado V, Versteegh MI, Dion RA, Klautz RJ, Bax JJ. Tricuspid annuloplasty prevents right ventricular dilatation and progression of tricuspid regurgitation in patients with tricuspid annular dilatation undergoing mitral valve repair. J Thorac Cardiovasc Surg. 2011 Jun;141(6):1431-9.

Vargas Abello LM, Klein AL, Marwick TH, et al. Understanding right ventricular dysfunction and functional tricuspid regurgitation accompanying mitral valve disease. J Thorac Cardiovasc Surg. 2013 May;145(5):1234-1241.e5.

Yilmaz O, Suri RM, Dearani JA, Sundt TM 3rd, Daly RC, Burkhart HM, Li Z, Enriquez-Sarano M, Schaff HV. Functional tricuspid regurgitation at the time of mitral valve repair for degenerative leaflet prolapse: the case for a selective approach. J Thorac Cardiovasc Surg. 2011 Sep;142(3):608-13.

Appendix I: Moderate Tricuspid Regurgitation Trial Echocardiographic Image Acquisition Protocol

General Considerations:

- For the echocardiogram, the patient will be positioned in left lateral recumbency or in the position that permits optimal imaging. All images should be acquired during quiet respiration unless otherwise specified.

- At least 3 and no more than 5 cardiac cycles are requested for two-dimensional imaging unless otherwise specified. 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. 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. Gain should be adjusted to reduce excess noise. Color Doppler Nyquist limits will be adjusted to the range of 50-70 cm/sec, unless otherwise specified. The following protocol is required however additional images should be obtained at the discretion of the sonographer/physician.

I. Protocol for Transthoracic Echocardiogram (TTE) pre and post-surgery

1. Parasternal long axis
   - 2D image
   - Color Doppler across aortic and mitral valves
   - Zoom image of LVOT
   - Zoom image of vena contracta

2. Parasternal right ventricular inflow view of the tricuspid valve
   - 2D image include RV and RA (optimize endocardium)
   - Color Doppler across tricuspid valve (TV) including distal jet into RA
   - Zoom view of TV annulus (for measurement of TV annulus)
   - Zoom view of vena contracta proximal jet of TR
   - Zoom view of the proximal flow convergence region of the TR jet after baseline shifted downward (same direction as TR jet flow) to a Nyquist of 25-35 cm/s
   - Continuous wave Doppler across TV valve to estimate TV gradient.

3. Parasternal outflow view of the pulmonic valve
   - 2D
   - Color Doppler across PV
   - Pulse wave Doppler
   - CW of the pulmonary valve

- Zoom 2D image of pulmonary valve annulus for measurement of the pulmonary annular diameter.

4. Basal PSAX (at the aortic valve level)
   - 2D image include TV, short axis of aortic valve and RVOT
   - Color Doppler of TV include distal jet into right atrium
   - Zoom view of Color Doppler view of vena contracta of TR
   - Zoom view of the proximal flow convergence region of the TR jet after baseline shifted downward (same direction as TR jet flow) to a Nyquist of 25-35 cm/s
   - 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.

5. PSAX of ventricles: ensure on-axis views and include right ventricle
   - Level of the mitral valve when both anterior and posterior leaflets are visualized.
   - Mid-papillary muscle level.
   - Level of the apex

6. Apical 4-chamber view
   - Full sector to include all four chambers
   - Focus on right heart: 2D to Include RV and RA, making sure to include lateral wall of RV (often requires a slight medial tilt of transducer)
   - Zoom view of RV only (include base of RV/TV annulus and optimize RV endocardium)
   - Color Doppler across TV one including right atrium to capture the distal jet taking care to include wall-impinging eccentric jets in the region of interest.
   - Zoom view of TV annulus (for measurement of TV annulus)
   - Zoom view of Color Doppler across TV to image the vena contracta of the TR jet
   - Zoom view of the proximal flow convergence region of the TR jet after baseline shifted downward (same direction as TR jet flow) to a Nyquist of 25-35 cm/s
   - PW of TV at leaflet tips and at level of TV annulus
   - CW of TV for estimation of pulmonary artery systolic pressure
   - M-mode across lateral tricuspid annulus (for TAPSE measurement)
   - Tissue Doppler of lateral tricuspid annulus (to measure peak annular velocity)
   - Focus on left heart:
     - 2D include both LV and LA
     - Zoom view of LV only (avoid foreshortening of LV apex)

- Color Doppler across MV one including left atrium to capture the distal jet taking care to include wall-impinging eccentric jets in the region of interest.
- Zoom view of MV annulus (for measurement of MV annulus)
- -Zoom view of the proximal flow convergence region of the MR jet after baseline shifted downward (same direction as MR jet flow) to a Nyquist of 30-40 cm/s
- PW of MV at leaflet tips and at level of MV annulus
- PW Doppler of right pulmonary vein flow. The sample volume should be placed at least 1 cm within the pulmonary vein
- CW of MV
- Tissue Doppler of lateral and septal mitral annulus

7. Apical 5-Chamber view
   - Color flow Doppler across LVOT/Aortic valve
   - PW Doppler in left ventricular outflow tract positioned such that closing artifact but not opening artifact of the valve is visible.
   - CW Doppler through the LVOT/aortic valve.

8. Apical 2-chamber view
   - 2D image include left ventricle and left atrium
   - Zoom view to include LV only (avoid foreshortening of LV apex)
   - Color Doppler cross mitral valve including distal jet into left atrium

9. Apical 3-chamber view (aka apical long-axis view)
   - 2D image include left ventricle and left atrium
   - Color Doppler cross mitral valve including distal jet into left atrium
   - PW Doppler in left ventricular outflow tract
   - CW Doppler through the LVOT/aortic valve.

10. Subcostal imaging
    - 2D of Inferior vena cava with and without a “sniff” (5-10 beat loop).
    - Pulse wave of hepatic vein flow
    - Color Doppler of IVC and RA junction
    - Color Doppler of inter-atrial septum to interrogate presence of SD.
    - 4-chamber view showing RV, RA LA and LV
    - Color Doppler of TV and MV in 4 chamber subcostal view
    - SAX views (particularly if parasternal evaluation was limited).

11. Contrast will be used for endocardial border delineation when less than 80% of the endocardium can be visualized on the harmonic image.

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.

II. 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. 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.

Pre-Procedure Imaging

The following checklist may be used with appropriate Doppler performed for valvular assessment:

1. Mid and High esophageal views
   - 4 Ch view (of entire LV/RV); maximize endocardial definition.
   - Tricuspid Valve/Right Ventricle/right atrium/Interatrial Septum
     - 4 Chamber view angled to focus on right heart –both include RA and RV
     - Focus on TV including right atrium by changing depth to and obtain 2D image and color Doppler at 0, 60, 90 and 120-140 degrees; please include entire TV annulus
     - Interatrial septum (IAS) at (50 to70 degrees-with aortic rim in view) and bicaval view (90-110°) 2D and Color Doppler across IAS
     - (if 3D available) 3D TEE image of TV and RV at 0 degrees and 60 degrees (Full volume acquisitions-1 beat and either 4 beat or HVR mode-please hold respiration for latter)
     - (if 3D available) 3D color Doppler TEE of TR jet at 0 and 90 degrees (Full volume acquisition-1 beat and either 4 beat or HVR mode-please hold respiration for latter)

2. Mitral Valve: (lower depth to maximize visualization of the valve but include chordal attachments to the papillary muscle level). Please obtain 2D and color Doppler images of the mitral valve and chordal structures. For color Doppler assessment: Please adjust color Doppler settings to optimize visualization of MR jet area and vena contracta (Nyquist between 50-70 cm/s). Please also

obtain in at least one view: baseline shifting (in direction of MR jet flow) to Nyquist of 0.3 to 0.4 m/s) with Zoom mode on the proximal flow region. This is for PISA calculation.

Please obtain views of the mitral valve in the following planes:

- Transverse Plane (0°)
  - Change depth to image entire LV as well; maximize endocardial definition)
- Commissural View (60°)
  - Change depth to image entire LV as well; maximize endocardial definition.
- Two-chamber View (90°)
- Three-chamber View (120-140°)
- Record CW of MR in at least one plane
- Record PISA region after baseline shifting Nyquist upward (in direction of flow) to 40 cm/s. Please record 3-5 beats and not a single frame

3. LVOT/AV/Aorta
   - Long-axis view (120-140°) 2D and with color Doppler
   - Ascending aorta (mid to high esophageal view) (90° to 110)
   - Ascending aorta SAX views (0°, high esophageal)
   - AV SAX (30°, mid esophageal) with color Doppler

4. Main PA/PV
   - Bifurcation view (0-30°, high esophageal)
   - RVOT view (70°, mid esophageal)

5. Left atrial appendage
   - 2D at 45, 75, and 120-135 degrees.

6. Pulmonary vein pulse wave Doppler: Sample volume placed in the vein, 1 cm from the orifice.
   - One left and one right PV

7. Transgastric views
   - Three 2D short axis views are requested
     - Mitral valve level
     - Mid papillary muscle
     - Apical level.
   - Short axis images of the right ventricle and tricuspid valve (0 degrees)
     - Long axis of right ventricle and tricuspid valve (60-100 degrees)
     - Pulse wave of hepatic vein flow
   - Deep Gastric views
     - 5Ch view Aortic valve (with color, PW and CW Doppler)

8. Aorta
    - Thoracic aorta (short axis views)
    - Aortic arch (SAX and LAX views)

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:

1. Tricuspid Valve/right ventricle

    - Right heart –both include RA and RV at 0 and 60, 90 degree view
    - 2D and color Doppler (for jet area and vena contracta) at 0, 60, 90 and 120-140 degrees; please include entire TV annulus
    - Pulse and continuous wave across tricuspid valve
    - (If 3D TEE available-3D TEE image of RA and RV at 0 degree (Full volume acquisitions-1 beat and either 4 beat or HVR mode-please hold respiration for latter)
    - (if 3D available)-3D TEE image of TV and RV at 0 degrees and 60 degrees (Full volume acquisitions-1 beat and either 4 beat or HVR mode-please hold respiration for latter)
    - (if 3D available)-3D color Doppler TEE of TR jet at 0 and 90 degrees (Full volume acquisition-1 beat and either 4 beat or HVR mode-please hold respiration for latter)

2. Mitral valve
    - 2D and color Doppler of mitral valve at 0, 60, 90, and 120 degrees
    - (include MR jet area and vena contracta for color Doppler views)
    - Zoom of PISA region (if MR is >mild by semi-qualitative assessment) with baseline shift to 40 cm/s
    - Continuous wave Doppler to assess post-procedure gradients and MR jet velocity
    - Pulmonary vein (one left and one right PV) pulse wave Doppler: Sample volume placed in the vein, 1 cm from the orifice.

3. Left ventricle
    - Mid-Esophageal views of LV at 0 and 60 degrees

III. Moderate TR: Echocardiographic Measurements

The degree of tricuspid valve regurgitation will be categorized according to American Society of Echocardiography guidelines as none/mild/moderate/severe (J Am Soc Echocardiogr 2003; 16:777-802).

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 (cm^2)§	< 5	5-10	> 10
VC width (cm)ϕ	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 cm^2 , maximal RA medio-lateral and supero-inferior dimensions ≤ 4.6 cm and 4.9 cm respectively, maximal RA volume ≤ 33 ml/m^2(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.
ϕ 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).

A. Tricuspid Valve/Right atrium and right ventricle

The following variables will be measured:

1. Degree of tricuspid regurgitation categorized as:
   a) None/Trace
   b) Mild
   c) Moderate
   d) Severe
2. Jet area of TR
3. Vena contracta
4. EROA by PISA
5. TV annulus dimension (Apical 4 Chamber)
6. TV: Mechanism of TR: Primary vs secondary
7. RA volume (ml)
8. RV function categorized as:
   a) Normal
   b) Mildly impaired
   c) Moderately impaired
   d) Severely impaired
9. Tricuspid annular peak systolic excursion (TAPSE)
10. Peak tricuspid annular velocity (PTAV)
11. RV fractional area change (%)
12. RV size categorized as
   a) Normal
   b) Mildly dilated
   c) Dilated
13. RV dimension (apical 4 chamber view)

14. RVSP

B. LV Measures
    1. Interventricular septum (mm)
    2. Posterior wall thickness
    3. LVID end-diastole
    4. LVID end-systole
    5. ESV
    6. EDV
    7. LVEF

C. Mitral Valve
    1. Degree of MR (Trace/none, mild, moderate, severe)
    2. Mechanism of MR

D. Aortic Valve
    1. Aortic stenosis (y/n)
    2. Aortic Regurgitation (None, trace, mild, moderate or severe)

Appendix II: New York Heart Association Classification (NYHA)

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: Six-Minute Walk Test Instructions

The walking test will be conducted in an enclosed corridor (preferably free of distractions) on a course that is 60 feet long (Guyatt, 1985[2]). The corridor will be divided into 5-foot sections using a method unnoticeable to the patient. Chairs will be placed at either end of the 60-foot course markers. The distance covered during the preceding walk test will not be revealed to the patient during the study.

Before the test, the patient will sit quietly for 10 minutes. These instructions will be read verbatim to the patient:

THE PURPOSE OF THIS TEST IS TO FIND OUT HOW FAR YOU CAN WALK IN SIX-MINUTES. YOU WILL START FROM THIS POINT AND FOLLOW THE HALLWAY TO THE CHAIR AT THE END, THEN TURN AROUND AND WALK BACK. WHEN YOU ARRIVE BACK AT THE STARTING POINT, YOU WILL GO BACK AND FORTH AGAIN. YOU WILL GO BACK AND FORTH AS MANY TIMES AS YOU CAN IN THE SIX-MINUTE PERIOD. IF YOU NEED TO, YOU MAY STOP AND REST. JUST REMAIN WHERE YOU ARE UNTIL YOU CAN GO ON AGAIN. HOWEVER, THE MOST IMPORTANT THING ABOUT THE TEST IS THAT YOU COVER AS MUCH GROUND AS YOU POSSIBLY CAN DURING THE SIX MINUTES. I WILL TELL YOU THE TIME, AND I WILL LET YOU KNOW WHEN THE SIX MINUTES ARE UP. WHEN I SAY STOP, PLEASE STAND RIGHT WHERE YOU ARE.

DO YOU HAVE ANY QUESTIONS ABOUT THE TEST?

PLEASE EXPLAIN TO ME WHAT YOU ARE GOING TO DO.

Repeat the entire instructions if the patient does not seem to understand.

Repeat the sentence:

THE MOST IMPORTANT THING ABOUT THE TEST IS THAT YOU COVER AS MUCH GROUND AS YOU POSSIBLY CAN DURING THE SIX MINUTES.

ARE YOU READY?

START WHEN I SAY "GO"

[2] Kirshner, B, Guyatt, G. (1985) A methodological framework for assessing health indices. Journal of Chronic Diseases 38: 27–36.

During the test, the walking pace of the patient should not be influenced. The test supervisor must walk behind the patient - not walk with, rush up behind, or rush past the patient.

While walking, the patient will be encouraged every 30 seconds with the following phrases:

0-3 minutes:

THAT'S IT; YOU'VE GOT THE IDEA.
YOU'RE DOING WELL.
KEEP IT UP NOW.

3-6 minutes:

REMEMBER, AS FAR AS YOU CAN GO.
WE'LL WANT YOU TO GO AS FAR AS YOU POSSIBLY CAN.
THAT'S IT; KEEP WORKING AT IT.
COME ON; KEEP GOING.

The patient should be spoken to only at the 30-second encouragements and no response should be made to the patient's questions about the time and distance elapsed. If the patient is not concentrating on the walking, the patient can be reminded at a 30-second mark:

THIS IS A WALKING TEST. TALKING WILL UTILIZE YOUR ENERGY RESERVE AND INTERFERE WITH YOUR PERFORMANCE.

Encouragement phrases can be repeated as needed. For example, if the patient is slowing down and expresses that he/she wants to stop, say:

REMEMBER, IF YOU NEED TO, YOU MAY REST. JUST REMAIN WHERE YOU ARE UNTIL YOU CAN GO ON AGAIN.

If necessary, the patient may rest in a course marker chair although he/she should not be encouraged to do so.

The patient will be told the time elapsed at 2 and 4 minutes, i.e.:

YOU HAVE COMPLETED 2 MINUTES
And
YOU HAVE COMPLETED 4 MINUTES

At the end of the test, the patient should not move from where he/she was told to "STOP" until the distance walked (measured to the nearest foot) has been recorded.

Record the DISTANCE WALKED during the six-minute test.

Cardiothoracic Surgical Trials Network

Protocol

EVALUATING THE BENEFIT OF CONCURRENT TRICUSPID VALVE REPAIR DURING MITRAL SURGERY

Sponsored By the NHLBI and DZHK

CT Surgery Network Research Group

Data and Clinical Coordinating Center
InCHOIR
Icahn School of Medicine at Mount Sinai
New York

January 2020
Revision 2.2

CONFIDENTIAL

Cardiothoracic Surgical Trials Network

Core Clinical Centers
Baylor Research Institute (Michael Mack, MD)
Cleveland Clinic Foundation (Marc Gillinov, MD)
Duke University (Peter Smith, MD)
Institut Universitaire de Cardiologie de Québec (Hôpital Laval) (Pierre Voisine, MD)
Montefiore Medical Center - Albert Einstein College of Medicine (Robert Michler, MD)
Montreal Heart Institute (Louis Perrault, MD)
Hôpital du Sacré-Cœur de Montréal (Hugues Jeanmart, MD)
University of Pennsylvania (Michael Acker, MD)
University of Southern California (Michael Bowdish, MD)
University of Virginia Health System (Gorav Ailawadi, MD)

Consortium Centers
Baylor College of Medicine (Todd Rosengart, MD)
Dartmouth-Hitchcock Medical Center (Jock McCullough, MD)
Emory University (Douglas Murphy, MD)
London Health Center (Michael Chu, MD)
Mayo Clinic (Juan Crestanello, MD)
Medstar Heart and Vascular Institute (Christian Shultz, MD)
Mission Hospital (Mark Groh, MD)
Stanford University (Joseph Woo, MD)
Toronto General Hospital (Mitesh Badiwala, MD)
University of Alberta (John Mullen, MD)
University of Maryland Medical Center (James Gammie, MD)
University of Michigan (Steve Bolling, MD)
University of Ottawa (Marc Ruel, MD)
WakeMed Health and Hospitals (Bryon Boulton, MD)
Yale University (Arnar Geirsson, MD)
University of Wisconsin (Nilto Carias De Oliveira, MD)

Universitäts-Herzzentrum Freiburg (Friedhelm Beyersdorf, MD)
Deutsches Herzzentrum Berlin, (Volkmar Falk, MD)
Deutsches Herzzentrum Munchen (Markus Krane, MD)
Herzzentrum, Leipzig (Friedrich Mohr, MD)
Herz-und Diabeteszentrum NRW Bad Oeynhausen (Kavous Hakim-Meibodi, MD)
Universitatsklinikum Frankfurt (Anton Moritz, MD)
Universitatsmedizin Gottingen (Bernd Danner, MD)
Universitares-Herzzentrum Hamburg (Lennard Conradi, MD)
Universitatsklinikum Jena (Torsten Doenst, MD)
Herzzentrum Leipzig (Bettina Pfannmuller MD)

Data Coordinating Center
International Center for Health Outcomes and Innovation Research, Icahn School of Medicine at Mount Sinai (InCHOIR), (Annetine Gelijns, PhD; Alan J. Moskowitz, MD; Emilia Bagiella, PhD; Ellen Moquete, RN; Karen O'Sullivan, MPH; Anh Phung, BS; Anu Lala, MD; Donna Mancini, MD, Jessica Overbey, PhD, Stephanie Pan, MS)

Study Chair, Co-Chair, Vice-Chairs

Marc Gillinov, MD, Cleveland Clinic Foundation; Mariell Jessup, MD, American Heart Association; Eric Rose, MD, Icahn School of Medicine at Mount Sinai; Michael Mack, MD, Baylor Research Institute

Study Sponsors

National Heart Lung and Blood Institute (Marissa Miller, DVM, MPH; Albert Lee, PhD; Wendy Taddei-Peters, PhD; Neal Jeffries, PhD; Nancy Geller, PhD)
German Centre for Cardiovascular Research (Deutsches Zentrum für Herz-Kreislauf-Forschung)

Protocol Development Committee

James S. Gammie, MD (U Maryland)
Steven Bolling, MD (U Michigan)
Michael Parides, PhD (Montefiore-Einstein)
Gorav Ailawadi, MD (UVA)
Michael Argenziano, MD (Columbia)
Emilia Bagiella, PhD (InCHOIR)
Eugene Blackstone, MD (CCF)
Denis Bouchard, MD (Montreal)
Michael Bowdish, MD (USC)
Helena L Chang, MS (InCHOIR)
Julia Collins, CRC (U Maryland)
Francois Dagenais, MD (Laval)
Stephanie Deasey, PhD (U Maryland)
Annetine Gelijns, PhD (InCHOIR)
Nancy L Geller, PhD (NIH/NHLBI)
Marc Gillinov, MD (CCF)
Judy Hung, MD (MGH)
Katherine Kirkwood, MS (InCHOIR)
Irving L. Kron, MD (UVA)
Anu Lala, MD (InCHOIR)
Albert Lee, PhD (NHLBI)
Michael Mack, MD (Baylor)
Marissa Miller, DVM, MPH (NHLBI)
Ellen Moquete, RN, BSN (InCHOIR)
Alan Moskowitz, MD (InCHOIR)
Patrick O'Gara, MD (Brigham and Women's)
Karen O'Sullivan, MPH (InCHOIR)
Jessica Overbey, PhD (InCHOIR)
Vivek Rao, MD (Toronto)
Eric Rose, MD (Mount Sinai)
Peter K. Smith, MD (Duke)
Robert Smith, MD (Baylor)
Wendy C. Taddei-Peters, PhD (NHLBI)
Vinod Thourani, MD (Piedmont Heart Institute)
Robert Villanueva, MPA (U Maryland)
Bryan Whitson, MD (OSU)
Volkmar Falk, MD (Berlin, Germany)
Richard Weisel, MD (Toronto)

TABLE OF CONTENTS

TABLE OF CHANGES

Revision	Section	Change	Reason	Page
2.0	Headers and Footers	Updated and reformatted	Consistency with CTSN protocols	All
2.0	Title page and other applicable pages	Updated to new protocol version and date; added "and Clinical" to Data Coordinating Center to reflect the actual name and function	Accuracy and consistency with other sections	1,7, 17,45
2.0	Protocol Development Committee	Updated Personnel affiliation	Staffing Update	2
2.0	Table of Contents	Added sections inadvertently left out in original protocol and new appendices	Protocol Correction and Update	4
2.0	Definitions, Acronyms, and Abbreviations	Updated trial language	Internal Protocol Consistency	7-8
2.0	Abstract	Added Frailty Assessment – Gait Speed Test	Addition of Secondary Endpoint	9
2.0	Abstract	Minor revision to Target Population, Rx Arms, Inclusion/Exclusion Criteria language	Protocol clarification for consistency	10-11
2.0	Data Collection Schedule	Revised baseline and visit windows; added Gait Speed assessment for frailty; revised assessment names (including UHC name to its current name, Vizient); added 6MWT to Day 30	Addition of secondary endpoint; Expansion of windows to allow for more complete data collection; and Clarification of assessment names; Corrected omission of Day 30 6MWT from Rev 1.0	11
2.0	Objectives, Endpoints	Clarification of "baseline" echo	Clarification for consistency across centers	12, 14
2.0	Endpoints	Addition of Gait Speed Test as an Endpoint	Addition of secondary endpoint	14
2.0	Study Design	Correction of when endpoints will be measured – added "18" months and deleted redundant wording	Correction and update to protocol	15
2.0	Study Population	Minor revision to Inclusion/Exclusion Criteria language for consistency; added Footnote 1 for clarification	Protocol Update and Clarification	16-17
2.0	Definitions and Measurements of Endpoints	Clarified primary endpoint language; updated Appendix numbers; added Appendix where 6MWT instructions are found; added Frailty endpoint; defined abbreviations upon first use	Protocol Update and Clarification	18-19
2.0	Definitions and Measurements of Endpoints – Economic Measures	Revised UHC's name to its current name, Vizient; corrected an incomplete sentence in the last paragraph of this subsection; and revised cost and cost-effectiveness analysis to include US centers only.	Protocol Update and Corrections	20-21
2.0	Definitions and Measurements of Endpoints – Specific Adverse Event Definitions	Clarified cardiac arrhythmias definition and neurologic dysfunction definition	Clarification for consistency across centers	21,24

Revision	Section	Change	Reason	Page
2.0	Investigators – Qualifications and Training	Revised the procedure for providing surgical qualifications to the DCC (instead of faxing, sites will now upload forms to the Florence eRegulatory binder); added information on Echocardiologist and echo team training.	Protocol Update	26
2.0	Investigators – Echocardiography Qualification	Revised this section to remove any reference to TEE and clarified TTE training; clarified TR grading	Protocol Update and Clarification	26-27
2.0	Investigators – Conflict of Interest and Financial Disclosure Agreement	Revised language for clarity	Clarification	27
2.0	Investigators – Site Approval	Updated language in this section and clarified who must attend site initiation.	Clarification and Update	27-28
2.0	Screening and Baseline	Updated "Echocardiogram" subsection - accreditation and reference to new appendix; added new subsection - Gait Speed Test; corrected the form name under "Randomization Eligibility"	Protocol Update	29-30
2.0	Screening and Baseline, Post-Randomization Data Collection	Expanded data collection windows to allow for more complete data collection	Protocol Update	29-35
2.0	Randomization	Deleted text on ID code, which is assigned at an earlier stage via the EDC	Protocol Update	31
2.0	Procedure	Corrected language; added Appendix II; revised to include additional TV Annuloplasty Rings	Clarification and Update	31-32
2.0	Post-Randomization Data Collection – Study Visits	Added 18-month visit, which was inadvertently omitted from protocol revision 1.0	Correction	32
2.0	Post-Randomization Data Collection – Study Visits and Echocardiogram	Clarified statement on primary endpoint assessment requirements	Clarification	32,34
2.0	Post-Randomization Data Collection	Updated or added Appendix numbers	Protocol Update	34-35
2.0	Post-Randomization Data Collection	Added Gait Speed Test subsection	Addition of secondary endpoint (frailty)	34
2.0	Post-Randomization Data Collection – Event Driven Data Collection	Added sentence to refer to the Manual of Procedures for partial withdrawal of consent and limited data collection in Study Completion/Early Termination subsection	Clarification	36
2.0	Analytical Plan— Methods of Analysis	Clarified definition of treatment failure	Clarification	38
2.0	Analytical Plan – Data Monitoring and Analysis	Revised futility sentence in Interim Analysis subsection	Correction	41
2.0	Analytical Plan – Data Monitoring and Analysis	Added Gait Speed data analysis to Analytical Plan (to 6MWT analysis paragraph) and updated analysis.	Addition of secondary endpoint	42
2.0	Appendix II	Added 3D Acquisition Protocol	Added for consistency across centers	57
2.0	Appendix II-IV	Renumbered appendices	Update	57-59
2.0	Appendix V	Added appendix on Gait Speed Test Instructions	Addition of secondary endpoint	61

Revision	Section	Change	Reason	Page
2.1	Headers and Footers	Updated and reformatted	Consistency with CTSN formatting	All
2.1	Title page	Updated to new protocol version and date	Protocol update	1
2.1	Throughout protocol	Administrative changes to correct spacing, numbering, and other inconsistencies; to add study sponsor; and to update abbreviations	Internal protocol consistency and accuracy	All
2.1	Consortium Centers	Updated listing of participating sites	Protocol update	2-3
2.1	Study Sponsors	Revised to reflect sponsorship by the Deutsches Zentrum für Herz-Kreislauf-Forschung	Protocol Update	3
2.1	Definitions, Acronyms and Abbreviations	Added abbreviations and acronyms for German collaborators and sponsor	Protocol update	8
2.1	Randomization	Updated specifics on timing of randomization	At the request of study investigators to allow for planning of surgical approach prior to randomization	16, 32
2.1	Pleural Effusion	Updated definition of pleural effusion to include medical management	At the request of study investigators to allow for analysis of fluid management in this patient population	23
2.1	Clinical Centers, Organization of the Study	Updated number of sites from 30 to 50	To account for the German clinical sites joining the protocol team	26, 45
2.1	Tricuspid Valve Surgery	Removed St. Jude Flexible Annuloplasty Band	For internal consistency within protocol	33
2.2	Headers and Footers	Updated and reformatted	Consistency with CTSN formatting	All
2.2	Title page	Updated to new protocol version and date	Protocol update	1
2.2	Throughout protocol	Administrative changes to correct spacing and other inconsistencies	Internal protocol consistency and accuracy	All
2.2	Cardiothoracic Surgical Trials Network pages	Updated sites participating, personnel, and affiliations	Site and staffing update	2-3
2.2	Abstract	Clarified TR severity strata used for randomization	Clarification	11
2.2	Data Collection Schedule	Added ‘X’ to denote that hospitalization form is completed at pre-discharge	For internal consistency within protocol	13
2.2	Definitions and Measurement of Endpoints	Clarified that readmissions and re-operations are collected through 24 months post-randomization	Clarification for consistency	22
2.2	Post-randomization Data Collection	Clarified that follow-up surgical procedures, re-hospitalizations, and outpatient interventions are collected through 24 months post-randomization	Clarification for consistency	35, 37
2.2	Analytical Plan	Added ‘potential’ before interim analysis	Clarification for consistency	40
2.2	Analytical Plan	Corrected the plan for handling missing data	Correction	41-42

Revision	Section	Change	Reason	Page
2.2	Analytical Plan	Added at statement that sample size re-estimation will not be done if no interim analysis is conducted or accrual is complete at the time of the first interim analysis	Clarification	43
2.2	Analytical Plan	Added that mortality will also be assessed at 24 months	Correction and Update	43
2.2	Analytical Plan	Revised the analytical approach for reoperation for TR to account for death as a competing risk	Correction and Update	43-44
2.2	Analytical Plan	Revised the analytical approach for MACCE to time to event	Update	44
2.2	Analytical Plan	Removed specification of alpha level for secondary analyses	Update	44
2.2	Analytical Plan	Clarified that Adverse Events will be assessed through 24 months post-randomization	Clarification for consistency	45
2.2	Analytical Plan	Removed sentence on “Readmissions” and revised the analytical approach for “Hospital readmission” to Poisson regression from chi-squared test	Correction and Update	45
2.2	Organization of the Study	Fixed incomplete sentence	Correction	47
2.2	References	Added a reference for Fine and Gray (1999)	Update	48

DEFINITIONS, ACRONYMS & ABBREVIATIONS

ACE	Angiotensin converting enzyme antagonist
AE	Adverse event
AICD	Automatic implantable cardioverter defibrillator
ARB	Angiotensin receptor blocker
ASD	Atrial septal defect
AV	Atrioventricular
CABG	Coronary artery bypass grafting
CEA	Cost-effectiveness analysis
CHF	Congestive heart failure
CIHR	Canadian Institutes of Health Research
CTA	Clinical Trial Agreement
CW	Continuous wave
DCC	Data and Clinical Coordinating Center
DGTHG	German Society for Thoracic and Cardiovascular Surgery (Deutschen Gesellschaft für Thorax-, Herz- und Gefäßchirurgie)
DSMB	Data and Safety Monitoring Board
DZHB	German Heart Center Berlin (Deutsches Herzzentrum Berlin)
DZHK	German Centre for Cardiovascular Research (Deutsches Zentrum für Herz- Kreislauf-Forschung)
EAC	Event Adjudication Committee
EC	Ethics Committee
EDC	Electronic data capture system
EDV	End diastolic volume
EROa	Effective Regurgitant Orifice area
EQ-5D	EuroQoL
ESV	End systolic volume
ESVI	End systolic volume index
GCP	Good Clinical Practice
HIPAA	Health Insurance Portability and Accountability Act
ICER	Incremental cost effectiveness ratio
InCHOIR	International Center for Health Outcomes & Innovation Research
IRB	Institutional Review Board
KCCQ	Kansas City Cardiomyopathy Questionnaire
LA	Left atrium
LAA	Left atrial appendage
LBBB	Left bundle branch block
LOS	Length of stay
LV	Left ventricle
LVEDP	Left ventricular end diastolic pressure
LVEF	Left ventricular ejection fraction
LVESVI	Left ventricular end systolic volume index
MACCE	Major adverse cardiac and cerebrovascular event

MI	Myocardial infarction
MR	Mitral regurgitation
mRS	modified Rankin scale
MV	Mitral valve
MVR	Mitral valve repair
MVRR	Mitral valve repair/replacement
MVS	Mitral valve surgery
NHLBI	National Heart, Lung, and Blood Institute
NIHSS	National Institutes of Health Stroke Scale
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-operative day
PR	Pulmonic regurgitation
PV	Pulmonic valve
PVI	Pulmonary vein isolation
PW	Pulsed wave
QALY	Quality adjusted life years
QOL	Quality of Life
REB	Research Ethics Board
RV	Right Ventricle
RVFAC	Right ventricular fractional area change
RVol	Regurgitant volume
SAE	Serious adverse event
SAX	Short axis
SF-12	Short Form 12
STEMI	ST segment elevation myocardial infarction
6MWT	Six Minute Walk Test
TAPSE	Tricuspid annular plane systolic excursion
TEE	Trans-esophageal echocardiography
TIA	Transient ischemic attack
TR	Tricuspid regurgitation
TTE	Transthoracic echocardiography
TV	Tricuspid valve
TVI	Tissue velocity imaging
VTI	Velocity time integral

ABSTRACT

Objectives	The *primary objective* of this trial is to evaluate the efficacy and safety of performing tricuspid valve (TV) repair in patients with either moderate tricuspid regurgitation (TR) or less than moderate TR with tricuspid annular dilation undergoing mitral valve surgery (MVS).
Study Design	Prospective, multi-center, randomized, controlled trial
Target Population	Patients undergoing MVS (*repair or replacement)* for degenerative mitral regurgitation (MR) who have *either* (a) moderate TR OR (b) tricuspid annular dimension ≥ 40 mm (index: ≥21mm/M^2 BSA) *and* none/trace or mild TR, determined by echocardiography.
Rx arms	(a) TV annuloplasty using a rigid, nonplanar, undersized (nominal 26, 28, or 30 mm) annuloplasty ring at the time of MVS (b) MVS alone Randomization will be stratified based on TR severity (i.e. moderate or less than moderate TR) and by clinical center.
Sample Size	400 patients provides 90% power to detect a decrease in "failure" from 25% without tricuspid valve repair to 12% in patients with repair.
Duration	60 months following randomization
1° Endpoints	• Composite of death, reoperation for TR, or progression of TR from baseline by two grades *or* the presence of severe TR at 24 months Degree of TV regurgitation will be categorized according to American Society of Echocardiography guidelines as none/trace/mild/moderate/severe
2° Endpoints	*Clinical and Functional Outcomes* • Composite of major adverse cardiac and cerebrovascular events (MACCE), including stroke, death, and serious heart failure events • NYHA classification and diuretic requirements • Six-minute walk test (6MWT) • Gait Speed Test for Frailty *Echocardiography* • Degree of TR at index hospital discharge • Degree of TR at 12 and 24 months • Right ventricular size at 12 and 24 months • Right ventricular function [normal, mildly impaired, moderately impaired, severely impaired, peak tricuspid annular velocity, tricuspid annular plane systolic excursion (TAPSE), right ventricular fractional area change (RVFAC)] at 12 and 24 months • Pulmonary artery pressure at 12 and 24 months • Right ventricular volume at 12 and 24 months *Quality of Life* • SF-12 • Kansas City Cardiomyopathy Questionnaire (KCCQ) • EuroQoL (EQ-5D)

	Survival • Perioperative mortality (greater in-hospital or 30 day mortality) • Mortality *Serious Adverse Events* • Frequency of serious adverse events (SAEs) • Atrioventricular (AV)-Block requiring pacemaker implantation • New-onset atrial fibrillation *Hospitalizations* • Index hospitalization length of stay (LOS) and intensive care unit (ICU) days • All-cause readmissions, and readmissions for heart failure and TR reoperations *Economic Outcomes* • Cost • Cost-effectiveness
Selected Inclusion Criteria	1. Age $\geq$ 18 years 2. Undergoing MVS for degenerative MR 3. (a) moderate TR as determined by echocardiography, or (b) none/trace or mild TR *and* tricuspid annular dimension $\geq$ 40 mm
Selected Exclusion Criteria	1. Functional MR 2. Evidence of sub-optimal fluid management (e.g., lack of diuretics, weight in excess of dry weight) in the opinion of the cardiology investigator 3. Structural/organic TV disease 4. Severe TR, as determined by echocardiography 5. Implanted pacemaker or defibrillator, where the leads cross the TV from the right atrium into the right ventricle 6. Concomitant cardiac surgery other than atrial fibrillation correction surgery [pulmonary vein isolation (PVI), Maze, left atrial appendage (LAA) closure, closure of patent foramen ovale (PFO) or atrial septal defect (ASD), or coronary artery bypass grafting (CABG) 7. Cardiogenic shock at the time of randomization 8. ST segment elevation myocardial infarction (STEMI) requiring intervention within 7 days prior to randomization 9. Evidence of cirrhosis or hepatic synthetic failure 10. Severe, irreversible pulmonary hypertension in the judgment of the investigator 11. Pregnancy at the time of randomization 12. Unable or unwilling to provide informed consent 13. Unable or unwilling to comply with study follow up in the opinion of the investigator

DATA COLLECTION SCHEDULE

Assessment	Screening/ Baseline (60 days pre-op)	Intra-Operative	Pre-discharge	30 Days (-7 days, +35 days)	6 Mos (± 30 days)	12 Mos (± 30 days)	18 Mos (± 30 days)	24 Mos (± 60 days)	36, 48 & 60 Mos (± 60 days)	Event Driven
General										
Eligibility Criteria	X									
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		
Gait Speed Test	X					X		X		
Laboratory Assessment	X									X
Screening Outcome	X									
Hospitalization	X		X							X
Vital Status Check									X	
Cardiac										
Surgical Procedure		X								X
TEE		X								
NYHA Heart Failure Classification	X			X	X	X		X		
2D Echo (TTE)	X		X		X	X		X		
Six Minute Walk Test (6MWT)	X			X	X	X		X		
3D Echo (TTE)	X					X		X		
Quality of Life (QOL)										
KCCQ	X				X	X	X	X		
SF-12	X				X	X	X	X		
EQ-5D	X				X	X	X	X		
Event Driven Data										
Adverse Events										X
Missed Visit										X
Protocol Deviation										X
Mortality										X
Study Completion/Early Termination										X
End of Study/Investigator Statement										X
Cost										
UB-92 Forms & Hospital Bills										X
Vizient Data										X

OBJECTIVES

The overall objective of this study is to evaluate the safety and efficacy of tricuspid valve (TV) repair in the setting of mitral valve surgery (MVS) for degenerative mitral valve (MV) disease. Specifically, this study compares the surgical approach of combining TV annuloplasty with clinically indicated MVS to performing MVS alone.

- The primary aim of this trial is to evaluate the impact of these two surgical approaches on the composite endpoint of death and reoperation for tricuspid regurgitation (TR), or progression of TR, either by two grades from baseline (i.e. *prior* to randomization), *or* by the presence of severe TR at 2 year follow-up.

- Secondary aims of this trial include assessment of the impact of these two surgical approaches on right heart performance and function, mortality, adverse events (AEs), quality of life (QOL), functional status, presence and severity of TR, and health resource use.

BACKGROUND AND SIGNIFICANCE

Etiology & Prognosis

The presence of moderate or severe TR is commonly encountered, affecting over 1.6 million people in the United States alone (Taramasso, Vanermen et al. 2012). Intrinsic pathology of the TV is rare resulting in most TR being functional, which is defined as regurgitation in the presence of anatomically normal leaflets and chords. TR produces fewer observable symptoms compared with other valvular pathology, and its assessment by physical exam can be challenging. As a result, the presence and severity of TR is often appreciated solely on echocardiography.

The precise mechanism by which functional TR develops is thought to be due to tricuspid annular dilation, as well as right ventricular (RV) enlargement and dysfunction associated with left heart disease and/or significant pulmonary hypertension (Dreyfus, Randolph et al. 2015). Left heart disease in this context mainly refers to MV pathology in the presence of systolic and/or diastolic dysfunction. Up to one third of patients with mitral stenosis have moderate or greater TR. However reports of the prevalence of TR and/or annular dilation in patients undergoing surgery for mitral regurgitation (MR) vary, ranging from 8-65% (Sagie, Freitas et al.1997; Dreyfus, Corbi et al. 2005; McCarthy 2007; Chan, Burwash et al. 2009; Chikwe, Itagaki et al. 2015; TM Koelling, Aaronson et al. 2002).

In 1967, Braunwald and colleagues demonstrated that correction of left-sided disease allowed for resolution of TR (Morrow, Oldham et al. 1967). In more recent years however this philosophy has been challenged by some, on account of observations that TR may in fact resolve only in a minority of cases. Overall data on the postoperative course and clinical sequelae of TR are conflicting, largely due to heterogeneous surgical management and MV pathologies. Dreyfus et al, for example, have reported that up to 48% of patients have an increase of up to 2 grades of TR (Raja and Dreyfus 2009), whereas other investigators have demonstrated only small increases in mean TR over a 5-year postoperative period.

Although the clinical context in which TR occurs may influence prognosis, there are numerous reports that demonstrate the presence of TR being associated with increased mortality. Nath and colleagues showed that moderate or more severe TR conferred inferior survival even after adjusting for age, left ventricular and RV function in a cohort of over 5000 male Veteran patients (Nath, Foster and Heidenreich 2004). These findings were supported by a study by Lee et al, who reported a 74% 5-year survival for patients with moderate or severe TR who were medically managed (Lee, Song et al. 2010; Nishimura, Otto et al. 2014). Importantly, TR may influence the quality of survival as well. Decreased exercise tolerance has been reported in patients with TR after MV replacement, and patients who go on to develop more severe TR are more likely to develop New York Heart Association class III-IV symptoms (Groves, Lewis et al. 1991; Ruel, Rubens et al. 2004).

Rationale for the Trial

Medical therapy for TR is limited only to diuretics and potential treatment of elevated pulmonary pressures. Echocardiographic assessment of severity can be dynamic in that degree of TR is highly dependent on preload, afterload and RV function. Though functional TR is a result of annular dilation, routine measurement on echocardiography is not common in clinical practice.

In patients with severe TR already undergoing surgery for left valvular pathology, surgical correction is recommended by the AHA/ACC and ESC guidelines (Nishimura, Otto et al. 2014). Significant equipoise exists, however, as to the optimal approach for patients with only moderate TR or mild TR with annular dilation. Some centers argue that performing a TV annuloplasty at the time of MVS influences the incidence of right heart failure and improves long term survival, yet others believe the risk of an additional surgical procedure outweighs the potential benefit (Yilmaz, Suri et al. 2011). According to the STS database, among 46,500 isolated primary MV operations performed between 2011 and 2014, TV repair was performed in 4% of patients with none or mild TR, 35% of patients with moderate TR, and 79% of patients with severe TR. These practice patterns serve to reflect an uncertainty of benefit of concomitant TV repair for moderate TR as well as variability in practice.

Establishing whether or not definitive benefit is conferred by performing TV repair at the time of MVS for degenerative MV disease should provide the level of evidence needed to provide rigorous recommendations for the management of this significant patient population. As such, the Network has designed a trial to evaluate the efficacy and safety of concomitant TR annuloplasty at the time of MVS.

Justification of Primary Endpoint Selection

Ideally, the effectiveness of TR repair should be measured by the degree to which it reduces relevant clinical events. However, the combination of the relatively low expected two-year event rate in the target population of degenerative MR with moderate or less TR, and logistical constraints on the sample size for the trial, precludes using an endpoint defined in terms of clinical events alone. Instead, we propose a composite endpoint of death from any cause, progression of TR (measured echocardiographically)

or TV reoperation. There is evidence that the presence of severe TR is independently correlated with decreased late survival (Nath, Foster et al. 2004) and that the presence of significant TR after MV operations is correlated with RV dysfunction and decreased RV reverse remodeling (Goldstone, Howard et al. 2014; Van de Veire, Braun et al. 2011; Benedetto, Melina et al. 2012; Bertrand, Koppers et al. 2014; Vargas Abello, Klein et al. 2013). Among patients with systolic heart failure, the presence of significant TR is associated with an increased risk of hospital admission for congestive heart failure, and TR in combination with RV dysfunction is associated with renal dysfunction and excess mortality (Agricola, Marini et al. 2015).

We also considered cardiac MRI for the primary evaluation modality but thought the test onerous and likely to constrain enrollment and increase missing data. While MRI is the gold standard for determination of RV structure and function, compliance with initial (preoperative) MRI in a pilot study has been obtained in only 67 % (N=40) of patients due to contraindications or patient refusal, with follow-up compliance and acquisition rates significantly lower. RV volume as measured by 3D echocardiography is a potential alternative to MRI. However, this promising but emerging modality still presents technical limitations. In addition, established longitudinal data on 3D echo assessment of RV remodeling after TR annuloplasty do not exist as of yet. We, therefore, felt that RV volume by 3D echo was not appropriate as the primary endpoint, but did include it as a secondary endpoint.

ENDPOINTS

Primary

Composite of death, reoperation for TR, or progression of TR from baseline (i.e., prior to randomization) by two grades or the presence of severe TR at 2 years.

Degree of TV regurgitation will be categorized according to American Society of Echocardiography guidelines as none/mild/moderate/severe. Trace regurgitation is also used in the event that regurgitation is barely detected.

Secondary

Clinical and Functional Outcomes

- Composite of major adverse cardiac and cerebrovascular events (MACCE), including stroke, death, and serious heart failure events
- NYHA classification
- 6MWT
- Gait Speed Test for Frailty

Echocardiography

- Degree of TR at index hospital discharge
- Degree of TR at 12 and 24 months

- RV size at 12 and 24 months
- RV function (normal, mildly impaired, moderately impaired, severely impaired, peak tricuspid annular velocity, TAPSE, RVFAC) at 12 and 24 months
- Pulmonary artery pressure at 12 and 24 months
- RV volume at 12 and 24 months

Quality of Life

- SF-12
- KCCQ
- EQ-5D

Survival

- Perioperative mortality (greater in-hospital or 30-day mortality)
- Mortality

Serious Adverse Events

- Frequency of SAEs
- AV-Block requiring pacemaker implantation
- New-onset atrial fibrillation

Hospitalizations

- Index hospitalization LOS and ICU days
- All-cause readmissions and readmissions for heart failure and TR re-operation

Economic Outcomes

- Cost
- Cost-effectiveness

STUDY DESIGN

This is a multi-center randomized clinical trial. The trial will be conducted in highly experienced clinical centers participating in the NIH/CIHR supported Cardiothoracic Surgical Trials Network (CTSN) and the Deutsches Zentrum für Herz- Kreislauf-Forschung (DZHK) supported German Society for Thoracic and Cardiovascular Surgery (DGTHG). The estimated enrollment period is 24 months (n = 400), and all patients will be followed for 60 months post-randomization. Endpoints will be measured at 30 days, 6, 12, 18, and 24 months. Survival will continue to be measured after the 24-month visit via vital sign checks at 36, 48 and 60 months.

RANDOMIZATION

Patients will be randomly assigned (1:1) to MVS + TV annuloplasty or MVS alone. Patient randomization will be stratified by TR severity and by clinical center. The randomization procedure will be performed intra-operatively, following **the placement of the TEE probe and after visualization and confirmation of cardiac anatomy eligibility**, in order to minimize the likelihood of enrolling patients in the study with

unexpected surgical contra-indications to TV repair. Randomization will be performed centrally through a Web-based data collection system that automates the delivery of the randomization assignments. The treatment assignment will be viewed by 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

Neither patients nor investigators will be blinded to treatment assignment due to the nature of the treatment intervention. Investigators will, however, be blinded to all data from other clinical sites, except serious unexpected AEs that are possibly or probably related to the investigational procedure for IRB/REB/EC reporting purposes. All echocardiograms will be analyzed by echocardiography core laboratory (Echo Core Lab) personnel who will be blinded to clinical outcomes. Adverse events (AEs) will be adjudicated by an Event Adjudication Committee (EAC) and trial oversight will be provided by an independent Data and Safety Monitoring Board (DSMB).

STUDY POPULATION

The patient population for this trial consists of adult patients undergoing MVS via full or minimal-access sternotomy or right thoracotomy for degenerative MV disease using legally marketed devices. Specific inclusion and exclusion criteria are listed below. All patients who meet the eligibility criteria may be included in the study regardless of gender, race, or ethnicity.

Inclusion Criteria

1. Undergoing MVS for degenerative MR[1] with

   (a) Moderate TR as determined by transthoracic 2D echocardiography, or

   (b) Tricuspid annular dimension ≥ 40 mm (index: ≥21mm/M^2 BSA) and none/trace or mild TR, determined by echocardiography.

2. Age ≥ 18 years

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

Exclusion Criteria

1. Functional MR

[1] "Degenerative mitral valve disease refers to a spectrum of conditions in which morphologic changes in the connective tissues of the mitral valve cause structural lesions . . ., such as chordal elongation, chordal rupture, leaflet tissue expansion, and annular dilation typically resulting in mitral regurgitation due to leaflet prolapse." This definition excludes rheumatic heart disease. (Anyanwu AC, Adams DH. (2007) Etiological classification of degenerative mitral valve disease: Barlow's disease and fibroelasticity deficiency. Semin Thorac Cardiovasc Surg; 19(2): 90-6).

2. Evidence of sub-optimal fluid management (e.g., lack of diuretics, weight in excess of dry weight) in the opinion of the cardiology investigator

3. Structural / organic TV disease

4. Severe TR as determined by preoperative transthoracic echocardiography (TTE)

5. Implanted pacemaker or defibrillator, where the leads cross the TV from the right atrium into the right ventricle

6. Concomitant cardiac surgery: other than atrial fibrillation correction surgery (PVI, Maze, LAA closure), closure of PFO or ASD, or CABG

7. Cardiogenic shock at the time of randomization

8. STEMI requiring intervention within 7 days prior to randomization

9. Evidence of cirrhosis or hepatic synthetic failure

10. Severe, irreversible pulmonary hypertension in the judgment of the investigator

11. Pregnancy at the time of randomization

12. 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

13. Any concurrent disease with life expectancy < 2 years

14. Unable or unwilling to provide informed consent

15. Unable or unwilling to comply with study follow up in the opinion of the investigator

Recruitment Strategies

Based on a survey of the clinical sites, it is estimated that approximately 150-200 patients could be enrolled annually through active screening and recruitment by the participating CTSN and DGTHG 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 Data and

Clinical Coordinating Center (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, and social reasons, and for the generalizability of trial results. The CTSN is strongly committed to ensuring a balanced recruitment of patients regardless of sex or ethnicity. The North American clinical sites 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

Patients will be randomly assigned to the following treatment groups:

Mitral Valve Surgery + Tricuspid Valve Annuloplasty

Mitral Valve Surgery Alone

DEFINITIONS AND MEASUREMENT OF ENDPOINTS

Primary Endpoint

The primary outcome of this trial is treatment failure defined as the composite of (1) death from any cause, (2) reoperation for TR, (3) presence of severe TR at two years post randomization or, for patients enrolled with less than moderate TR and annular dilatation, progression by two grades (i.e., from none/trace TR to moderate TR) at two years post randomization.

Secondary Endpoints

Clinical and Functional Outcomes

MACCE (Major Adverse Cardiac and Cerebrovascular Events)

MACCE is defined as a non-weighted composite score comprised of the following components:

- Death
- Stroke
- Serious heart failure events

NYHA Classification and Diuretic Use

Functional status will be assessed by the NYHA Classification scale. Complete NYHA classification guidelines can be found in Appendix III. The diuretic requirements of patients will be assessed.

Six Minute Walk Test (6MWT)
The total distance walked in six minutes will be assessed. Complete 6MWT guidelines can be found in Appendix IV.

Gait Speed Test for Frailty
Frailty will be assessed using the Gait Speed Test administered at baseline and reassessed at 12 and 24 months post-randomization. Complete Gait Speed Test guidelines can be found in Appendix V.

Physiologic

Echocardiographic Parameters (Appendix I and Appendix II)

- Degree of TR at Index Hospital Discharge
- Degree of TR at 12 and 24 months
- RV Size at 12 and 24 months
- RV Function (normal, mildly impaired, moderately impaired, severely impaired, peak tricuspid annular velocity, TAPSE, RVFAC) at 12 and 24 months
- Pulmonary Artery Pressure at 12 and 24 months
- RV volume at 12 and 24 months as measured by transthoracic 3D echocardiography

Quality of Life

The change in QOL from baseline will be measured, using the disease-specific KCCQ score, the SF-12 general health status index, and EQ-5D measures of health state preference from the individual and societal perspective. The KCCQ is a widely used tool in heart failure populations. 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 EQ-5D 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.

For this trial, the SF-12, EQ-5D, and KCCQ are available in English, Spanish, French and German. 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).

Survival

Perioperative and all-cause mortality over 60 months will be assessed.

Hospitalizations

Length of Index Hospitalization

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

Readmission and Reoperations

Readmission rates will be calculated for the first 30 days following intervention and through 24 months post-randomization. Hospitalizations will be classified for all causes, including cardiovascular and heart failure readmissions and readmissions for TR operation. Classification of a readmission as heart failure related requires *at least 2* out of the following signs and symptoms of acute decompensated heart failure:

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

All readmissions will be classified by the investigator and adjudicated by the EAC.

All re-operations and re-operation for TR in particular will be recorded through 24 months post-randomization. Freedom from re-operation will be analyzed.

Economic Measures

Inpatient costs will be measured through the collection of hospital billing and resource utilization information. 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 visit if they have been hospitalized at another hospital and if yes for how long.

For those institutions who participate in Vizient (formerly the University Healthsystems Consortium [UHC]), hospital costs and resource utilization data will be collected. Vizient works with academic medical centers around the country to collect and warehouse clinical, safety, operational and financial data. These data are used to compare performance among peer hospitals and identify best practice patterns. Participating centers will provide unique trial information and the dates of participation in the trial to Vizient who will provide a de-identified data set of the financial data for the trial to the investigators for analysis.

For institutions who do not participate in Vizient, hospital billing data from the UB-92 form will be collected in a de-identified manner from the institutional billing departments. As hospitalization practices differ substantially and detailed accounting data are unavailable for the participating Canadian and German centers, the cost and cost-effectiveness analysis will be restricted to US centers only.

Safety

Adverse Events

Please refer to the CTSN Clinical and Adverse Event Reporting and Adjudication Procedures guidance document for general reporting procedures and guidance on the determination of intervention-expected AEs.

Specific Adverse Event Definitions

AV Conduction Block leading to Permanent Pacemaker Placement

See "Cardiac Arrhythmias" below

New-onset Post-Operative Atrial Fibrillation

See "Cardiac Arrhythmias" below

Bleeding

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

- Transfusion of > 5 units RBC within the first 24 hours following surgery
- Death due to hemorrhage
- 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 follows:

- Cardiac arrest
- Sustained ventricular arrhythmia requiring defibrillation or cardioversion.
- Sustained supraventricular arrhythmia requiring drug treatment or cardioversion (classified as either pre-existing or post-operative onset)
- Cardiac conduction abnormalities or sustained bradycardia requiring permanent pacemaker placement (includes all PPMs whether associated with a serious AE or not)

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, chest tube or pigtail placement or medical management such as diuresis.

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

Liver injury **and** impaired liver function defined as:

- ALT ≥ 3xURL *and* total bilirubin* ≥ 2xURL (>35% direct), **or**
- ALT ≥ 3xURL *and* INR** > 1.5.

* Serum bilirubin fractionation should be performed if testing is available; if unavailable, measure urinary bilirubin via dipstick. If fractionation is unavailable and ALT ≥ 3xURL and total bilirubin ≥ 2xURL, then the event is still to be reported as an SAE.

** INR testing not required per protocol and the threshold value does not apply to subjects receiving anticoagulants. If INR measurement is obtained, the value is to be recorded on the SAE form.

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"* below), 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 ≥ 38.0^{o} C, positive blood cultures, new regurgitant murmurs or heart failure, evidence of embolic events (e.g., focal neurologic

impairment, glomerulonephritis, renal and splenic infarcts, and septic pulmonary infarcts), and peripheral cutaneous or mucocutaneous lesions (e.g., petechiae, conjunctival or splinter hemorrhages, Janeway lesions, Osler's nodes, and Roth spots). Echocardiographic evidence of 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]:

Myocardial Infarction (Non-Procedure Related)

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:

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

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.

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 indicative of peri-procedural

[1] Joint ESC/ACCF/AHA/WHF Task for the Redefinition of Myocardial Infarction, *Circulation*. 2007; 116:0-0.

myocardial necrosis. By convention, increases in biomarkers > 3 x 99th percentile URL have been designated as defining PCI-related MI. A subtype related to a documented stent thrombosis is recognized.

Note: 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 on neuroimaging). The NIH Stroke Scale (NIHSS) and Modified Rankin Scale (mRS) must be administered within 24 hours following the event if the event is not captured at a protocol-defined assessment time point, to document the presence and severity of neurological deficits.

Each neurological event must be subcategorized as:

- TIA defined as an acute event that resolves completely within 24 hours with no imaging evidence of infarction.
- Hemorrhagic stroke
- Ischemic stroke
- Toxic Metabolic Encephalopathy, defined as a disorder of the brain function that arises from abnormal systemic metabolism, infection, or exogenous substances, altering awareness and/or consciousness, in which there is a non-focal neurological examination and a negative brain image.
- Seizure, defined as an abnormal paroxysmal cerebral neuronal discharge that results in alteration of sensation, motor function, behavior, or consciousness
- Other

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 ventilator support within 48 hours post-surgical intervention. This excludes 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:

- intravenous therapy (diuretics, inotropic support, or vasodilators) *and* prolongs hospital stay in the judgment of the investigator, ***or***
- introduction of intravenous therapy (diuretics, inotropic support, or vasodilators) at any point following discharge from the index hospitalization, ***or***
- 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:

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

This definition excludes 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

All other SAEs (events that cause 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 50 clinical centers participating in the NIH/CIHR supported CTSN and the DZHK supported DGTHG. Each clinical center will be required to obtain IRB/REB/EC approval for the protocol and consent revisions in a timely fashion, to recruit patients, to collect data and enter it accurately into the electronic data capture (EDC) system, to faithfully follow the protocol and adhere to the standards of Good Clinical Practice (GCP) and HIPAA regulations (US sites), the Personal Information Protection and Electronic Documents Act (PIPEDA) regulations (Canadian sites) or the European Union's Privacy Directive (German sites). In addition, centers will be required to provide the 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.

INVESTIGATORS

All surgeons, cardiologists, coordinators and other investigators involved in the trial must complete the Investigator Contact Form with their hospital affiliation, address, contact numbers (phone, fax, cell, pager), and email address. All investigators must send their CV, Clinical Study Agreement/Conflict of Interest Statement, Good Clinical Practice Certificates, and HIPAA or other Privacy Protection certification as required by the local institution to the DCC.

Qualifications and Training

Clinical investigators will be cardiothoracic surgeons with expertise in surgical management of the mitral and tricuspid valves. To qualify as a surgeon participating in this trial, the surgical investigator must have performed at least 10 MV and 5 TV procedures annually (averaged over a 2-year period). Surgical qualifications for all participating surgical investigators will be collected on the Surgical Certification Form and uploaded to the Florence eRegulatory binder prior to accreditation. The clinical site Principal Investigator (PI) will be responsible for overseeing the ongoing performance of the other participating surgical investigators at that site over the course of the study.

All clinical site investigators and coordinators will be trained by the DCC in the specifics of the protocol during site initiation in advance of patient enrollment. The designated echo cardiologist and echocardiography teams will be trained in echo acquisition protocols separate from the site initiation. In addition, the investigators and coordinators will undergo a separate training session to gain familiarity with the EDC.

Echocardiography Qualification

Each clinical site echocardiography lab involved in image acquisition for this trial will be certified by the Echocardiography Core Lab to perform the protocol defined TTE. Importantly, the TTE assessments will be used to determine eligibility in terms of patients having moderate TR or a tricuspid annular dimension ≥ 40 mm (index: ≥21mm/M^2 BSA) and none/trace or mild TR.

The site certification for the TTE is as follows:

Prior to being open to enrollment, the site will send a sample 2D and 3D TTE which follows the echo acquisition protocol. The site must receive Echo Core Lab approval for the TTE in advance of performing any study related images.

Once open to enrollment, the site will acquire and adjudicate the degree of TR on the research TTE 2D images for consented patients. Prior to the scheduled surgical procedure, the site will upload the de-identified images along with the adjudication of the degree of TR to the EDC for review and over-reading by the Echo Core Lab to confirm eligibility. Once the Echo Core Lab has confirmed that the site has successfully adjudicated the degree of TR for eligibility inclusion in the trial for 3 patients, the site will be certified to continue eligibility determination independently.

The clinical sites will upload all echoes to the EDC website as they are acquired. The Echo Core Lab will read these echoes as they are uploaded. The Core Lab will carefully monitor compliance of site acquisition and interpretation of the TTE images used for eligibility determination. If the Core Lab determines that the eligibility TTE did not meet the protocol defined criteria, the Core Lab will provide immediate feedback to the site echocardiography site investigator and create a corrective action plan which will include re-training of site echocardiography investigators.

Delegation of Authority and PI Oversight
Principal Investigators are responsible for all study activities at their sites. They may delegate study tasks to qualified staff members while continuing to oversee all study activities. The Delegation of Authority Log will list each staff member's title and responsibilities for the study. The PI is responsible for careful review of each staff member's qualifications which includes training for the tasks to which each staff member is delegated. Each task should be assigned to more than one staff member to ensure proper coverage. Only staff members delegated for each task on the Delegation of Authority Log may conduct study-specific assessments. The Delegation Log will also contain the signature of each staff member. The PI will initial any additions to the Delegation of Authority Log that occur during the course of the study. The PI should document oversight of study activities throughout the life of the trial by indicating review of key elements such as eligibility, abnormal laboratory values and AEs via signature and date on appropriate source documentation.

Conflict of Interest and Financial Disclosure Agreement
This statement verifies that an investigator has no conflict of interest with any institution that may influence his/her participation in this study. All investigators must complete this statement. Investigators will also submit a financial disclosure agreement.

Site Approval
The following documents must be collected prior to site approval to open to enrollment:

- Fully executed Clinical Trial Agreement (CTA) with the CTSN DCC: InCHOIR, Department of Population Health Science & Policy, Icahn School of Medicine at Mount Sinai or Deutsches Herzzentrum Berlin (DZHB) for German research sites.
- Curricula vitae
- IRB/REB/EC roster
- IRB/REB/EC approval, version and date for protocol and consent
- HIPAA/PIPEDA/Privacy Directive compliance approval
- Surgical Investigator Certification
- Echo Core Lab Certification for TTE 2D and 3D image acquisition
- National Institutes of Health Stroke Scale (NIHSS) Training Certification
- Modified Rankin Scale (mRS) Certification
- Delegation of Authority Log
- Clinical Center Laboratory Certification(s)
- Laboratory normal ranges

Other regulatory and training documentation may be required prior to site initiation.

Prior to enrolling the first patient, representatives from the DCC will conduct a site initiation for all investigators, echocardiologists, study coordinators and any other health care professionals who may be involved in the conduct of the study.

Patient Confidentiality

All patients' records will be kept confidential according to privacy regulations. Study Investigators, site IRBs/REBs/ECs, the DCC, EAC, medical monitors and NHLBI personnel may review source documentation as necessary but all unique patient and hospital identifiers will be removed from source documents which are sent to the DCC. The aggregate data from this study may be published as per publication policy documented in the CTA; however, no data with patient identifiers will be published.

SCREENING AND BASELINE

Screening Registration 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 on the top portion of the screening registration form. The data collected is compliant with privacy regulations 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 IRB/REB/EC 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 and monitors.

Demographics Form

At initiation of screening

A screened patient is defined as a consented subject 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, date of birth, ethnic origin, and sex will be captured on the registration form. The EDC will generate a unique 5-digit identification code that will identify the patient throughout the course of the study.

Echocardiogram

Within 60 days prior to randomization

A complete TTE will be performed according to the specifications defined in the Echocardiographic Image Acquisition Protocol (Appendix I and Appendix II) within 60 days prior to randomization. ***The pre-randomization 2D echo will be read by the clinical site echocardiography investigator to assess the degree of TR which will determine echocardiographic eligibility for participation in the trial.*** (See Echocardiography Qualification above) After this initial assessment, the study echo will be sent to the Echocardiography Core Lab for centralized reading. The site echocardiography lab must be accredited by the Echo Core Lab in advance of performing any study echocardiograms. In addition, the sites will perform a 3D TTE to assess RV volume.

Medical History

Within 60 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 RV or biventricular pacemaker, stroke and other comorbidities such as diabetes and peripheral vascular disease.

Six Minute Walk Test

Within 60 days of randomization

This form captures the distance in feet walked on a level hallway in six minutes (See Appendix IV). A research clinician trained on the protocol and designated by the PI will oversee the 6MWT. This assessment is repeated at various protocol-defined periods during the trial.

Gait Speed Test for Frailty

Within 60 days prior to randomization

A patient's frailty status will be assessed through the use of the Gait Speed assessment (see Appendix V). The assessment averages the time it takes a patient to walk 5 meters during three separate attempts.

New York Heart Association Classification (NYHA)
Within 60 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 delegated to perform this assessment and documented on either the New York Heart Association Classification form or in the body of the medical record. The NYHA classification scheme is detailed in Appendix III.

Medications
Within 60 days prior to randomization
This form captures current medications at one pre-operative time point.

Physical Examination
Within 60 days prior to randomization
This form captures the comprehensive physical examination including vital signs cardiopulmonary examination, abdominal examination, and anthropometrics (height, weight).

Quality of Life
Within 60 days prior to randomization
The KCCQ, SF-12, and EQ-5D questionnaires will be completed by the patient to assess QOL. Data regarding completeness of QOL data collection and reasons for missing responses to questionnaires will be collected on the QOL Checklist.

Laboratory Assessment
Within 60 days prior to randomization
- Hematology, including white blood cell *($10^3/\mu L$)*, Hemoglobin *(g/dL)*, Hematocrit *(%)*, Platelet count *($10^3/\mu L$)*
- Coagulation profile, including 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 (BUN, *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)*.

At time of randomization
- Urine or serum beta HCG *(IU/L)* is required for women who have the potential to become pregnant

Randomization Eligibility
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 Randomization Eligibility Form. The degree of TR will also be recorded for stratification purposes. All screened patients (patients who are consented) who are not randomized in the trial will have the reasons for non-randomization documented in the Randomization Eligibility

Form. The data collected is compliant with privacy regulations and includes reason for not being randomized.

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

RANDOMIZATION

The randomization procedure will be performed intra-operatively, following the placement of the TEE probe and after visualization and confirmation of cardiac anatomy eligibility. Randomization to the study assignment will be generated by the EDC 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.

PROCEDURE

Surgical Procedure

Patients will be randomized to either (a) TV repair using a legally marketed annuloplasty ring in addition to the MVS, or (b) MVS alone.

After induction of anesthesia, all patients will undergo a TEE. The TEE will be performed under loading conditions as close as possible to the patient's baseline. Intra-operative TEEs will be performed according to standardized acquisition protocol developed by the Echo Core Lab (Appendix I and Appendix II). A laminated copy of this acquisition protocol will be provided to the site and affixed to the operating room echo machine.

All procedures will be performed using cardiopulmonary bypass support and cardioplegic arrest. The management of cardiopulmonary bypass and myocardial protection will be at the discretion of the surgeon, using standard techniques. MV repair or replacement will be performed using standard techniques.

Tricuspid valve surgery

Patients randomly assigned to receive TV repair in addition to MVS will undergo concomitant TV repair.

It is recognized that surgical techniques for TV surgery may need to be adjusted at the discretion of the surgeon based on intra-operative findings that may not be previously recognized in the preoperative evaluation. The common elements for tricuspid annuloplasty planned as part of this study are listed below:

- All procedures will be performed with cardiopulmonary bypass and with bicaval cannulation
- Both trans-septal and bi-atriatomies are acceptable as the approach to the TV
- Performance of TV repair on the arrested or the beating heart will be at the discretion of the surgeon

- TV repair will be performed with a rigid, incomplete, nonplanar, undersized annuloplasty ring
- Nominal annuloplasty ring sizes 26, 28, or 30 mm will be used. It is anticipated that normal tricuspid annular dimensions will be restored in most cases with a size 26 or 28 mm annuloplasty ring
- Commercially available rigid incomplete nonplanar tricuspid annuloplasty rings include:

    - Edwards MC3 tricuspid annuloplasty ring (model 4900)
    - Medtronic Contour 3D tricuspid annuloplasty ring (model 690R)
    - Medtronic Tri-Ad tricuspid annuloplasty ring (model 900SFC)
    - ATS TriAd Tricuspid Annuloplasty Ring
    - Carpentier-Edwards Classic tricuspid annuloplasty ring (model 4500)[2]
    - Carpentier-Edwards Physio Tricuspid ring (model 6200)

- Interrupted non-pledgeted mattress sutures will be placed from 9:00 o'clock to 6:00 o'clock (the mid-point of the septal leaflet) around the tricuspid annulus. In general, 10 to 12 sutures will be required to assure reliable seating of the tricuspid annuloplasty ring.

Peri-operative Management

Peri-operative hemodynamic support may be necessary. A variety of strategies may be utilized to optimize postoperative ventricular function. These strategies may include pacing, infusions of vasopressors or positive inotropic agents including both beta receptor agonists and/or phosphodiesterase inhibitors such as milrinone. Occasionally, patients may require mechanical support, either intra-aortic balloon pumping or ventricular assist devices.

Other Treatment

All patients enrolled in this trial are to receive standard medical management for their regurgitant mitral / tricuspid valvular disease and other co-morbid conditions in accordance with current medical practice guidelines. This includes when clinically indicated and tolerated, but is not limited to, beta-blockade, angiotensin converting enzyme inhibitors (ACE) or angiotensin receptor blockers (ARB), antiplatelet agents, statin therapy (or alternative lipid lowering agent), aldosterone antagonists, antiarrhythmic therapy, implantable defibrillators and cardiac resynchronization therapy.

POST-RANDOMIZATION DATA COLLECTION

Study Visits

- Post-Randomization Day 30 *(-7 days, + 35 days)*
- 6 *(± 30 days*), 12 *(± 30 days*), 18 *(± 30 days*) and 24 months *(± 60 days*) post-randomization

[2]Needs to be manually bent into nonplanar shape similar to other commercially available annuloplasty rings

- 36, 48 and 60 months vital status check *(± 60 days*)

For patients who are unable to return to the clinical site for the *6- and 12-month* assessments because of extreme geographic distance, the clinical coordinator will obtain the required data from a remote clinical site outside of the 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 24-month (Primary Endpoint) assessments must be performed in accordance with the protocol defined data collection whether the visit is conducted at a CTSN clinical site or remotely.* The 36, 48 and 60 month vital status checks may be conducted via telephone or via a search of medical records.

Surgical Procedures
Initial surgical intervention and event driven
The initial surgical procedure (MV surgery ± TV repair) will be reported on the initial surgical Procedure form and all subsequent operations must be reported on the follow up 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 AE report.

Initial Surgical Procedure
Routine information will be collected on the standard surgical procedure, the MV procedure, TV procedure and any concomitant procedures.

Follow-up Surgical Procedure
Information about any surgical procedure(s) performed following the initial surgical procedure and during the follow-up period through 24 months post-randomization will be collected on this form.

Hospitalizations
Index hospitalization
For all patients, the index (baseline) hospitalization must be reported on the Hospitalization form. This form collects limited information about LOS, days in ICU, and disposition at time of discharge (home, skilled nursing facility, rehabilitation facility, death).

Medications
At 30 days (-7 days, +35 days), 6 (± 30 days), 12(± 30 days), and 24 months (± 60 days) post randomization and event driven
All cardiovascular medications will be recorded at each study visit, and also as indicated at the time of associated AEs.

Physical Examination
At 30 days (-7 days, +35 days), 6 (± 30 days), 12 (± 30 days), and 24 months (± 60 days) post randomization

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

New York Heart Association Classification
At 30 days (-7 days, + 35 days), 6(± 30 days), 12(± 30 days), and 24 months (± 60 days) post randomization
The presence of heart failure will be assessed, and when present, classified according to the NYHA scale. We will assess diuretic requirements of patients as well.

Six Minute Walk Test
At 30 days (-7 days, +35 days), 6 (± 30 days), 12 (± 30 days), and 24 months (± 60 days) post randomization
This form captures the distance in feet walked on a level hallway in six minutes (See Appendix IV). A research clinician trained on the protocol and designated by the PI will oversee the 6MWT.

Gait Speed Test for Frailty
At 12 (± 30 days) and 24 months (±60 days)
A patient's frailty status will be assessed through the use of the Gait Speed assessment at 12 and 24 months post-randomization. Refer to Appendix V for instructions.

Echocardiogram
At Pre-discharge, 6(±30 days), 12(± 30 days), and 24 months (± 60 days) post randomization
A complete TTE 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. **All patients must be euvolemic, (i.e., optimal fluid management in the judgment of the cardiology investigator) at all follow up echos.** For patients who are unable to return to the clinical site for the *6*- and *12*-month assessments because of extreme geographic distance, an echo may be obtained at a remote center (see Echocardiogram Image Acquisition section). 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 24-month (Primary Endpoint) assessments must be performed in accordance with the protocol defined data collection whether the visit is conducted at a CTSN clinical site or remotely.* All study echos will be sent to the Echo Core Lab for centralized reading by a blinded investigator. In addition, a 3D TTE (Appendix II) will be performed to measure RV volume at 12 and 24 months.

Quality of Life
At 6(±30 days), 12(±30 days), 18 (±30 days) and 24 months (± 60 days) post randomization
The KCCQ, SF-12, and EQ-5D Questionnaires will be completed by the patient to assess QOL. Data regarding completeness of QOL data collection and reasons for missing responses to questionnaires will be collected on the QOL Case Report Form.

Vital Status Check
At 36, 48 and 60 months (± 60 days) post randomization
The patient's vital status will be collected via telephone or a review of medical records.

Cost
Direct costing data for all randomized patients (from US sites) will be obtained by the DCC at the conclusion of the trial.

Event Driven Data Collection

Follow-Up Surgical Procedures
Event Driven
All operations following the initial study defined surgical intervention 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 AE report. All intra-operative transfusion requirements must be documented. All follow-up surgical procedures will be recorded through month 24.

Adverse Events
Event Driven
Detailed information regarding AEs will be recorded at the time an AE occurs. Investigators will be asked to make a judgment as to the seriousness and relationship of the event to the surgical intervention. All AEs will be recorded through month 24.

Re-Hospitalizations
Event driven
All ED visits (of any duration) and re-hospitalizations (>24 hours for any reason) must be reported on the Re-Hospitalization Form. This form collects limited information about hospital procedures, LOS, days in ICU, and discharge if applicable, as well as patient condition and disposition for each hospitalization. All re-hospitalizations will be recorded through month 24.

Outpatient Intervention
Event driven within 48 hours of knowledge of event
All outpatient procedures following the index hospitalization must be reported on the surgical procedure form within 48 hours of the knowledge of the event. If the intervention is to address a complication, the coordinator must also complete an AE report. All outpatient interventions will be recorded through month 24.

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 recorded on the protocol deviation form.

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 anticipated reasons for a patient to be withdrawn from this study, is either the patient's request or at the physician's discretion, details of which will also be documented on this form. Please refer to the Manual of Procedures for partial withdrawal of consent and limited data collection.

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 EDC (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 (VPN). 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. 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.

Additional external cross-form checks for data consistency and validation will be made by the DCC's data management team. Data will be monitored remotely at the DCC on an ongoing basis to check for inconsistencies in information across forms and for data outliers (typically values that fall in the highest or lowest 10% of the accumulated data

and/or values that are outside the range of what is typically considered to be physiologically possible). Monitors will enter these queries through the EDC for site coordinators to either correct or verify.

Monitoring

The DCC monitoring team employs a risk-based approach to centralized and on-site monitoring. This approach focuses efforts on the most crucial data and process elements to allow for more efficient monitoring practices while maintaining the quality of the overall study conduct. Through the combination of centralized and on-site monitoring, instantaneous electronic validation via the EDC, and visual cross-validation by the InCHOIR monitors to detect complex errors, it is anticipated that the best possible quality and most complete data will be collected.

The centralized, or remote, monitoring of clinical trial data via the EDC is performed with a focus on safety, study endpoints, data completion and data outliers. DCC monitors will remotely monitor source documentation, study logs including the Informed Consent Log, the Protocol Violation/Deviation Log and the Serious Adverse Event/Safety Report Log periodically to ensure that the sites are adhering to the study protocol and procedures. In collaboration with the DCC data management team, the monitors will create and utilize reports outlining data completeness and timeliness, missing and outlier values as well as cross form consistency validations to generate queries and optimize reconciliation of data. This process significantly increases the efficiency of monitoring both remotely and while on site.

The DCC may conduct on-site monitoring visits after enrollment begins approximately once each year for every clinical site depending on site enrollment and other data quality metrics 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 are complete and accurate. They will also verify that all AEs 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 AEs and outcomes.

The monitors will also confirm that the regulatory 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/REB/EC roster, IRB/REB/EC approvals for all of the above documents, IRB/REB/EC correspondence, investigator's agreements, delegation of authority log, CVs of all study personnel, Human Subjects Protection training certificates, institutional HIPAA or other privacy training certificates, monitor site visit log, telephone contact log, and correspondence with the DCC.

Given the combination of approximately yearly on-site monitoring and ongoing monitoring using the EDC 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.

ANALYTICAL PLAN

General Design Issues

This study is a prospective, multi-center, randomized clinical trial. Enrolled patients will have degenerative MV disease with a clinical indication for MVS. This trial will compare the surgical approach of combining TV annuloplasty with clinically indicated MVS to performing the MVS alone.

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 TV repair (Goldstone, Howard et al. 2014; Nath, Foster and Heidenreich 2004; Koelling, Aaronson et al. 2002).

For computing sample size, we assume that at two years post randomization, 25% of patients treated with only MVS will experience the primary composite endpoint. We believe a meaningful effect worth detecting is at least a 50% relative reduction to 12%, for patients undergoing TV annuloplasty in addition to MVS. A total of 400 patients, randomized with equal probability to each arm, provides approximately 90% power to detect such a difference. For simplicity, power is based on a 0.05 level two-tailed chi-squared test. The sample size takes account of a potential single interim analysis to be performed in addition to the final analysis, and a minimal (less than 3%) rate of crossover.

Randomization Design and Procedure

Patients will be randomized using a 1:1 allocation to TV annuloplasty plus MVS or to MVS alone. The randomization will be stratified by clinical center (i.e., a separate randomization scheme will be employed in each center) and by whether severity of TR is moderate or not. 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.

Data Monitoring and Analysis

Methods of Analysis

The primary outcome of this trial is treatment failure defined as the composite of (1) death from any cause, (2) reoperation for TR, (3) presence of severe TR at two years post randomization or, for patients enrolled with less than moderate TR and annular dilatation, progression by two grades (i.e., from none/trace TR to moderate TR) at two years. The null hypothesis is that there is no difference in the probability of treatment failures at two years post randomization between patients randomized to undergo TV repair during MVS

compared to patients randomized to undergo MVS alone. The primary null hypothesis will be tested in an intent-to-treat analysis using a 0.05 level two-tailed normal approximation (Wald) test.

A log binomial regression model will be used to estimate and test differences in treatment failure between randomization groups. Similar to the logistic regression model, the log-binomial model is a generalized linear model. The models differ only in the link function used for the "success" probability *p*; logit (log odds) for logistic regression and log (log *p*) for log-binomial. The different links parameterize the model differently, with parameters of the log-binomial model yielding log relative risks rather than the log odds ratios of the logistic model.

The basic form of the log binomial models is:

$$\log P[Y_i = 1|X_{1i}, X_{2i}] = \beta_0 + \beta_1 X_{1i} + \beta_2 X_{2i} \ ,$$

where Y_i is a binary indicator of treatment failure for the i^{th} patient, X_{1i} is a binary indicator of randomization assignment for the i^{th} patient and X_{2i} is an indicator of moderate or less TR at baseline, a factor by which randomization will be stratified. While randomization will also be stratified by randomizing center, the analysis will not adjust for center due to their relatively large number compared to the proposed sample size. The exponentiated estimate of β_1 ($e^{\widehat{\beta}_1}$) in this model is the risk ratio for the composite endpoint for patients randomized to TV repair compared to patients randomized to no TV repair. The risk ratio and its associated 95% confidence interval will be used to quantify the relative risk of the composite endpoint. Differences between randomization groups in the risk of the composite endpoint will be determined by testing the null hypothesis H_0:$\beta_1 = 0$ versus a two-sided alternative (H_1:$\beta_1 \neq 0$) using a 0.05 level intention-to-treat normal approximation test (i.e., the Wald test).

Imputation of missing data

We expect relatively few patients to be missing the primary endpoint due to withdrawal or refusal. Patients with missing data will have their 24 month status imputed via multiple imputation assuming that the data are missing at random, 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 and will be included in an accompanying statistical analysis plan.

The main feature of the imputation approach is the creation of a set of clinically reasonable imputations for treatment failure 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 30 datasets. 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.

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 (200) reach the primary endpoint. The utility of performing this analysis will depend on the rate of accrual of patients into the trial. 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 to 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 relative 52% reduction (from 25% to 12%) in the incidence of treatment failure for patients receiving TV annuloplasty in addition to MVS and patients randomized to MVS alone is less than 10%.

We do not propose any a priori stopping criteria based on AEs. The treatments in this trial are not experimental, and have well known AE profiles. Moreover, we believe that incident rates of AEs 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 MR. 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, based on all relevant information reported by the DCC and the Medical Monitors. We therefore recommend that the DSMB should

be responsible for defining its deliberative processes, including event triggers that would call for an unscheduled review.

Sample Size Re-estimation
We propose considering increasing sample size should the observed primary endpoint event rate among patients randomized to no repair of the TV be appreciably less than the assumed rate of 25%. The planned sample size of 400 patients has been determined to ensure that power is at least 90% to detect a 52% relative reduction of "failure" for patients randomized to tricuspid repair compared to no repair. Should the "failure" rate among controls be 20%, 400 patients provides approximately 83% power to detect a 52% relative reduction; for a 15% "failure" rate among controls there is approximately 70% power to detect a 52% relative reduction. Therefore, we suggest that the primary endpoint event rate be examined in control patients, using the same analysis set to be used for the interim analysis, and that the sample size be increased by up to 100 additional patients in order to maintain 80% power under the original alternative hypothesis for control rates as low as 15%. If no interim analysis is conducted or accrual is complete at the time of the first interim analysis, the sample size re-estimation will not be considered.

Assessment of Balance of the Randomization
The success of the randomization procedure in balancing important covariates 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 400 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 a secondary analysis of the primary endpoint.

Additional analysis of the primary endpoint
A subgroup analysis of the primary endpoint will be performed with subgroups defined by whether or not patients received a CABG procedure during the initial surgery. This analysis will be performed in the same manner as that described for the primary analysis.

Analyses of Secondary Endpoints
Individual components of the primary endpoint
Mortality: Differences in the rate of mortality between randomization groups over the first 24 months and the planned 60 months of follow-up will be assessed using Cox proportional hazards regression.

Reoperation for TR: The difference in the rate of requiring subsequent TV annuloplasty after the initial MVS will be compared between randomization groups. Reoperation for TR may not occur because death from any cause precedes the event; thus, it is possible that censoring patients at all-cause mortality will lead to biased estimates when analyzing time to first event. Therefore, competing risks analysis using the methods of Fine and Gray (1999) will be used to estimate group differences.

Degree of TR: Between group differences in the presence of severe TR at two years post randomization or, for patients enrolled with less than moderate TR, the progression by two grades will be compared using a two-tailed 0.05 level chi-squared test of the equality of two proportions.

MACCE: The proportion of patients experiencing major adverse cerebrovascular and cardiac events, defined as the composite event of death, stroke, and the serious heart failure events, is of particular interest. Given that this trial's primary endpoint is likely to be determined by echocardiographic assessments, 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 more clinical endpoint such as MACCE (and its component elements). As the trial is not powered to detect a difference in MACCE, a statistically significant treatment difference in MACCE is not expected; however, an observed difference in MACCE, consistent in direction with that observed for the primary endpoint 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 MACCE observed between treatment groups. The rate of major cerebrovascular or cardiac events will be compared between randomization groups over 24 months post-randomization using a Cox proportional hazards regression model. We expect MACCE two-year event rates to be approximately 15% for patients randomized to MVS alone. With a total of 400 patients randomized with equal allocation to MVS alone or to TR repair plus MVS, there is 90% power to detect an absolute decrease in MACCE to approximately 9-10% for patients randomized to TR plus MVS compared to MV surgery alone.

A number of additional secondary analyses are planned to supplement the primary analysis and aid interpretation of the trial's results.

Six Minute Walk and Gait Speed Tests: Differences between groups in gait speed and the distances travelled during the 6MWT will be compared using the Wilcoxon Rank-Sum test. We will also assess the extent to which changes over time (in gait speed and distance walked) are related to other outcomes.

Additional echo parameters: RV function (normal, mildly impaired, moderately impaired, severely impaired, peak tricuspid annular velocity, TAPSE, RVFAC) at 12 and 24 months and pulmonary artery pressure at 12 and 24 months will be compared between groups. RV volume as assessed by 3D TTE at 12 and 24 months will be compared between groups. Continuous variables will be compared for between group differences using the Wilcoxon Rank Sum test, and the level of function by chi-squared test.

Quality of life: QOL will be measured using the KCCQ, SF-12, and EQ-5D. We will employ two approaches to the analysis of QOL. 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. 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.

Adverse Events: Differences in the incidence of individual AEs within 24 months post-randomization will be compared between randomization arms using Poisson regression. Ninety-five percent confidence intervals (based on the Poisson distribution) for the risk ratios for individual AEs for treatment with MVS and TV annuloplasty versus MVS alone will be computed.

NYHA classification: The distribution of NYHA at 12 and 24 months will be presented for each randomization arm and compared using a chi-squared test.

Hospital length of stay and days in Intensive Care: We will compare hospital LOS and days spent in ICU between treatment groups, separately by region (North America and Germany). A Wilcoxon Rank-Sum test will be used to test for differences within each geographic subgroup.

Hospital readmission: Rates of all-cause hospitalizations and rates of cardiovascular and heart failure specific hospitalizations, both within 30 days and within two years will be compared using Poisson regression.

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. Cost data will only be collected in the North American sites. 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 QOL 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 sampling variation and variations in discount rates.

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 TV annuloplasty who do not receive it during the trial can be considered crossovers. In addition, patients who are randomized to no annuloplasty but receive it during the index procedure are considered to have crossed over. As the primary analysis is by intention to treat, crossovers will be analyzed as belonging to the group to which they were randomized. Given the short duration between randomization and surgery, crossovers are assumed to be rare (no more than 3%).

ORGANIZATION OF THE STUDY

This section describes the overall study organization. The study will be conducted at up to 50 sites in the CTSN sponsored by NHLBI, in collaboration with NINDS and CIHR, and the DZHK supported DGTHG. The following committees and institutions will be involved in the administration of the study.

Event Adjudication Committee

The charge of the EAC is to review source documents and adjudicate all AEs, causes of mortality and cardiovascular and heart failure related readmissions. The individuals who will serve on the committee are unaffiliated with the conduct of the clinical trial or the DCC. The committee will consist of experienced clinicians with expertise in cardiothoracic surgery, cardiology, infectious disease and neurology. Additional specialty clinicians can be added as deemed necessary. The EAC will meet every 2-4 months or as needed to review outcomes data for each subject enrolled.

Data and Safety Monitoring Board

To meet the study's ethical responsibility to its subjects, an independent DSMB will monitor results during the study. The board consists of physicians, biostatisticians,

ethicists, neurologists 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 EAC every 6 months. These data include AEs 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 and Clinical Coordinating Center
A university-based DCC (InCHOIR) will collaborate with the Network Investigators. The DCC will coordinate and monitor the trial and will administrate the DSMB and EAC. It bears responsibility for monitoring interim data and analyzing the study's results in conjunction with the investigators and the sponsor.

Echocardiography Core Laboratory
All echocardiograms will be performed according to a standardized protocol and will be centrally analyzed by the Network Echo Core Lab directed by Judy W. Hung, MD, located at the Massachusetts General Hospital, Boston, MA.

Network 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; (c) collaborate in data analysis, interpretation, and publication; (d) establish criteria for authorship on all manuscripts, publications and presentations that arise from the study.

REFERENCES

Agricola E, Marini C, Stella S, et al. Effects of functional tricuspid regurgitation on renal function and long-term prognosis in patients with heart failure. J Cardiovasc Med (Hagerstown). 2015 Aug 7. [Epub ahead of print]

Benedetto U, Melina G, Angeloni E, Refice S, Roscitano A, Comito C, Sinatra R. Prophylactic tricuspid annuloplasty in patients with dilated tricuspid annulus undergoing mitral valve surgery. J Thorac Cardiovasc Surg. 2012 Mar;143(3):632-8.

Bertrand PB, Koppers G, Verbrugge FH, et al. Tricuspid annuloplasty concomitant with mitral valve surgery: effects on right ventricular remodeling. J Thorac Cardiovasc Surg. 2014 Apr;147(4):1256-64.

Chan V, Burwash IG, Lam BK, Auyeung T, Tran A, Mesana TG, Ruel M. Clinical and echocardiographic impact of functional tricuspid regurgitation repair at the time of mitral valve replacement. Ann Thorac Surg. 2009 Oct;88(4):1209-15.

Chikwe J, Itagaki S, Anyanwu A, Adams DH. Impact of Concomitant Tricuspid Annuloplasty on Tricuspid Regurgitation, Right Ventricular Function, and Pulmonary Artery Hypertension After Repair of Mitral Valve Prolapse. J Am Coll Cardiol. 2015 May 12;65(18):1931-8.

Dreyfus GD, Corbi PJ, Chan KM, Bahrami T. Secondary tricuspid regurgitation or dilatation: which should be the criteria for surgical repair? Ann Thorac Surg. 2005 Jan;79(1):127-32.

Dreyfus, GD, Martin, RP, Chan, KMJ, Dulguerov, F, Alexandrescu, C. Functional Tricuspid Regurgitation: A Need to Revise our Understanding. J Am Coll Cardiol. 2015;65(21):2331-2336.

Fine JP, Gray RJ. A proportional hazards model for the sub distribution of a competing risk. J Am Stat Assoc. 1999; 94:496–509.

Goldstone AB, Howard JL, Cohen JE, et al. Natural history of coexistent tricuspid regurgitation in patients with degenerative mitral valve disease: implications for future guidelines. J Thorac Cardiovasc Surg. 2014 Dec;148(6):2802-9.

Groves PH, Lewis NP, Ikram S, Maire R, Hall RJ. Reduced exercise capacity in patients with tricuspid regurgitation after successful mitral valve replacement for rheumatic mitral valve disease. Br Heart J. 1991 Oct; 66(4):295-301.

Koelling TM, Aaronson KD, Cody RJ, Bach DS, Armstrong WF. Prognostic significance of mitral regurgitation and tricuspid regurgitation in patients with left ventricular systolic dysfunction. Am Heart J. 2002 Sep; 144(3):524-9.

Lee JW, Song JM, Park JP, Lee JW, Kang DH, Song JK. Long-term prognosis of isolated significant tricuspid regurgitation. Circ J. 2010 Feb; 74(2):375-80. Epub 2009 Dec 14.

McCarthy PM. Adjunctive procedures in degenerative mitral valve repair: tricuspid valve and atrial fibrillation surgery. Semin Thorac Cardiovasc Surg. 2007 Summer;19(2):121-6.

Morrow AG, Oldham HN, Elkins RS, Braunwald E. Prosthetic replacement of the mitral valve. Preoperative and postoperative clinical and hemodynamic assessments in 100 patients. Circulation. 1967 May; 35(5):962-79.

Nath J, Foster E, Heidenreich PA. Impact of tricuspid regurgitation on long-term survival. J Am Coll Cardiol. 2004 Feb 4; 43(3):405-9.

Nishimura RA, Otto CM, Bonow RO, Carabello BA, Erwin JP 3rd, Guyton RA, O'Gara PT, Ruiz CE, Skubas NJ, Sorajja P, Sundt TM 3rd, Thomas JD; American College of Cardiology/American Heart Association Task Force on Practice Guidelines. 2014 AHA/ACC guideline for the management of patients with valvular heart disease: executive summary: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol. 2014 Jun 10;63(22):2438-88.

Pinney SP. The role of tricuspid valve repair and replacement in right heart failure. Curr Opin Cardiol. 2012 May;27(3):288-95.

Raja SG, Dreyfus GD Surgery for functional tricuspid regurgitation: current techniques, outcomes and emerging concepts. Expert Rev Cardiovasc Ther. 2009 Jan;7(1):73-84.

Ruel M, Rubens FD, Masters RG, Pipe AL, Bédard P, Mesana TG. Late incidence and predictors of persistent or recurrent heart failure in patients with mitral prosthetic valves. J Thorac Cardiovasc Surg. 2004 Aug; 128(2):278-83.

Sagie A, Freitas N, Chen MH, Marshall JE, Weyman AE, Levine RA. Echocardiographic assessment of mitral stenosis and its associated valvular lesions in 205 patients and lack of association with mitral valve prolapse. Am Soc Echocardiogr. 1997 Mar;10(2):141-8.

Taramasso M, Vanermen H, Maisano F, Guidotti A, La Canna G, Alfieri O. The growing clinical importance of secondary tricuspid regurgitation. J Am Coll Cardiol. 2012 Feb 21;59(8):703-10.

Van de Veire NR, Braun J, Delgado V, Versteegh MI, Dion RA, Klautz RJ, Bax JJ. Tricuspid annuloplasty prevents right ventricular dilatation and progression of tricuspid regurgitation in patients with tricuspid annular dilatation undergoing mitral valve repair. J Thorac Cardiovasc Surg. 2011 Jun;141(6):1431-9.

Vargas Abello LM, Klein AL, Marwick TH, et al. Understanding right ventricular dysfunction and functional tricuspid regurgitation accompanying mitral valve disease. J Thorac Cardiovasc Surg. 2013 May;145(5):1234-1241.e5.

Yilmaz O, Suri RM, Dearani JA, Sundt TM 3rd, Daly RC, Burkhart HM, Li Z, Enriquez-Sarano M, Schaff HV. Functional tricuspid regurgitation at the time of mitral valve repair for degenerative leaflet prolapse: the case for a selective approach. J Thorac Cardiovasc Surg. 2011 Sep;142(3):608-13.

Appendix I: Moderate Tricuspid Regurgitation Trial Echocardiographic Image Acquisition Protocol

General Considerations:

- For the echocardiogram, the patient will be positioned in left lateral recumbency or in the position that permits optimal imaging. All images should be acquired during quiet respiration unless otherwise specified.

- At least 3 and no more than 5 cardiac cycles are requested for two-dimensional imaging unless otherwise specified. 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. 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. Gain should be adjusted to reduce excess noise. Color Doppler Nyquist limits will be adjusted to the range of 50-70 cm/sec, unless otherwise specified. The following protocol is required however additional images should be obtained at the discretion of the sonographer/physician.

I. Protocol for Transthoracic Echocardiogram (TTE) pre and post-surgery

1. Parasternal long axis
   - 2D image
   - Color Doppler across aortic and mitral valves
   - Zoom image of LVOT
   - Zoom image of vena contracta

2. Parasternal right ventricular inflow view of the tricuspid valve
   - 2D image include RV and RA (optimize endocardium)
   - Color Doppler across tricuspid valve (TV) including distal jet into RA
   - Zoom view of TV annulus (for measurement of TV annulus)
   - Zoom view of vena contracta proximal jet of TR
   - Zoom view of the proximal flow convergence region of the TR jet after baseline shifted downward (same direction as TR jet flow) to a Nyquist of 25-35 cm/s
   - Continuous wave Doppler across TV valve to estimate TV gradient.

3. Parasternal outflow view of the pulmonic valve
   - 2D
   - Color Doppler across PV

- Pulse wave Doppler
- CW of the pulmonary valve
- Zoom 2D image of pulmonary valve annulus for measurement of the pulmonary annular diameter.

4. Basal PSAX (at the aortic valve level)
   - 2D image include TV, short axis of aortic valve and RVOT
   - Color Doppler of TV include distal jet into right atrium
   - Zoom view of Color Doppler view of vena contracta of TR
   - Zoom view of the proximal flow convergence region of the TR jet after baseline shifted downward (same direction as TR jet flow) to a Nyquist of 25-35 cm/s
   - 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.

5. PSAX of ventricles: ensure on-axis views and include right ventricle
   - Level of the mitral valve when both anterior and posterior leaflets are visualized.
   - Mid-papillary muscle level.
   - Level of the apex

6. Apical 4-chamber view
   - Full sector to include all four chambers
   - Focus on right heart: 2D to Include RV and RA, making sure to include lateral wall of RV (often requires a slight medial tilt of transducer)
   - Zoom view of RV only (include base of RV/TV annulus and optimize RV endocardium)
   - Color Doppler across TV one including right atrium to capture the distal jet taking care to include wall-impinging eccentric jets in the region of interest.
   - Zoom view of TV annulus (for measurement of TV annulus)
   - Zoom view of Color Doppler across TV to image the vena contracta of the TR jet
   - Zoom view of the proximal flow convergence region of the TR jet after baseline shifted downward (same direction as TR jet flow) to a Nyquist of 25-35 cm/s
   - PW of TV at leaflet tips and at level of TV annulus
   - CW of TV for estimation of pulmonary artery systolic pressure
   - M-mode across lateral tricuspid annulus (for TAPSE measurement)
   - Tissue Doppler of lateral tricuspid annulus (to measure peak annular velocity)
   - Focus on left heart:

- 2D include both LV and LA
- Zoom view of LV only (avoid foreshortening of LV apex)
- Color Doppler across MV one including left atrium to capture the distal jet taking care to include wall-impinging eccentric jets in the region of interest.
- Zoom view of MV annulus (for measurement of MV annulus)
- -Zoom view of the proximal flow convergence region of the MR jet after baseline shifted downward (same direction as MR jet flow) to a Nyquist of 30-40 cm/s
- PW of MV at leaflet tips and at level of MV annulus
- PW Doppler of right pulmonary vein flow. The sample volume should be placed at least 1 cm within the pulmonary vein
- CW of MV
- Tissue Doppler of lateral and septal mitral annulus

7. Apical 5-Chamber view
   - Color flow Doppler across LVOT/Aortic valve
   - PW Doppler in left ventricular outflow tract positioned such that closing artifact but not opening artifact of the valve is visible.
   - CW Doppler through the LVOT/aortic valve.

8. Apical 2-chamber view
   - 2D image include left ventricle and left atrium
   - Zoom view to include LV only (avoid foreshortening of LV apex)
   - Color Doppler cross mitral valve including distal jet into left atrium

9. Apical 3-chamber view (aka apical long-axis view)
   - 2D image include left ventricle and left atrium
   - Color Doppler cross mitral valve including distal jet into left atrium
   - PW Doppler in left ventricular outflow tract
   - CW Doppler through the LVOT/aortic valve.

10. Subcostal imaging
    - 2D of Inferior vena cava with and without a “sniff” (5-10 beat loop).
    - Pulse wave of hepatic vein flow
    - Color Doppler of IVC and RA junction
    - Color Doppler of inter-atrial septum to interrogate presence of SD.
    - 4-chamber view showing RV, RA LA and LV
    - Color Doppler of TV and MV in 4 chamber subcostal view

- SAX views (particularly if parasternal evaluation was limited).

11. Contrast will be used for endocardial border delineation when less than 80% of the endocardium can be visualized on the harmonic image.

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.

II. 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. 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.

Pre-Procedure Imaging
The following checklist may be used with appropriate Doppler performed for valvular assessment:

1. Mid and High esophageal views
   - 4 Ch view (of entire LV/RV); maximize endocardial definition.
   - Tricuspid Valve/Right Ventricle/right atrium/Interatrial Septum
     - 4 Chamber view angled to focus on right heart –both include RA and RV
     - Focus on TV including right atrium by changing depth to and obtain 2D image and color Doppler at 0, 60, 90 and 120-140 degrees; please include entire TV annulus
     - Interatrial septum (IAS) at (50 to70 degrees-with aortic rim in view) and bicaval view (90-110°) 2D and Color Doppler across IAS
     - (if 3D available) 3D TEE image of TV and RV at 0 degrees and 60 degrees (Full volume acquisitions-1 beat and either 4 beat or HVR mode-please hold respiration for latter)
     - (if 3D available) 3D color Doppler TEE of TR jet at 0 and 90 degrees (Full volume acquisition-1 beat and either 4 beat or HVR mode-please hold respiration for latter)

2. Mitral Valve: (lower depth to maximize visualization of the valve but include chordal attachments to the papillary muscle level). Please obtain 2D and color

Doppler images of the mitral valve and chordal structures. For color Doppler assessment: Please adjust color Doppler settings to optimize visualization of MR jet area and vena contracta (Nyquist between 50-70 cm/s). Please also obtain in at least one view: baseline shifting (in direction of MR jet flow) to Nyquist of 0.3 to 0.4 m/s) with Zoom mode on the proximal flow region. This is for PISA calculation.

Please obtain views of the mitral valve in the following planes:

- Transverse Plane (0°)
  - Change depth to image entire LV as well; maximize endocardial definition)
- Commissural View (60°)
  - Change depth to image entire LV as well; maximize endocardial definition.
- Two-chamber View (90°)
- Three-chamber View (120-140°)
- Record CW of MR in at least one plane
- Record PISA region after baseline shifting Nyquist upward (in direction of flow) to 40 cm/s. Please record 3-5 beats and not a single frame

3. LVOT/AV/Aorta
   - Long-axis view (120-140°) 2D and with color Doppler
   - Ascending aorta (mid to high esophageal view) (90° to 110)
   - Ascending aorta SAX views (0°, high esophageal)
   - AV SAX (30°, mid esophageal) with color Doppler

4. Main PA/PV
   - Bifurcation view (0-30°, high esophageal)
   - RVOT view (70°, mid esophageal)

5. Left atrial appendage
   - 2D at 45, 75, and 120-135 degrees.

6. Pulmonary vein pulse wave Doppler: Sample volume placed in the vein, 1 cm from the orifice.
   - One left and one right PV

7. Transgastric views
   - Three 2D short axis views are requested
     - Mitral valve level
     - Mid papillary muscle
     - Apical level.
   - Short axis images of the right ventricle and tricuspid valve (0 degrees)
     - Long axis of right ventricle and tricuspid valve (60-100 degrees)

    - Pulse wave of hepatic vein flow
  - Deep Gastric views
    - 5Ch view Aortic valve (with color, PW and CW Doppler)

8. Aorta
   - Thoracic aorta (short axis views)
   - Aortic arch (SAX and LAX views)

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:

1. Tricuspid Valve/right ventricle

   - Right heart –both include RA and RV at 0 and 60, 90 degree view
   - 2D and color Doppler (for jet area and vena contracta) at 0, 60, 90 and 120-140 degrees; please include entire TV annulus
   - Pulse and continuous wave across tricuspid valve
   - (If 3D TEE available-3D TEE image of RA and RV at 0 degree (Full volume acquisitions-1 beat and either 4 beat or HVR mode-please hold respiration for latter)
   - (if 3D available)-3D TEE image of TV and RV at 0 degrees and 60 degrees (Full volume acquisitions-1 beat and either 4 beat or HVR mode-please hold respiration for latter)
   - (if 3D available)-3D color Doppler TEE of TR jet at 0 and 90 degrees (Full volume acquisition-1 beat and either 4 beat or HVR mode-please hold respiration for latter)

2. Mitral valve
   - 2D and color Doppler of mitral valve at 0, 60, 90, and 120 degrees
   - (include MR jet area and vena contracta for color Doppler views)
   - Zoom of PISA region (if MR is >mild by semi-qualitative assessment) with baseline shift to 40 cm/s
   - Continuous wave Doppler to assess post-procedure gradients and MR jet velocity
   - Pulmonary vein (one left and one right PV) pulse wave Doppler: Sample volume placed in the vein, 1 cm from the orifice.

3. Left ventricle
   - Mid-Esophageal views of LV at 0 and 60 degrees

III. Moderate TR: Echocardiographic Measurements

The degree of tricuspid valve regurgitation will be categorized according to American Society of Echocardiography guidelines as none/mild/moderate/severe (J Am Soc Echocardiogr 2003; 16:777-802).

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 (cm^2)§	< 5	5-10	> 10
VC width (cm)ϕ	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 cm^2 , maximal RA medio-lateral and supero-inferior dimensions ≤ 4.6 cm and 4.9 cm respectively, maximal RA volume ≤ 33 ml/m^2(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.
ϕ 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).

A. Tricuspid Valve/Right atrium and right ventricle

The following variables will be measured:

1. Degree of tricuspid regurgitation categorized as:
   a) None/Trace
   b) Mild
   c) Moderate
   d) Severe
2. Jet area of TR
3. Vena contracta
4. EROA by PISA
5. TV annulus dimension (Apical 4 Chamber)
6. TV: Mechanism of TR: Primary vs secondary
7. RA volume (ml)
8. RV function categorized as:
   a) Normal
   b) Mildly impaired
   c) Moderately impaired
   d) Severely impaired
9. Tricuspid annular peak systolic excursion (TAPSE)
10. Peak tricuspid annular velocity (PTAV)

11. RV fractional area change (%)
12. RV size categorized as
    a) Normal
    b) Mildly dilated
    c) Dilated
13. RV dimension (apical 4 chamber view)
14. RVSP

B. LV Measures
    1. Interventricular septum (mm)
    2. Posterior wall thickness
    3. LVID end-diastole
    4. LVID end-systole
    5. ESV
    6. EDV
    7. LVEF

C. Mitral Valve
    1. Degree of MR (Trace/none, mild, moderate, severe)
    2. Mechanism of MR

D. Aortic Valve
    1. Aortic stenosis (y/n)
    2. Aortic Regurgitation (None, trace, mild, moderate or severe)

Appendix II: Moderate Tricuspid Regurgitation Trial Echocardiographic Image Acquisition Protocol: 3D Image Echo Protocol

General Considerations:
Optimize ECG tracing, avoid stitching artifacts.
Maximize frame rate-minimum frame rate needed 10 Hz but the higher the better.
Only Full Volume Datasets; Do not acquire in Live 3D or 3D Zoom modes

a. *Focused RV Apical 4 Chamber view:*
-Full volume 3D data set in modified AP4 view focused on RV and RA. This view is obtained in apical 4 chamber window with probe positioned LATERALLY and tilted ANTERIORLY to include the RVOT. If biplane or x-plane imaging is available, visualization of RVOT can be confirmed (see figure). Obtain a FV 4 beat acquisition (with breath hold), HVR mode (if available) and one beat acquisition; repeat x 1
-Full volume 3D color Doppler dataset across tricuspid valve: 4 beat acquisition with breath hold and one beat acquisition

b. *Standard apical 4 chamber view:* Optimize depth and sector image to obtain standard apical 4 chamber including both ventricles and atria
-Full volume 3D data set in AP4 view- 4 beat acquisition (with breath hold), HVR mode and one beat acquisition; repeat x1
c. Full volume 3D data set of RV outflow view (parasternal window)-4 beat acquisition (with breath hold), HVR mode and one beat acquisition; repeat x 1

Appendix III: New York Heart Association Classification (NYHA)

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 IV: Six-Minute Walk Test Instructions

The walking test will be conducted in an enclosed corridor (preferably free of distractions) on a course that is 60 feet long (Guyatt, 1985[3]). The corridor will be divided into 5-foot sections using a method unnoticeable to the patient. Chairs will be placed at either end of the 60-foot course markers. The distance covered during the preceding walk test will not be revealed to the patient during the study.

Before the test, the patient will sit quietly for 10 minutes. These instructions will be read verbatim to the patient:

THE PURPOSE OF THIS TEST IS TO FIND OUT HOW FAR YOU CAN WALK IN SIX-MINUTES. YOU WILL START FROM THIS POINT AND FOLLOW THE HALLWAY TO THE CHAIR AT THE END, THEN TURN AROUND AND WALK BACK. WHEN YOU ARRIVE BACK AT THE STARTING POINT, YOU WILL GO BACK AND FORTH AGAIN. YOU WILL GO BACK AND FORTH AS MANY TIMES AS YOU CAN IN THE SIX-MINUTE PERIOD. IF YOU NEED TO, YOU MAY STOP AND REST. JUST REMAIN WHERE YOU ARE UNTIL YOU CAN GO ON AGAIN. HOWEVER, THE MOST IMPORTANT THING ABOUT THE TEST IS THAT YOU COVER AS MUCH GROUND AS YOU POSSIBLY CAN DURING THE SIX MINUTES. I WILL TELL YOU THE TIME, AND I WILL LET YOU KNOW WHEN THE SIX MINUTES ARE UP. WHEN I SAY STOP, PLEASE STAND RIGHT WHERE YOU ARE.

DO YOU HAVE ANY QUESTIONS ABOUT THE TEST?

PLEASE EXPLAIN TO ME WHAT YOU ARE GOING TO DO.

Repeat the entire instructions if the patient does not seem to understand.

Repeat the sentence:

THE MOST IMPORTANT THING ABOUT THE TEST IS THAT YOU COVER AS MUCH GROUND AS YOU POSSIBLY CAN DURING THE SIX MINUTES.

ARE YOU READY?

START WHEN I SAY "GO"

[3] Kirshner, B, Guyatt, G. (1985) A methodological framework for assessing health indices. Journal of Chronic Diseases 38: 27–36.

During the test, the walking pace of the patient should not be influenced. The test supervisor must walk behind the patient - not walk with, rush up behind, or rush past the patient.

While walking, the patient will be encouraged every 30 seconds with the following phrases:

0-3 minutes:
THAT'S IT; YOU'VE GOT THE IDEA.
YOU'RE DOING WELL.
KEEP IT UP NOW.

3-6 minutes:
REMEMBER, AS FAR AS YOU CAN GO.
WE'LL WANT YOU TO GO AS FAR AS YOU POSSIBLY CAN.
THAT'S IT; KEEP WORKING AT IT.
COME ON; KEEP GOING.

The patient should be spoken to only at the 30-second encouragements and no response should be made to the patient's questions about the time and distance elapsed. If the patient is not concentrating on the walking, the patient can be reminded at a 30-second mark:

THIS IS A WALKING TEST. TALKING WILL UTILIZE YOUR ENERGY RESERVE AND INTERFERE WITH YOUR PERFORMANCE.

Encouragement phrases can be repeated as needed. For example, if the patient is slowing down and expresses that he/she wants to stop, say:

REMEMBER, IF YOU NEED TO, YOU MAY REST. JUST REMAIN WHERE YOU ARE UNTIL YOU CAN GO ON AGAIN.

If necessary, the patient may rest in a course marker chair although he/she should not be encouraged to do so.

The patient will be told the time elapsed at 2 and 4 minutes, i.e.:

YOU HAVE COMPLETED 2 MINUTES
And
YOU HAVE COMPLETED 4 MINUTES

At the end of the test, the patient should not move from where he/she was told to "STOP" until the distance walked (measured to the nearest foot) has been recorded.

Record the DISTANCE WALKED during the six-minute test.

Appendix V: Frailty Assessment – Gait Speed Test Instructions

The addition of the Gait Speed test to assess frailty offers a quantifiable way to capture frailty in this trial population. Other approaches to assessing frailty were reviewed, but the Gait Speed test serves as the simplest and most effective test in measuring frailty. The assessment is an average of three 5 meter walks.
The test can be performed on any patient able to walk 5 meters using the guidelines below.

Accompany the patient to the designated area – well lit, unobstructed, and containing clearly indicated markings at 0 and 5 meters.

Position patient with feet behind, but just touching the 0 meter start line.

Instruct the patient to "walk at a comfortable pace" until a few steps past the 5 meter mark. Note, the patient should not slow down before the 5 meter mark.

Begin each trial with the word "Go."

Start the timer at the first footfall after the 0 meter line.

Stop the timer at the first footfall after the 5 meter line.

Repeat the 5 meter walk three times, allowing for sufficient time for recuperation between trials.

Record the times, in seconds, it takes to complete each trial, on the data collection form and calculate the average speed.

Note: A patient can use a walking aid (cane, walker). For patients receiving an IV drip, that test should be performed without the IV only if it can be interrupted temporarily without any potential risk to the patient. If not, it can be performed with the patient pushing the IV pole.

Statistical Analysis Plan

Cardiothoracic Surgical Trials Network

Evaluating the Benefit of Concurrent Tricuspid Valve Repair During Mitral Surgery (TR)

Sponsored by the National Heart, Lung, and Blood Institute (NHLBI) and the German Society for Thoracic and Cardiovascular Surgery (DGTHG)

CT Surgical Trials Network Research Group

Data and Clinical Coordinating Center
InCHOIR
Icahn School of Medicine at Mount Sinai
New York

Version: 1.0
Version Date: 7/14/2020

MODIFCATION HISTORY

Version Number	Date of Document Version	Significant Changes from Previous Authorized Version
1.0	7/14/2020	Not applicable – first version

TABLE OF CONTENTS

ABBREVIATIONS AND DEFINITIONS

AE	Adverse event
AV	Atrioventricular
CABG	Coronary artery bypass grafting
CEA	Cost-effectiveness analysis
CTSN	Cardiothoracic Surgical Trials Network
DCC	Data and Clinical Coordinating Center
DGTHG	German Society for Thoracic and Cardiovascular Surgery (Deutschen Gesellschaft für Thorax-, Herz- und Gefäßchirurgie)
DSMB	Data and Safety Monitoring Board
EAC	Event Adjudication Committee
EC	Ethics Committee
EQ-5D	EuroQoL
ICER	Incremental cost effectiveness ratio
InCHOIR	International Center for Health Outcomes & Innovation Research
IRB	Institutional Review Board
KCCQ	Kansas City Cardiomyopathy Questionnaire
LOS	Length of stay
MACCE	Major adverse cardiac and cerebrovascular event
MR	Mitral regurgitation
MV	Mitral valve
MVS	Mitral valve surgery
NHLBI	National Heart, Lung, and Blood Institute
NYHA	New York Heart Association
QALY	Quality adjusted life years
QOL	Quality of Life
REB	Research Ethics Board
RV	Right Ventricle
RVFAC	Right ventricular fractional area change
SAE	Serious adverse event
SAP	Statistical Analytical Plan
SF-12	Short Form 12
6MWT	Six Minute Walk Test
TAPSE	Tricuspid annular plane systolic excursion
TEE	Trans-esophageal echocardiography
TR	Tricuspid regurgitation
TTE	Transthoracic echocardiography
TV	Tricuspid valve

PURPOSE OF STATISTICAL ANALYTICAL PLAN (SAP)

The purpose of this SAP is to outline the planned analyses to be completed for the TR trial. The analyses identified in this SAP will be included in abstracts and manuscripts reporting the results of the trial. Exploratory analyses not necessarily identified in this SAP may also be performed. Any post hoc, or unplanned, analyses not explicitly identified in this SAP will be clearly identified as such in any published papers from this study. This SAP may be updated in response to additional developments, either within or outside the trial. All revisions will be made prior to the data lock and the primary analysis.

1. INTRODUCTION

The presence of moderate or severe TR is commonly encountered, affecting over 1.6 million people in the United States alone (Taramasso et al., 2012). As intrinsic pathology of the TV is rare, most TR is functional, defined as regurgitation in the presence of anatomically normal leaflets and chords. The precise mechanism by which functional TR develops is thought to be due to tricuspid annular dilation as well as by right ventricular (RV) enlargement and dysfunction associated with MV pathology in the presence of systolic and/or diastolic dysfunction and/or significant pulmonary hypertension (Dreyfus, Martin, Chan, Dulguerov, & Alexandrescu, 2015).

Although the clinical context in which TR occurs may influence prognosis, there are numerous reports that demonstrate the presence of TR being associated with increased mortality. Patients who do survive and develop more severe TR are more likely to develop New York Heart Association class III-IV symptoms (Groves, Lewis, Ikram, Maire, & Hall, 1991; Ruel et al., 2004) and decreased quality of life.

In 1967, Braunwald and colleagues demonstrated that correction of left-sided disease allowed for resolution of TR (Morrow, Oldham, Elkins, & Braunwald, 1967). In more recent years, however, this philosophy has been challenged by some, on account of observations that TR may in fact resolve only in a minority of cases. Overall data on the postoperative course and clinical sequelae of TR are conflicting, largely due to heterogeneous surgical management and MV pathologies.

In patients with severe TR already undergoing surgery for left valvular pathology, surgical correction is recommended by the AHA/ACC and ESC guidelines (Nishimura et al., 2014). Significant equipoise exists, however, as to the optimal approach for patients with only moderate TR or mild TR with annular dilation. Some argue that performing a TV annuloplasty at the time of MVS influences the incidence of right heart failure and improves long term survival, yet others believe the risk of an additional surgical procedure outweighs the potential benefit (Yilmaz et al., 2011).

The CTSN, therefore, designed a trial to evaluate the efficacy and safety of concomitant TR annuloplasty at the time of MVS. This document serves as the SAP for the TR trial.

2. STUDY OBJECTIVES

The overall objective of this study is to evaluate the safety and efficacy of tricuspid valve (TV) repair in the setting of mitral valve surgery (MVS) for degenerative mitral valve (MV) disease. Specifically, this study compares the surgical approach of combining TV annuloplasty with clinically indicated MVS to performing MVS alone.

2.1 Primary Objective

The primary aim of this trial is to evaluate the impact of these two surgical approaches on the composite endpoint of death and reoperation for tricuspid regurgitation (TR), or progression of TR, either by two grades from baseline (i.e. *prior* to randomization), *or* by the presence of

severe TR at 2 year follow-up.

2.2 Secondary Objectives

Secondary aims of this trial include assessment of the impact of these two surgical approaches on right heart performance and function, mortality, adverse events (AEs), quality of life (QOL), functional status, presence and severity of TR, and health resource use.

3. STUDY OVERVIEW

3.1 Study Design

This is a prospective, multi-center, randomized clinical trial in patients undergoing MVS for degenerative MV disease. Patients will be randomized (1:1) to receive either MVS + TV annuloplasty or MVS alone.

3.1.1 Study Duration and Time Points

All patients will be followed for 60 months post-randomization. Endpoints will be measured at 30 days, 6, 12, 18, and 24 months. Survival will continue to be measured after the 24-month visit via vital sign checks at 36, 48 and 60 months.

3.1.2 Randomization and Masking

Patients will be randomly assigned (1:1) to MVS + TV annuloplasty or MVS alone. Patient randomization will be stratified by TR severity and by clinical center. The randomization procedure will be performed intra-operatively, following the placement of the TEE probe and after visualization and confirmation of cardiac anatomy eligibility, in order to minimize the likelihood of enrolling patients in the study with unexpected surgical contra-indications to TV repair. Randomization will be performed centrally through a Web-based data collection system that automates the delivery of the randomization assignments. The treatment assignment will be viewed by the site coordinator electronically, in a secure fashion, and electronic verification of the treatment assignment will be required before proceeding with the treatment intervention.

Neither patients nor investigators will be blinded to treatment assignment due to the nature of the treatment intervention. Investigators will, however, be blinded to all data from other clinical sites, except serious unexpected AEs that are possibly or probably related to the investigational procedure for IRB/REB/EC reporting purposes. All echocardiograms will be analyzed by echocardiography core laboratory (Echo Core Lab) personnel who will be blinded to clinical outcomes. Adverse events (AEs) will be adjudicated by an Event Adjudication Committee (EAC) and trial oversight will be provided by an independent Data and Safety Monitoring Board (DSMB).

4. ANALYSIS POPULATIONS

Two populations will be used for all summaries and analyses.

Screened Population

The screened population will consist of all screened patients. A screened patient is defined as a consented subject 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.

Intent-to-Treat (ITT) Population

The ITT population will consist of all randomized subjects grouped by their assignment at randomization whether or not they actually received the treatment to which they were assigned. This sample will be used for summaries and analyses of the primary endpoint and the secondary clinical endpoints.

5. STUDY ENDPOINTS

5.1 Primary Endpoint

The primary endpoint will be a composite of death, reoperation for TR, or progression of TR from baseline, prior to randomization, by two grades or the presence of severe TR at 2 years post randomization.

Degree of TV regurgitation will be categorized according to American Society of Echocardiography guidelines as none/mild/moderate/severe. Trace regurgitation is also used in the event that regurgitation is barely detected.

5.2 Secondary Clinical Endpoints

The following secondary clinical endpoints will be assessed:

5.2.1 Clinical and Functional Outcomes

- A composite of major adverse cardiac and cerebrovascular events (MACCE), including stroke, death, and serious heart failure events by 24 months post-randomization
- Re-operation for TR by 24 months post-randomization
- NYHA classification at 30 days, 6, 12 and 24 months post-randomization.
- Diuretic Use at 30 days, 6, 12 and 24 months
- 6MWT at 30 days, 6, 12 and 24 months post-randomization.
- Gait Speed Test for Frailty at 12 and 24 months post-randomization.

5.2.2 Echocardiography

All echocardiography outcomes are measured by transthoracic 2D echocardiography unless otherwise noted

- Degree of TR at index hospital discharge
- Degree of TR at 12 and 24 months
- RV size at 12 and 24 months
- RV function (normal, mildly impaired, moderately impaired, severely impaired, peak tricuspid annular velocity, TAPSE, RVFAC) at 12 and 24 months
- Pulmonary artery pressure at 12 and 24 months
- RV volume at 12 and 24 months as measured by transthoracic 3D echocardiography

5.2.3 Quality of Life

- SF-12 at 6, 12, 18 and 24 months post-randomization.
- KCCQ at 6, 12, 18 and 24 months post-randomization.
- EQ-5D at 6, 12, 18 and 24 months post-randomization.

5.2.4 Survival

- Perioperative mortality (in-hospital or 30-day mortality)
- Mortality through 24 months post-randomization
- Mortality through 60 months post-randomization

5.2.5 Serious Adverse Events

- Frequency of SAEs
- AV-Block requiring pacemaker implantation
- New-onset atrial fibrillation

5.2.6 Hospitalizations

- Index hospitalization LOS and ICU days
- All-cause readmissions and readmissions for heart failure and TR re-operation through the first 30 days following surgery and through 24 months post-randomization

5.2.7 Economic Outcomes

- Cost
- Cost-effectiveness

6. STATISTICAL METHODOLOGY

6.1 General Principles

Study day will be calculated from the reference start date, and will be used to show the study days of assessments and events. Reference start date is defined as the date of randomization unless otherwise specified. In analyses of index length of stay, index ICU days, peri-operative (30 day) mortality, and peri-operative (30 day) readmissions the reference date is

the date of surgery. In the situation where the event date is partial or missing, study day, and any corresponding durations are to appear partial or missing in listings. If a missing event date, such as a discharge date for a hospital readmission, is necessary to calculate patient-time at risk, the missing event date will be imputed using the median length observed for similar events.

Continuous variables will be summarized using the following descriptive statistics: number of non-missing values, means, standard deviations, medians, interquartile range, maximum, and minimum. Categorical variables will be summarized using number of non-missing values, counts and percentages.

Rates of events will be calculated as the ratio of the total number of events recorded divided by the total patient-time. Total patient-time will be calculated by summing the time (in study time units, e.g., days, months or years) that patients were at risk for a specific event from the reference time point until either study exit or the end of the time period of interest. Rates and 95% confidence intervals will be reported.

Time-to-event variables will be summarized using the Kaplan-Meier method or, in the presence of competing risk, the Gray method (Gray, 1988).

For any variable measured at multiple points in time, change from baseline will be calculated as the difference between the value of the variable at a specific point in time (e.g. 1 year) minus the baseline value. Relative change from baseline will be calculated as the value of a parameter at a specific point in time minus the baseline value of the parameter divided by the baseline value of the parameter. Percent change will be calculated as the relative change multiplied by 100.

All hypothesis testing will be conducted at the 0.05 two-sided significance level unless otherwise specified. P-values will be rounded to three decimal places. P-values less than 0.001 will be reported as <0.001 in tables. P-values greater than 0.999 will be reported as >0.999.

Should any of the statistical methods proposed prove unsuitable during data analysis, more appropriate methods will be used. These include data transformation (for example to a logarithmic scale) to satisfy model assumptions such as normally distributed residuals with constant variance, the application of non-parametric techniques or the use of a different link function or modeling technique.

Additional ad-hoc analyses may be conducted as deemed appropriate.

All analyses will be conducted using SAS V9.4 or higher.

6.2 Missing Data

6.2.1 Missing Baseline Data

Missing baseline values will not be imputed and summaries will be based on all available

data.

6.2.2 Missing Primary Outcome Data

The plan for handling missing primary outcome data is outlined in section *6.5.1.3* below.

6.2.3 Missing Secondary Outcomes Data

In general, missing outcome values for secondary endpoints will not be imputed and analyses will be based on all available data. Multiple imputation may be used for specific analyses (e.g., cost analysis).

6.3 Crossover

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 TV annuloplasty who do not receive it during the trial can be considered crossovers. In addition, patients who are randomized to no annuloplasty but receive it during the index procedure are considered to have crossed over. As the primary analysis is by intention to treat, crossovers will be analyzed as belonging to the group to which they were randomized. Given the short duration between randomization and surgery, crossovers are assumed to be rare (no more than 3%).

6.4 Patient Characteristics

6.4.1 Patient Disposition

Disposition will be summarized in the screened and ITT populations.

Disposition summaries of the screened population will include:

- The number of patients screened
- The number and percentage of screened patients eligible
- The number and percentage of screened patients ineligible and the reasons for ineligibility summarized as the number and percentage of ineligible patients who met each ineligibility criteria
- The number and percentage of eligible patients randomized

Disposition in the ITT population will be summarized by randomization group and will include:

- The number of patients randomized
- The number and percentage of patients who received their assigned procedure
- The number and percentage of patients withdrawn or lost to follow-up by the primary outcome visit at 24 months and the primary reason for withdrawals
- The number and percentage of patients withdrawn or lost to follow-up by the final study visit at 60 months and the primary reason for withdrawals

6.4.2 Protocol Deviations

Protocol deviations and violations are defined as deviations from the procedures outlined in the protocol. There is no "Per Protocol" population defined for this study. All statistical analyses and summaries will be conducted on an intent-to-treat basis.

6.4.3 Patient Characteristics

6.4.3.1 Demographic characteristics

Demographics including age, gender, race and ethnicity will be summarized by randomization assignment using the appropriate descriptive statistics.

6.4.3.2 Baseline characteristics

Baseline characteristics will be summarized by randomization assignment using the appropriate descriptive statistics. The specific baseline variables collected are detailed in the protocol and include medical history, physical exam findings, medications, laboratory assessments, echocardiographic measures, quality of life, and functional status.

6.4.3.3 Operative characteristics

Operative data including primary procedure type, duration of operation, duration of aortic cross clamp time, duration of cardiopulmonary bypass time, and concomitant procedures will be summarized by randomization assignment using the appropriate descriptive statistics.

6.5 Primary and Secondary Outcome Analyses

All analyses will be performed using the ITT population.

6.5.1 Analysis of the Primary Outcome and Determination of Sample Size

The primary outcome is treatment failure defined as the composite of (1) death from any cause, (2) reoperation for TR, (3) presence of severe TR at two years post randomization or, for patients enrolled with less than moderate TR and annular dilatation, progression by two grades (i.e., from none/trace TR to moderate TR) at two years. The null hypothesis is that there is no difference in the probability of treatment failures at two years post randomization between patients randomized to undergo TV repair during MVS compared to patients randomized to undergo MVS alone. The primary null hypothesis will be tested in an intent-to-treat analysis using a 0.05 level two-tailed normal approximation (Wald) test.

6.5.1.1 Determination of Sample Size

Based on previously published data we assume that at two years post randomization, 25% of patients treated with only MVS will experience the primary composite endpoint (Goldstone et al., 2014; Koelling, Aaronson, Cody, Bach, & Armstrong, 2002; Nath, Foster, & Heidenreich, 2004). We believe a meaningful effect worth detecting is at least a 50% relative reduction to 12%, for patients undergoing TV annuloplasty in addition to MVS. A total of 400 patients, randomized with equal probability to each arm, provides approximately 90% power to detect such a

difference. For simplicity, power is based on a 0.05 level two-tailed chi-square test. The sample size takes account of a potential single interim analysis to be performed in addition to the final analysis, and a minimal (less than 3%) rate of crossover.

6.5.1.2 Primary Analysis

A log binomial regression model will be used to estimate and test differences in treatment failure between randomization groups. Similar to the logistic regression model, the log-binomial model is a generalized linear model. The models differ only in the link function used for the "success" probability p; logit (log odds) for logistic regression and log (log p) for log-binomial. The different links parameterize the model differently, with parameters of the log-binomial model yielding log relative risks rather than the log odds ratios of the logistic model.

The basic form of the log binomial models is:

$$\log P[Y_i = 1|X_{1i}, X_{2i}] = \beta_0 + \beta_1 X_{1i} + \beta_2 X_{2i} \,,$$

where Y_i is a binary indicator of treatment failure for the i^{th} patient, X_{1i} is a binary indicator of randomization assignment for the i^{th} patient and X_{2i} is an indicator of moderate or less TR at baseline, a factor by which randomization will be stratified. While randomization will also be stratified by randomizing center, the analysis will not adjust for center due to their relatively large number compared to the proposed sample size. The exponentiated estimate of β_1 ($e^{\widehat{\beta}_1}$) in this model is the risk ratio for the composite endpoint for patients randomized to TV repair compared to patients randomized to no TV repair. The risk ratio and its associated 95% confidence interval will be used to quantify the relative risk of the composite endpoint. Differences between randomization groups in the risk of the composite endpoint will be determined by testing the null hypothesis H_0:$\beta_1 = 0$ versus a two-sided alternative (H_1:$\beta_1 \neq 0$) using a 0.05 level intention-to-treat normal approximation test (i.e., the Wald test).

6.5.1.3 Imputation of Missing Primary Endpoint Data

We expect relatively few patients to be missing the primary endpoint due to withdrawal or refusal. Patients with missing data will have their 24 month status imputed via multiple imputation assuming that the data are missing at random. The imputation model will be stratified by randomization assignment and include age, sex, randomization strata for moderate or less TR at baseline, degree of TR at 6 months, and degree of TR at 12 months. Since this model includes a mixture of variables types (i.e. continuous, ordinal, and binary), a fully conditional specification method will be used (Berglund, Heeringa, & SAS Institute., 2014).

The main feature of the imputation approach is the creation of a set of clinically reasonable imputations for treatment failure 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. Thirty datasets will be imputed.

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 (Rubin & Schenker, 1986).

6.5.1.4 Assessment of Balance of the Randomization

The success of the randomization procedure in balancing important covariates between randomization groups will be assessed. Continuous measures will be compared using t-tests, while chi-square tests will be used to compare categorical variables. As 400 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 a secondary analysis of the primary endpoint.

6.5.1.5 Examination of Subgroups

A subgroup analysis of the primary endpoint will be performed with subgroups defined by whether or not patients received a CABG procedure during the initial surgery. This analysis will be performed in the same manner as that described for the primary analysis.

6.5.1.6 Impact of COVID-19 Pandemic

Due to the COVID-19 pandemic, patients randomized after January 2018 may be unable to do the on-site, in-person two-year follow up visit. To mitigate the risk of missing primary endpoint data, a revision to the protocol was issued via a study wide memo to widen the two-year visit window from ±60 days to ±120 days. The number and percentage of two-year visits missed due to COVID-19 and the number and percentage done outside of the original ±60 day window due to COVID-19 will be reported.

The primary analysis will be conducted as outlined in section 6.5.1.2 using all available two-year visit echocardiogram results with missing data imputed as outlined in section 6.5.1.3. A sensitivity analysis excluding data collected outside of the original ±60 day window due to COVID-19 will be conducted to explore the impact of enlarging the window of capture.

6.5.2 Analyses of Secondary Clinical Endpoints

6.5.2.1 Clinical and Functional Outcomes

MACCE: The rate of major cerebrovascular or cardiac events (defined as the

composite event of death, stroke, and serious heart failure events) will be compared between randomization groups over 24 months post-randomization using a Cox proportional hazards regression model.

Reoperation for TR: The difference in the rate of requiring subsequent TV annuloplasty after the initial MVS will be compared between randomization groups over 24 months post-randomization. Reoperation for TR may not occur because death from any cause precedes the event; thus, it is possible that censoring patients at all-cause mortality will lead to biased estimates when analyzing time to first event. Therefore, competing risks analysis using the methods of Fine and Gray (Fine & Gray, 1999) will be used to estimate group differences.

NYHA: The distribution of NYHA at 30 days, 6, 12 and 24 months will be presented for each randomization arm and compared using chi-squared tests.

Diuretic Use: The distribution of diuretic use at 30 days, 6, 12 and 24 months will be presented for each randomization arm and compared using chi-squared tests.

Six Minute Walk: Differences between groups in the distances travelled during the 6MWT at 30 days, 6, 12 and 24 months will be compared using Wilcoxon Rank-Sum tests.

Gait Speed Tests: Differences between groups in gait speed at 12 and 24 months will be compared using Wilcoxon Rank-Sum tests.

6.5.2.2 Echocardiography

Degree of TR: The distribution of the degree of TR at hospital discharge, 12, and 24 months will be presented for each randomization arm and compared using chi-squared tests. Between group differences in TR progression defined as presence of severe TR at 24 months, or for patients enrolled with less than moderate TR, progression by two grades compared to baseline will be compared using a two-tailed 0.05 level chi-squared test.

Additional echo parameters: RV size, RV function (normal, mildly impaired, moderately impaired, severely impaired, peak tricuspid annular velocity, TAPSE, RVFAC), and pulmonary artery pressure at 12 and 24 months will be compared between groups. RV volume as assessed by 3D TTE at 12 and 24 months will be compared between groups. Continuous variables will be compared for between group differences using the Wilcoxon Rank Sum test, and the level of function by chi-square test.

6.5.2.3 Quality of life

QOL will be measured using the KCCQ, SF-12, and EQ-5D. We will employ two

approaches to the analysis of QOL. 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. Of course, this assumption may not hold, and moreover it is impossible to test robustly from the data at hand. An alternative approach, 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 (Wu & Bailey, 1989).

6.5.2.4 Survival

Perioperative Mortality: The distribution of vital status at 30 days post-surgery will be presented for each randomization arm and compared using chi-squared tests.

Mortality at 2 and 5 years post-randomization: Differences in the rate of mortality between randomization groups over the first 24 months and the planned 60 months of post-randomization follow-up will be assessed using Cox proportional hazards regression.

6.5.2.5 Serious Adverse Events

Differences in the rate of individual serious AEs, AV-Block requiring pacemaker implantation, and new-onset atrial fibrillation within 24 months post-randomization will be compared between randomization groups using Poisson regression. Ninety-five percent confidence intervals for the rate ratios for individual AEs for treatment with MVS and TV annuloplasty versus MVS alone will be computed.

6.5.2.6 Hospitalizations

Index hospitalization length of stay and days in Intensive Care: We will compare post-surgery hospital LOS and days spent in ICU between treatment groups, separately by region (North America and Germany). A Wilcoxon Rank-Sum test will be used to test for differences within each geographic subgroup.

Perioperative readmission by 30 days: The distribution of the incidence of all-cause readmission, cardiovascular readmission, heart failure readmission, and TR re-operation by 30 days post-surgery will be presented for each randomization arm and compared using chi-squared tests.

Hospital readmission by 2 years: Rates of all-cause hospitalizations and rates of

cardiovascular and heart failure specific hospitalizations, within two years of randomization will be compared using Poisson regression.

6.5.2.7 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. Cost data will only be collected in the North American sites. 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 QOL 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 sampling variation and variations in discount rates.

6.6 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 (200) reach the primary endpoint. The utility of performing this analysis will depend on the rate of

accrual of patients into the trial. 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 to 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 relative 52% reduction (from 25% to 12%) in the incidence of treatment failure for patients receiving TV annuloplasty in addition to MVS and patients randomized to MVS alone is less than 10%.

We do not propose any a priori stopping criteria based on AEs. The treatments in this trial are not experimental, and have well known AE profiles. Moreover, we believe that incident rates of AEs 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 MR. 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, based on all relevant information reported by the DCC and the Medical Monitors. We therefore recommend that the DSMB should be responsible for defining its deliberative processes, including event triggers that would call for an unscheduled review.

REFERENCES

Berglund, P., Heeringa, S., & SAS Institute. (2014). *Multiple imputation of missing data using SAS*. Cary, N.C.: SAS Institute.

Dreyfus, G. D., Martin, R. P., Chan, K. M. J., Dulguerov, F., & Alexandrescu, C. (2015). Functional Tricuspid Regurgitation A Need to Revise Our Understanding. *Journal of the American College of Cardiology, 65*(21), 2331-2336. doi:10.1016/j.jacc.2015.04.011

Fine, J., & Gray, R. (1999). A proportional hazards model for the sub distribution of a competing risk. *J Am Stat Assoc.*(94), 496–509.

Goldstone, A. B., Howard, J. L., Cohen, J. E., MacArthur, J. W., Jr., Atluri, P., Kirkpatrick, J. N., & Woo, Y. J. (2014). Natural history of coexistent tricuspid regurgitation in patients with degenerative mitral valve disease: implications for future guidelines. *J Thorac Cardiovasc Surg, 148*(6), 2802-2809. doi:10.1016/j.jtcvs.2014.08.001

Gray, R. J. (1988). A Class of K-Sample Tests for Comparing the Cumulative Incidence of a Competing Risk. *Annals of Statistics, 16*(3), 1141-1154. Retrieved from <Go to ISI>://WOS:A1988Q161700019

Groves, P. H., Lewis, N. P., Ikram, S., Maire, R., & Hall, R. J. (1991). Reduced exercise capacity in patients with tricuspid regurgitation after successful mitral valve replacement for rheumatic mitral valve disease. *Br Heart J, 66*(4), 295-301. doi:10.1136/hrt.66.4.295

Koelling, T. M., Aaronson, K. D., Cody, R. J., Bach, D. S., & Armstrong, W. F. (2002). Prognostic significance of mitral regurgitation and tricuspid regurgitation in patients with left ventricular systolic dysfunction. *Am Heart J, 144*(3), 524-529. doi:10.1067/mhj.2002.123575

Morrow, A. G., Oldham, H. N., Elkins, R. S., & Braunwald, E. (1967). Prosthetic replacement of the mitral valve. Preoperative and postoperative clinical and hemodynamic assessments in 100 patients. *Circulation, 35*(5), 962-979. doi:10.1161/01.cir.35.5.962

Nath, J., Foster, E., & Heidenreich, P. A. (2004). Impact of tricuspid regurgitation on long-term survival. *J Am Coll Cardiol, 43*(3), 405-409. doi:10.1016/j.jacc.2003.09.036

Nishimura, R. A., Otto, C. M., Bonow, R. O., Carabello, B. A., Erwin, J. P., 3rd, Guyton, R. A., . . . Members, A. A. T. F. (2014). 2014 AHA/ACC Guideline for the Management of Patients With Valvular Heart Disease: executive summary: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *Circulation, 129*(23), 2440-2492. doi:10.1161/CIR.0000000000000029

Rubin, D. B., & Schenker, N. (1986). Multiple Imputation for Interval Estimation from Simple Random Samples with Ignorable Nonresponse. *Journal of the American Statistical Association, 81*(394), 366-374. Retrieved from <Go to ISI>://WOS:A1986C648000012

Ruel, M., Rubens, F. D., Masters, R. G., Pipe, A. L., Bedard, P., & Mesana, T. G. (2004). Late incidence and predictors of persistent or recurrent heart failure in patients with mitral prosthetic valves. *J Thorac Cardiovasc Surg, 128*(2), 278-283. doi:10.1016/j.jtcvs.2003.11.048

Taramasso, M., Vanermen, H., Maisano, F., Guidotti, A., La Canna, G., & Alfieri, O. (2012). The growing clinical importance of secondary tricuspid regurgitation. *J Am Coll Cardiol, 59*(8), 703-710. doi:10.1016/j.jacc.2011.09.069

Wu, M. C., & Bailey, K. R. (1989). Estimation and Comparison of Changes in the Presence of Informative Right Censoring - Conditional Linear-Model. *Biometrics, 45*(3), 939-955. doi:Doi 10.2307/2531694

Yilmaz, O., Suri, R. M., Dearani, J. A., Sundt, T. M., Daly, R. C., Burkhart, H. M., . . . Schaff, H. V. (2011). Functional tricuspid regurgitation at the time of mitral valve repair for degenerative leaflet prolapse: The case for a selective approach. *Journal of Thoracic and Cardiovascular Surgery, 142*(3), 608-613. doi:10.1016/j.jtcvs.2010.10.042