The NIH-Sponsored Cardiothoracic Surgical Trials Network: An Update

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Welcome to The Cardiothoracic Surgical Trials Network

Goal

The goal of the CTSN is to foster a culture of rigorous scientific comparisons and to promote the evaluation of newer surgical techniques, devices, and innovative pharmaceutical and bioengineered products directed at improving cardiovascular disease outcomes in adult populations.

With support from the National Heart, Lung, and Blood Institute (NHLBI), the National Institute of Neurological Disorders and Stroke (NINDS) at the National Institutes of Health (NIH), and the Canadian Institutes of Health Research (CIHR), the CTSN provides the infrastructure to develop, coordinate, and conduct multiple collaborative proof-of-concept studies and interventional protocols to improve cardiovascular disease outcomes. Our network enables research teams led by cardiac surgeons to evaluate newer therapies and techniques as they move from laboratory science to broad clinical use.

News

Surgeon/Investigator Recruitment Opportunity
The Clinical Research Skills Development Core is recruiting. Become certified in Clinical Research while meeting your clinical requirements! Download the brochure for more information.

http://www.ctsurgerynet.org/
NHLBI Approaches for Support of Clinical Research


- **Institute-Initiated** – i.e. SCCOR (Specialized Centers of Clinically Oriented Research). Typically, Bench to Bedside focus, in response to an Institute RFA

NHLBI Clinical Research Networks

- 1st Institute Network Begun in 1993
- In Lung Division:
NHLBI Cardiac Clinical Networks

- Pediatric Heart Network, in 2nd 5-year cycle
- Clinical Research Consortium to Improve Resuscitation (ROC)
- Heart Failure Clinical Research Network (new 2006)
- Cell Based Therapy Clinical Research Network (new 2006)
- “Network for Cardiothoracic Surgical Investigations in Cardiovascular Medicine” CTSN (Aug 2007)
NHLBI’s Goals for Clinical Networks

- Address Clinical Topics of Significant Public Health Concern
- Address Clinical Questions that Require Multiple Centers to Secure Sufficient Patients
- Address Multiple Therapeutic Studies and Trials Simultaneously
- Conduct Studies Quickly and Efficiently with Well-trained Clinical Teams that are Prepared to Work Collaboratively with the Other Teams and Closely with NHLBI
Clinical Research Network Structure

- **Steering Committee (SC):** Main governing body, with an Institute-appointed Chair and NHLBI Project Officer, and that includes the Principal Investigators of the Clinical Centers and the Data Coordinating Center PI.

- **CTSN SC Committees include:** Protocol Development Committees, Publication Committee, Satellite Selection Committee, Core Lab Committees including Echo Core Lab and Biorepository Subcommittees, etc.
Clinical Centers and PIs in CTSN

- Cleveland Clinical Foundation (Eugene H. Blackstone)
- Columbia University (Michael Argenziano)
- Duke University (Peter K. Smith)
- Emory University (John D. Puskas)
- Montefiore Medical Center–Albert Einstein College of Medicine (Robert E. Michler)
- Montreal Heart Institute (Louis P. Perrault)
- University of Pennsylvania (Michael A. Acker)
- University of Virginia (Irving L. Kron)
Active Ancillary & Affiliate Sites in CTSN and PIs

- East Carolina Heart Institute (T. Bruce Ferguson)
- NIH Heart Center at Suburban Hospital (Keith A. Horvath)
- Hôpital du Sacré-Coeur de Montréal (Pierre Pagé)
- Institut Universitaire de Cardiologie de Québec (Hôpital Laval) (Pierre Voisine)
Clinical Research Network Structure

- **Data Coordinating Center (DCC)** Selected through peer review. Organizes and administers central research activities, including data management, recruitment and AE monitoring, statistical analysis, and specific administrative functions, i.e. communication among CCs, budgets, reports. Typically administers “per patient” payments to CCs, as well as expenses of core labs, DSMB and PRC meetings, and site visits to each CC.
Other key members of CTSN

- **Data Coordinating Center**: InCHOIR (International Center for Health Outcomes and Innovation Research), Mount Sinai School of Medicine
  - Annetine Gelijns, (DCC Principal Investigator); Deborah Ascheim; Michael K. Parides; Alan Moskowitz; Ellen Moquete; Alejandra Guerchicoff

- **Study Co-Chair**: Patrick T. O'Gara, Cardiovascular Medicine, Brigham and Women's Hospital

- **Study Sponsors**:
  - **National Heart Lung and Blood Institute**, Marissa Miller, (Program Director); Karen Ulisney (Deputy Program Director); Wendy Taddei-Peters
  - Canadian Institute of Health Research, Ilana Gombos
  - National Institute of Neurological Disorders & Stroke, Claudia Moy
Time-line of Cardiothoracic Surgery Network (CTSN)

- 2006 – Announcement, Submission and Review of Applications for CTSN
- July 2007 – Notification of Awards
- Sept 2007 -- Inaugural meeting of CTSN investigators
- Oct 2007-2008 – Development and refinement of initial study protocols
- May 2008-Oct 2008 – Protocol reviews and approval by Network PRC and DSMB
- Nov 2008-Mar 2009 – Protocol approvals by site IRBs
- Dec 2008-Apr 2009 – Initiation of the 2 mitral protocols
Time-line of Cardiothoracic Surgery Network (CTSN)

- Feb - Jun 2009 -- Initial enrollment period for mitral trials
- Spring 2009 -- Submission of Challenge Grant application for Hybrid Revascularization Study
- Jul-Dec 2009 – Site visits with focus on mitral trials, identification of Ancillary Sites for mitral trials
- Feb 2010 – Initiation of Atrial Fibrillation Ablation Trial
- Mar 2010 – Initiation of Infection Registry
- Apr 2010 – Solicitation of Satellite Site participation in both Mitral Regurgitation trials
Network for CT Surgical Investigations

Protocol

SURGICAL INTERVENTIONS FOR MODERATE ISCHEMIC MITRAL REGURGITATION

Sponsored By NHLBI, NINDS & CIHR
Surgical Interventions for Moderate Ischemic Mitral Regurgitation

OBJECTIVES:

The overall objective of this study is to evaluate the safety and efficacy of mitral valve repair for moderate ischemic mitral regurgitation. Specifically, this study compares mitral valve repair combined with coronary artery bypass grafting to coronary artery bypass grafting alone in this patient population.

- The primary aim of this trial is to evaluate the impact of these two surgical approaches on left ventricular remodeling.
- Secondary aims of this trial include assessment of the impact of these two surgical interventions on cardiac performance, mortality, adverse events, quality of life, functional status, presence and severity of MR, and health resource use.

Enrollment as of April 29, 2010 = 74/300
Patients with Moderate Ischemic MR (Per site echocardiographer)

Determination of Eligibility and Collection of Baseline Data

Random Assignment of Treatment

Valve Repair + CABG

CABG Alone

Outcomes Measured at 6, 12 and 24 months

Primary Outcome
LVESVI at 12 mos

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

Data Analysis
Echo Inclusion criteria for MMR Trial

- Moderate mitral regurgitation, in the judgment of the clinical site echocardiographer, assessed by transthoracic echocardiogram. Assessment of mitral regurgitation will be performed using an integrative method.* Quantitative guidelines are: ERO (effective regurgitant orifice area) between $0.2 \text{ cm}^2$ to $0.39 \text{ cm}^2$. If ERO $< 0.2$, then the degree of mitral regurgitation will be guided by other color Doppler quantitative methods (including jet area/left atrial area ratio, vena contracta, used in an integrated fashion).

Exclusion criteria for Mitral Trials

- Any evidence of structural (chordal or leaflet) mitral valve disease
- Planned concomitant procedure with exception of PFO/ASD closure, Maze or tricuspid valve procedure
- Cardiogenic shock at time of randomization
- STEMI requiring intervention within 7 days prior to randomization
- Severe irreversible pulmonary hypertension
- Chronic renal insufficiency, defined as Creatinine >2.5 d/L
- Cirrhosis or hepatic failure
- Any concurrent disease with life expectancy < 2 years
Network for CT Surgical Investigations

Protocol

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

Sponsored By NHLBI, NINDS & CIHR
Evaluation of Outcomes Following Mitral Valve Repair/Replacement in Severe Chronic Ischemic Mitral Regurgitation

OBJECTIVES:

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

- The primary aim of this trial is to evaluate the impact of these two surgical approaches on left ventricular remodeling.
- Secondary aims of this trial include assessment of the impact of these two surgical interventions on cardiac performance, mortality, adverse events, quality of life, functional status, severity of MR, and health resource use.

Enrollment as of April 29, 2010 = 84/250
Echo Inclusion criteria for SMR Trial

- Severe mitral regurgitation (often with tethering as a major mechanism), in the judgment of the clinical site echocardiographer, assessed by transthoracic echocardiogram. Assessment of mitral regurgitation will be performed using an integrative method. *Quantitative guideline would be ERO > 0.4 cm². If ERO is < 0.4, assessment of the degree of mitral regurgitation will be guided by other color Doppler quantitative methods (including jet area/left atrial area ratio, vena contracta, used in an integrated fashion).*

Patients with Severe Ischemic MR (Per site echocardiographer)

Determination of Eligibility and Collection of Baseline Data

Random Assignment of Treatment

Mitral Ring Annuloplasty ± CABG (subvalvular procedure for severe tethering)  Mitral Valve Replacement ± CABG (complete subvalvular preservation)

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

Primary Outcome
LVESVI at 12 mos

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

Data Analysis
Surgical options in SMR Trial

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

- Mitral valve replacement will include complete preservation of the subvalvar apparatus. The technique of preservation, choice of prosthetic valve, and technique of suture placement will be guided by the surgeon’s preference.
Summary Update of CTSN Ischemic Mitral Regurgitation Trials

- 40% of initial funding period for CTSN has transpired
- 33% of the patient enrollment target has been met for the Severe Mitral Regurgitation Trial
- 25% of the patient enrollment target has been met for the Moderate Mitral Regurgitation Trial
- Additional investigator sites are being recruited for participation in both Mitral Trials
- Strategies for enhancing enrollment at primary CTSN Clinical Sites have been explored and activated
Recently Activated Affiliate Sites to increase patient enrollment in mitral trials

- Centre Hospitalier de l'Université de Montréal (Nicolas Noiseux)
- Valley Hospital, Ridgewood, NJ (Alexander Zapolanski)
- Inova Heart & Vascular Institute, Fairfax, Va (Alan M. Speir)
- Kennestone Hospital, Marietta, Ga (William A. Cooper)
- Ohio State University Medical Center (Sai Sudhakar)

Solicitation of 5 or more Satellite Sites is currently underway for further patient enrollment opportunities
Network for CT Surgical Investigations
Protocol

SURGICAL ABLATION VERSUS
NO SURGICAL ABLATION FOR PATIENTS WITH
PERSISTENT OR LONGSTANDING PERSISTENT ATRIAL
FIBRILLATION UNDERGOING MITRAL VALVE
SURGERY
Atrial Fibrillation Trial Design

- 260 patients with chronic persistent A Fib and mitral valve disease requiring surgery will be randomized 1:1 to surgical ablation plus left atrial appendage ligation versus left atrial appendage ligation alone
- Ablation patients will be further randomized to PVI alone versus PVI and biatrial ablation lesion sets
- Primary end point: freedom from A Fib at 6 and 12 mos
- Secondary endpoints include clinical outcomes, functional status and QOL at 6, 12 and 24 months
- 11 patients have been enrolled within the first 8 weeks
Network for CT Surgical Investigations

Protocol

MANAGEMENT PRACTICES AND THE RISK OF INFECTIONS FOLLOWING CARDIAC SURGERY

Rev 1.2

October 2009
Risk of Infection and Management Practices in Cardiac Surgery: An observational study

- All cardiac surgery patients at the 10 CTSN sites will be monitored for infections occurring within 60 days of surgery.
- Objectives are identification of modifiable management practices & pt. characteristics predictive of post op infection.
- Sample size is based on need to detect 200 or more infections. Observations on 3000 to 4000 patients are anticipated.
- 2311 patients have been entered into this registry as of April 28, 2010.
Another Network Activity: The Skills Development Core

Clinical Research Skills Development Core (CRSDC)

Now Recruiting
Become certified in Clinical Research while meeting your clinical requirements.

The National Heart, Lung, and Blood Institute (NHLBI)—funded Cardiothoracic Surgical Trials Network (CSTN) is supporting two Clinical Research Skill Development Core (CRSDC) sites, dedicated to developing academic surgeon-investigators.
2 CTSN Clinical Research Opportunities

Cleveland Clinic

The Cleveland Clinic Clinical Research Skills Development Core
Dr. Eugene Blackstone
Phone: 216-444-6712
Email: blackse@ccf.org
Dr. Edward Nowicki
Phone: 216-444-6712
Email: nowicke@ccf.org

Duke University

The joint Duke University and East Carolina Heart Institute Clinical Research Skills Development Core
Dr. Peter Smith
Phone: 919-684-2890
Email: smith058@mc.duke.edu
Dr. Bruce Ferguson
Phone: 252-744-5232
Email: fergusont@ecu.edu

- Ideal candidate is Resident, Fellow or Jr Faculty in Cardiothoracic, Vascular or General Surgery
- Curriculum focuses on Research Methodology, Biostatistics, Regulatory Issues, Medical Ethics, Multidisciplinary Collaboration, Communication Skills
HYBRID REVASCULARIZATION OBSERVATIONAL STUDY

Study Protocol

Sponsored By NHLBI

Developed for

Randomized Trial of Hybrid Revascularization versus Percutaneous Coronary Intervention – Planning Grant Study Group

Data Coordinating Center
InCHOIR
Mount Sinai School of Medicine
New York
The Cardiothoracic Surgery Network: Randomized clinical trials in the operating room

Timothy J. Gardner, MD, a and Patrick T. O’Gara, MD b
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