The MITRAL Trial: Mitral Implantation of TRAnscatheter vaLves (Data Coordinating Center)

NCT02370511

September 20, 2017

IRB Minimal Risk Protocol Template

Note: If this study establishes a human specimen repository (biobank) for research purposes, do not use this template. Use the Mayo Clinic Human Specimen Repository Protocol Template found on the IRB home page under Forms and Procedures at http://intranet.mayo.edu/charlie/irb/

First-time Use: Use this template to describe your study for a new IRB submission.

1. Complete the questions that apply to your study.
2. Save an electronic copy of this protocol for future revisions.
3. When completing your IRBe application, you will be asked to upload this document to the protocol section.

Modification: To modify this document after your study has been approved:

1. Open your study in IRBe. Click on the study 'Documents' tab and select the most recent version of the protocol. Save it to your files.
2. Open the saved document and activate "Track Changes".
3. Revise the protocol template to reflect the modification points, save the template to your files
4. Create an IRBe Modification for the study and upload the revised protocol template.

General Study Information

Principal Investigator: Mayra Guerrero

Study Title: The MITRAL Trial: Mitral Implantation of TRAnscatheter vaLves (Data Coordinating Center)

Protocol version number and date: Version 3, 12-19-218

Research Question and Aims

Purpose

The purpose of this trial is to establish the safety and feasibility of the Edwards SAPIEN XT TM and SAPIEN 3 devices and delivery systems in patients with severe symptomatic calcific mitral valve disease with severe mitral annular calcification and patients with failing mitral surgical rings of bioprostheses who are not candidates for mitral valve surgery.

Mayo Clinic as Data Coordinating Center for the MITRAL trial

This clinical trial was initiated at Northshore University by Dr. Mayra Guerrero before being recruited to Mayo Clinic in June 2018. When the trial was initiated, Mayo Clinic was a subsite and the study was approved under IRB 14-009069 with Dr. Mackram Eleid as the principal investigator. The trial commenced enrollment on March 2015 and enrollment was completed December 2017. All enrolled patients have been treated and the trial is currently at the one-year follow up stage for all remaining patients. This clinical trial is being transferred to

the Mayo clinic and we will be the data coordinating center for this trial going forward. Please see coordinating center documents for sites list and data management plan.

Study Design and Methods

Design

As of Dr. Guerrero's recruitment to Mayo on June 2018, all remaining patients in this trial are at the at the 1-year follow-up stage or beyond. These visits will be conducted at the respective sites in accordance to the procedural protocol and under approved IRBs at the different sites. The data gathered at the follow up visits will be entered into the existing electronic data capture database. Mayo Clinic staff will gather the data collected at all sites for analysis, and work with the sites to address any issues or protocol deviations.

Plan for collection and management of data from all centers:

The electronic case report forms (e-CRFs) are designed to accommodate the study design and requirements. Modification of e-CRFs will only be made if deemed necessary by the sponsor investigator. Primary data collection based on source documented hospital chart reviews will be performed by study coordinators at each clinical site. Electronic CRFs will be completed online. All applicable eCRFs will be automatically available to the study coordinator at the sites as new patients are enrolled in the study. All clinical sites will be monitored periodically by the Mayo Clinic staff for protocol adherence, accuracy of e-CRFs, and compliance to applicable regulations. Evident patterns of non-compliance with respect to these standards will be cause for the site to be put on probation. If corrective actions are not subsequently undertaken, the clinical site will be asked to withdraw from the trial.

The online database will reside on a central server accessible through the Internet by Mayo Clinic staff. Conventional data verification sub-routines will be extensively programmed to test entry and logical errors, while all individual (study patient based) case report forms will be linked for cross-reference. Periodic analysis of each data field (across cases) will be performed in order to examine the expected distributions of data, and to identify outliers for possible data errors. All e-CRFs will be subjected to initial inspection for omitted data, data inconsistencies, and deviations. The resolution of data inconsistencies will be done using electronic tracking and will be resolved by the clinical site.

Process for reporting and evaluating protocol events and deviations from all centers:

The patients will be followed closely by their cardiologist per standard of care in addition to scheduled visits per study protocol. All adverse events (AEs) will be reported by the Investigators and reviewed by the Sponsor in compliance with applicable regulations. For the purpose of this study, an adverse event is any undesirable medical occurrence in a patient. This definition does not depend on a causal relationship with the device or the protocol requirements. Expected clinical and non-significant clinical adverse events will not be reported. Adverse events may be volunteered by patients, elicited by the Investigator or designee, or collected via observation by the Investigator. All AEs will be assessed by the Investigator who will determine whether or not the event is related to the device and/or procedure, and whether or not the event meets serious criteria. If it is

determined that an AE has occurred, the investigator should obtain all the information required to complete the AE Form of the CRF. Source documents will be acquired by Mayo Clinic staff and provided to the Clinical Event Adjudication Committee (CEC) in a timely manner to ensure timely assessment and adjudication of the event as appropriate. In addition, patients will be instructed to contact the investigator, and/or study coordinator if any significant adverse events occur between study visits.

The investigators at each site will not deviate from the protocol without the prior written approval of the sponsor investigator except in medical emergencies or in unforeseen, isolated instances where minor changes are made that will not increase the patient's risk or affect the validity of the trial. In medical emergencies, prior approval for protocol deviations will not be required, but the sponsor investigator must be notified within 2 days of the incident. Periodic monitoring of protocol compliance will be performed for each site. The Sponsor has the right to suspend enrollment at sites deemed to have excessive protocol compliance issues.

Resources: *Describe the available resources to conduct the research (personnel, time, facilities, mentor commitment, etc.)*:

☒ (1a) This is a multisite study involving Mayo Clinic and non Mayo Clinic sites. *When checked, describe in detail the research procedures or activities that will be conducted by Mayo Clinic study staff.*

☐ (1b) Mayo Clinic study staff will be engaged in research activity at a non Mayo Clinic site. *When checked, provide a detailed description of the activity that will be conducted by Mayo Clinic study staff.*

Subject Information

Target accrual is the proposed total number of subjects to be included in this study at Mayo Clinic. A "Subject" may include medical records, images, or specimens generated at Mayo Clinic and/or received from external sources.

Target accrual: 91 patients (31 patients per arm – Native Mitral Valve Arm, Valve-in-Ring arm, Valve-in-Valve arm)

Subject population:

Patients are 22 years of age or older with severe calcific native mitral valve stenosis, a failing surgical ring in the mitral position, or a failing surgical bioprosthesis in the mitral position who are not candidates for mitral valve surgery.

Inclusion Criteria

Patients that are currently enrolled in the MITRAL trial.

Exclusion Criteria

Patient not enrolled in the MITRAL trial.

Research Activity

Check all that apply and complete the appropriate sections as instructed.

1. ☐ **Drug & Device**: Drugs for which an investigational new drug application is not required. Device for which (i) an investigational device exemption application is not required; or the medical device is cleared/approved for marketing and being used in accordance with its cleared/approved labeling. (Specify in the Methods section)

2. ☐ **Blood**: Collection of blood samples by finger stick, heel stick, ear stick, or venipuncture.

3. ☐ **Biological specimens other than blood**: Prospective collection of human biological specimens by noninvasive means that may include: urine, sweat, saliva, buccal scraping, oral/anal/vaginal swab, sputum, hair and nail clippings, etc.

4. ☐ **Tests & Procedures:** Collection of data through noninvasive tests and procedures routinely employed in clinical practice that may include: MRI, surface EEG, echo, ultrasound, moderate exercise, muscular strength & flexibility testing, biometrics, cognition testing, eye exam, etc. (Specify in the Methods section)

5. ☒ **Data** (medical record, images, or specimens): Research involving use of existing and/or prospectively collected data.

6. ☐ **Digital Record**: Collection of electronic data from voice, video, digital, or image recording. (Specify in the Methods section)

7. ☐ **Survey, Interview, Focus Group:** Research on individual or group characteristics or behavior, survey, interview, oral history, focus group, program evaluation, etc. (Specify in the Methods section)

☐ NIH has issued a *Certificate of Confidentiality* (COC). *When checked, provide the institution and investigator named on the COC and explain why one was requested*. _____

Biospecimens – Categories 2 and 3

(2) Collection of blood samples. When multiple groups are involved copy and paste the appropriate section below for example repeat section b when drawing blood from children and adults with cancer.

a. **From healthy, non-pregnant, adult subjects who weigh at least 110 pounds**. For a minimal risk application, the amount of blood drawn from these subjects may not exceed 550ml in an 8 week period and collection may not occur more frequently than 2 times per week.
   Volume per blood draw: _____ml
   Frequency of blood draw (e.g. single draw, time(s) per week, per year, etc.) _____

b. **From other adults and children considering age, weight, and health of subject.** For a minimal risk application, the amount of blood drawn from these subjects may not exceed the lesser of 50 ml or 3 ml per kg in an 8 week period, and collection may not occur more frequently than 2 times per week.
   Volume per blood draw: _____ml
   Frequency of blood draw (e.g. single draw, time(s) per week, per year, etc.) _____

(3) Prospective collection of biological specimens other than blood: _____

Review of medical records, images, specimens – Category 5

For review of existing data: provide a date range or an end date for when the data was generated. The end date can be the date this application was submitted to the IRB. Example: *01/01/1999 to 12/31/2015* or all records through *mm/dd/yyyy*.

Date Range:

Check all that apply (data includes medical records, images, specimens).

☐ (5a) Only data that exists before the IRB submission date will be collected.

☐ (5b) The study involves data that exist at the time of IRB submission **and** data that will be generated after IRB submission. Include this activity in the Methods section.
Examples
- The study plans to conduct a retrospective chart review and ask subjects to complete a questionnaire.
- The study plans to include subjects previously diagnosed with a specific disease and add newly diagnosed subjects in the future.

☐ (5c) The study will use data that have been collected under another IRB protocol. Include in the Methods section and enter the IRB number from which the research material will be obtained. *When appropriate, note when subjects have provided consent for future use of their data and/or specimens as described in this protocol*.

Enter one IRB number per line, add more lines as needed

☐ Data ☐ Specimens ☐ Data & Specimens _____

☐ Data ☐ Specimens ☐ Data & Specimens _____

☐ Data ☐ Specimens ☐ Data & Specimens _____

☒ (5d) This study will obtain data generated from other sources. Examples may include receiving data from participating sites or an external collaborator, accessing an external database or registry, etc. Explain the source and how the data will be used in the Methods section.

☐ (6) Video audio recording: *Describe the plan to maintain subject privacy and data confidentiality, transcription, store or destroy, etc.*

HIPAA Identifiers and Protected Health Information (PHI)

Protected health information is medical data that can be linked to the subject directly or through a combination of indirect identifiers.

Recording identifiers (including a code) during the conduct of the study allows you to return to the medical record or data source to delete duplicate subjects, check a missing or questionable entry, add new data points, etc. De-identified data is medical information that has been stripped of all HIPAA identifiers so that it cannot be linked back to the subject. De-identified data is **rarely** used in the conduct of a research study involving a chart review.

Review the list of subject identifiers below and, if applicable, check the box next to each HIPAA identifier being recorded at the time of data collection or abstraction. Identifiers apply to any subject enrolled in the study including Mayo Clinic staff, patients and their relatives and household members.

Internal refers to the subject's identifier that will be recorded at Mayo Clinic by the study staff.
External refers to the subject's identifier that will be shared outside of Mayo Clinic.

Check all that apply:	INTERNAL	EXTERNAL
Name		
Mayo Clinic medical record or patient registration number, lab accession, specimen or radiologic image number		
Subject ID, subject code or any other person-specific unique identifying number, characteristic or code that can link the subject to their medical data	Yes	
Dates: All elements of dates [month, day, and year] directly related to an individual, their birth date, date of death, date of diagnosis, etc. **Note:** Recording a year only is not a unique identifier.	Yes	
Social Security number		
Medical device identifiers and serial numbers	Yes	
Biometric identifiers, including finger and voice prints, full face photographic		

images and any comparable images		
Web Universal Resource Locators (URLs), Internet Protocol (IP) address numbers, email address		
Street address, city, county, precinct, zip code, and their equivalent geocodes		
Phone or fax numbers		
Account, member, certificate or professional license numbers, health beneficiary numbers		
Vehicle identifiers and serial numbers, including license plate numbers		
Check 'None' when none of the identifiers listed above will be recorded, maintained, or shared during the conduct of this study. (exempt category 4)	☐ None	☐ None

Data Analysis

The analysis of clinical outcomes will be based on the principle of intention to treat. There will be three intervention groups in the study: 1) Native Mitral Valve and 2) Valve-in-Ring and 3) Valve-in-Valve. The three groups will be evaluated separately for the primary and secondary outcomes.

Sample Size

Using a sample size of 30 total patients and a 2-sided alpha level of 0.05, the McNemar matched pairs test would have a power of 0.80 to detect an underlying pre to post change in proportions of 0.30 (i.e., proportions of 0.35 at pre versus 0.65 at post). Using the same sample size and alpha level, the paired t-test would have a power of 0.80 to detect an underlying effect size of 0.53 (i.e., a mean change which is 0.53 times the size of the corresponding standard deviation) for comparing pre and post change in continuous variables. A total of 30 patients in each group will be enrolled in this preliminary feasibility study.

Analysis and reporting of results:

The technical success, hemodynamics results and clinical outcomes will be analyzed and reported. The primary objective is to evaluate the short-term (<30 days) and mid term (12 months) safety and feasibility of transcatheter mitral valve implantation to treat severe calcific mitral valve disease or failing surgical mitral rings or bioprostheses in patients who are not candidates for standard surgical mitral valve replacement. The primary safety and effectiveness endpoints will be analyzed on an intention- to-treat basis. Therefore, all patients will be included in the analysis regardless of subsequent events.