STUDY TITLE: Surgical Implantation of TRAnscatheter vaLve in native mitral annular calcification (SITRAL) Study

Study Sponsor: Baylor Scott & White Research Institute
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Proposed Study Clinical SITES:

Cedars-Sinai Medical Center
Los Angeles, CA

Emory University Hospital
Atlanta, Georgia

St. Thomas West Hospital
Nashville, Tennessee

St. Vincent Hospital
Indianapolis, Indiana

The Heart Hospital Baylor Plano
Plano, TX

Hospital of the University of Pennsylvania
Philadelphia, Pennsylvania

University of Virginia Medical Center
Charlottesville, Virginia

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SIGNATURE PAGE

Surgical Implantation of TRAnscatheter vaLve in native mitral annular calcification (SITRAL) Study

Investigator's Signature

I have read this protocol and agree to participate in the clinical investigation sponsored by Baylor Scott & White Research Institute. I agree to conduct this investigation according to the requirements of the study protocol and in accordance with Good Clinical Practice, applicable State and U.S. Federal regulations and conditions imposed by the reviewing Investigational Review Board. I agree to supervise all sub-investigators at my site as well as the use of all of the investigational devices at my institution and to ensure appropriate informed consent is obtained from all subjects prior to inclusion in this study.

_____ _____

Investigator's Signature Date

_____

Printed Name

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1.0 BACKGROUND & STUDY RATIONALE

Extensive mitral annular calcification (MAC) poses a significant risk in elderly subjects undergoing mitral valve surgery. MAC has been associated with higher risk of cardiovascular disease, cardiovascular death, and all-cause death.[1] Surgical replacement of such valves presents a technically challenging procedure with the potential for rupture at the atrial ventricular junction and of the left ventricular wall.[2] Thus, new surgical and minimally invasive techniques for mitral replacement could improve treatment of high-risk subjects with MAC.

Recently, isolated reports of deployment of the Edwards SAPIEN™ XT (Edwards Lifesciences, Irvine, CA, USA) valve in native mitral valves with extensive MAC have shown early anecdotal feasibility in a limited number of cases. There are several reports using transapical, transeptal, or transatrial approaches with varying degrees of success.[3,4,5,6] The multi-center IDE Mitral Implantation of TRAnscatheter vaLves in native mitral stenosis (MITRAL) Study initiated by Northshore University Health System is currently studying this technique, primarily focusing on the transcatheter, transseptal approach. Early experience with this procedure demonstrates limited success with treatment of subjects with mitral stenosis and regurgitation associated with extensive MAC. However, technical challenges with this approach have included left ventricular outflow tract (LVOT) obstruction (11% of subjects), valve embolization (7%), and a 30-day mortality (34%) in the limited data available.[7] In order to possibly mitigate some of the challenges with this approach, we propose to study a limited access surgical approach with the Edwards SAPIEN 3 valve placed in the mitral valve position under direct vision to optimize procedural safety and success. From our own limited experience with the successful treatment of 3 subjects with this approach, we feel that an expanded study in a larger number of subjects including other investigators is warranted.

2.0 DESCRIPTION OF STUDY PROCEDURE

Surgical access is allowed via any accepted heart team approach. Any commercially approved delivery system for the SAPIEN 3 valve may be used.

Surgical access is via a mini-anterolateral thoracotomy with the patient under general anesthesia and on

cardiopulmonary bypass support. Cannulation for cardiopulmonary bypass is typically achieved through the common femoral arterial and venous circulation, though axillary arterial cannulation is a suitable substitute for subjects in which there is concern for arterial occlusive disease. There are several methods to prepare for cardiac entry. These include a cardioplegic or cold, fibrillatory arrest, depending on the individual patient circumstances. A left atriotomy is performed to access the mitral valve. The mitral valve is then evaluated to determine whether conventional replacement is a reasonable depending upon the severity of MAC. If not, the anterior leaflet is then resected, leaving approximately 0.5cm to 1cm of residual leaflet tissue adjacent to the annulus. Pledgetted mattress sutures are placed in both of the fibrous trigones and the mid-portion of the posterior leaflet. The valve is then sized with a 25ml valvuloplasty balloon. If there is a reasonable fit with no gap between the inflated balloon and the annulus, then a 26mm Edwards SAPIEN 3 is selected. If there is a gap, then a 29mm Edwards SAPIEN 3 is selected. If there are concerns about the native annulus being too large, a cuff of felt material can be placed to minimize paravalvular leak.

The valve implant is performed with thoracoscopic guidance (30 degree, 5mm-10mm endoscope). The commisures of the prosthetic valve are aligned with the fibrous trigones. To control the delivery, two separate operators are required. One slowly delivers the valve correcting for depth and orientation while the other inflates the balloon slowly within the native valve to maximal dilation for at least 10 seconds, and thoracoscopic confirmation of a fully deployed valve is obtained. The fibrous trigone sutures are then placed through the skirt on the prosthetic valve and tied. The valve is tested with cold saline to ensure appropriate leaflet mobility and assess for paravalvular leak. Following confirmation, a vent may be placed across the valve for de-airing, and the atrium is closed.

3.0 PURPOSE

The purpose of this study is to establish the safety and feasibility of the Edwards SAPIEN 3 valve in subjects with mitral annular calcification (MAC) associated with mitral stenosis (MS) and/or mitral regurgitation who are at high-risk for mitral valve surgery or deemed inoperable due to the extent of calcification.

4.0 STUDY DESIGN

This is a multi-center, prospective feasibility study. The study cohort will comprise all consecutive subjects undergoing mitral valve replacement with the Edwards SAPIEN 3 heart valve by a standardized minimally invasive surgical approach at investigational centers and will consist of up to 30 subjects. Subjects will undergo follow-up visits at 30 days, 6 months and 12 months post procedure.

5.1 STUDY POPULATION

The study cohort will consist of up to 30 subjects who are candidates for mitral valve replacement using the Edwards SAPIEN 3 heart valve as per the inclusion and exclusion criteria below:

5.2 Inclusion Criteria:

- Subject has severe native mitral annular calcification associated with mitral stenosis and/or regurgitation. Qualifying echo must be within 60 days of the date of the procedure.
- Subject has a clinical indication for mitral valve replacement, as demonstrated by reported New York Heart Association (NYHA) Functional Class II or greater.
- The subject is at least 22 years old.
- The Heart Team agrees that the subject is high-risk or inoperable for surgical mitral valve repair or replacement (MVR), based on a conclusion that the probability of death or serious, irreversible morbidity exceeds the probability of meaningful improvement. The following concomitant procedures, are allowed MAZE, TVP, and AF ablation.
- The study subject has been informed of the nature of the study, agrees to its provisions and has provided written informed consent as approved by the Institutional Review Board (IRB) of the respective clinical site.
- The study subject agrees to comply with all required post-procedure follow-up visits

5.3 Exclusion Criteria

- Evidence of an acute myocardial infarction (MI) ≤ 30 days before the intended treatment [defined as: Q wave MI, or non-Q wave MI with total CK elevation of CK-MB ≥ twice normal in the presence of MB elevation and/or troponin level elevation (WHO definition)].

- Untreated coronary artery disease in need of revascularization
- Any therapeutic invasive cardiac procedure resulting in a permanent implant that is performed within 30 days of the index procedure (unless part of planned strategy for treatment of concomitant coronary artery disease).
- Leukopenia (white blood cell count < 2000 cell/mL), acute anemia (hemoglobin < 8 g/dL), or thrombocytopenia (platelet count < 50,000 cell/mL).
- Hemodynamic or respiratory instability requiring vasoactive medications, mechanical ventilation at time of procedure.
- Need for emergency surgery for any reason.
- Severe left ventricular dysfunction with Left Ventricular Ejection Fraction (LVEF) < 30%.
- Severe right ventricular dysfunction
- Pregnancy, lactation, or planning to become pregnant
- Echocardiographic evidence of left ventricular mass, thrombus, or concerns of active infective endocarditis.
- Active upper GI bleeding within 3 months prior to procedure without treatment or 30 days prior to procedure with definitive treatment.
- A known contraindication or hypersensitivity to all anticoagulation regimens, or inability to be maintained on oral anticoagulant following the study procedure.
- An estimated Glomerular Filtration Rate (eGFR) <30 as calculated using the Modification of Diet in Renal Disease (MDRD) formula or End stage renal disease requiring dialysis
- Clinically (by neurologist) or neuroimaging confirmed stroke or transient ischemic attack (TIA) within 30 days of the procedure.
- Estimated life expectancy < 12 months

6.0 STUDY OBJECTIVES

6.1 **Primary Outcome Measures:**

a. Primary objective(s)

- <u>Primary safety endpoints:</u>

- Technical success at exit from cath lab/OR
- Device success at 30 days
- Procedural success at 30 days

Technical Success:

- Alive, with
- Successful access, delivery and retrieval of the device delivery system, and
- Deployment and correct positioning (including repositioning/recapture if needed) of the single intended device, and
- No need for additional unplanned or emergency surgery or re-intervention related to the device or access procedure

Device Success:

- Alive and stroke free, with
- Original intended device in place, and
- No additional surgical or interventional procedures related to access or the device since completion of the original procedure (i.e., exit from the cath lab/OR), and
- Intended performance of the device:
  - Structural performance: No migration, embolization, detachment, fracture, hemolysis, thrombosis (including reduced leaflet motion) or endocarditis, etc, and
  - Hemodynamic performance: Maintenance of relief of stenosis or insufficiency without producing the opposite (Stenosis = MVA < 1.5cm2 and MV gradient $\geq$ 5mmHg, Insufficiency = MR >1+), and
  - Absence of para-device complications (e.g., PVL > mild, need for a PPM, erosion, Annular rupture or AV Groove disruption, LVOT gradient increase > 10mmHg)

Procedural Success:

Device success, and

- No device or procedure related SAE's (Life threatening bleed; major vascular or cardiac structural complications requiring unplanned reintervention or surgery; stage 2 or 3 AKI (includes new dialysis); MI or need for PCI/CABG; severe HF or hypotension requiring IV inotrope, ultrafiltration or mechanical circulatory support; prolonged intubation (> 48 hours)
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6.2 Secondary objective(s)

- Device Success (at 6 months and 1 year)

- Subject success 1 year

Device Success:

- Alive and stroke free, with
- Original intended device in place, and
- No additional surgical or interventional procedures related to access or the device since completion of the original procedure (i.e., exit from the cath lab/OR), and
- Intended performance of the device:
  - Structural performance: No migration, embolization, detachment, fracture, hemolysis, thrombosis (including reduced leaflet motion) or endocarditis, etc, and
  - Hemodynamic performance: Maintenance of relief of stenosis or insufficiency without producing the opposite (Stenosis = MVA < 1.5cm2 and MV gradient ≥ 5mmHg, Insufficiency = MR >1+), and
  - Absence of para-device complications (e.g., PVL > mild, need for a PPM, erosion, Annular rupture or AV Groove disruption, LVOT gradient increase > 10mmHg)

7.0 STUDY METHODS

Methods for required study activities in the clinical investigational plan (CIP) are specified in the following subsections. Deviations from the CIP must be documented and reported to the Sponsor. All subjects must sign an IRB approved informed consent prior to performing any study activities described in this CIP.

Study data supporting enrollment eligibility must be recorded on the applicable case report forms. Source documentation supporting all case report form entries must be maintained at the investigational site and copies of source documents may be maintained by the Sponsor to support monitoring activities.

Investigators are expected to complete all applicable case report forms within 5 business days of the related follow-up visit or study activity. To ensure CIP compliance, data integrity, and protection of Subjects' rights, safety and welfare, Sponsor or its representative and other regulatory agencies may monitor the conduct of the study.

8.0 SUBJECT CONFIDENTIALITY

All Subject information collected during the study is kept strictly confidential. All data and information pertaining to the Subject and their participation in the study are considered confidential by Sponsor. All public reporting of study results must eliminate references to individual subjects. Information contained in paper form must be stored in secure areas. Electronic information that is kept on computers must be protected by secure passwords.

9.0 ENROLLMENT AND SCREENING

In order to protect the rights and welfare of subjects, the study is conducted in accordance with the 21 CRF 50, Protection of Human Subjects. All subjects are required to sign and date an IRB approved consent prior to participation in the study. All Subjects who sign an informed consent are assigned a unique identification number in order to maintain Subject traceability.

If during the course of the preoperative evaluations, the subject is found to be ineligible for study participation, the subject will be notified, and the reason for ineligibility will be documented on the Screening Log. Ineligible subjects are considered screen failures, and they will not be counted towards total enrollment and their subject ID number will not be reused. Sites are not required to enter data into the EDC system for any screen failures.

After screening assessments are made, the study candidate's qualifying criteria will be presented via the case review process where experienced study investigators will review the submitted criteria. Upon case review approval, the supporting evidence for approval and the names of the reviewer(s) will be

documented. Once the review and the eligibility criteria are documented, the subject can be enrolled in the study.

Subjects are considered enrolled at the time of initial skin incision.

10.0 BASELINE FUNCTIONAL ASSESSMENTS

Functional Assessments such as 6 minute walk test (6MWT), NYHA classification, Quality of Life (QOL) assessments (Kansas City Cardiomyopathy Questionnaire [KCCQ]) and 5 meter walk test are collected as part of the screening activities for baseline comparative purpose against scheduled follow-ups post-procedure.

11.0 ANTICOAGULATION MEDICATION

Subjects should be maintained on a once daily dose of warfarin (Coumadin) for a minimum of 3 months post study procedure to maintain an international normalized ratio (INR) of between 2.5 and 3.5. If a subject is not eligible for warfarin, the subject should be maintained on appropriate anticoagulation per investigator. If the subject was on novel oral anticoagulation (NOAC) pre-study procedure, that medication may be continued in lieu of warfarin at the investigators discretion.

12.0 STUDY DEVICES

Investigators selected to participate in the study will have prior experience with Edwards SAPIEN 3 system. The Edwards SAPIEN 3 valve is approved by the Food and Drug Administration (FDA). The study sites will be authorized to utilize devices for the study procedure after receiving IRB approval and signing the clinical study agreement.

13.1 PREGNANCY TESTING AND CONTRACEPTION

13.2 Pregnancy Testing

A Woman of Child Bearing Potential (WOCBP) who is planning pregnancy should not participate in the study. For participation in this study, pregnancy has to be excluded in any female study participant below age 60.

13.3 Contraception

WOCBP (Women of Child Bearing Potential) who are considering participation in the study must be informed about the study related risks to pregnancy/embryonic development and must receive contraceptive counseling. WOCBP must agree to use effective contraception while participating in the study.

Female subjects who are considered WOCBP and who are engaging in intercourse with a male partner(s), must begin using an acceptable method of contraception as soon as feasible prior to enrollment and must continue throughout the duration of their study enrollment

13.4 Female subjects are considered non-WOCBP if they are either:

A. Post-menopausal (12 months of natural (spontaneous) amenorrhea with an appropriate clinical profile (e.g., age appropriate, history of vasomotor symptoms) or six months of spontaneous amenorrhea with serum FSH levels > 40 mIU/mL)

B. Have had surgical bilateral oophorectomy (with or without hysterectomy) at least six weeks prior to enrollment into the study. In the case of surgical bilateral oophorectomy only, this will only be acceptable when the reproductive status of the woman has been confirmed by a follow up hormone level assessment

14.1 ENROLLMENT AND STUDY PROCEDURES

14.2 Baseline/Screening

The following information will be collected for all study subjects prior to procedure. Baseline assessments must be completed within 30 days of subject enrollment unless otherwise specified. Subjects are considered enrolled at the time of initial skin incision.

A. Society of Thoracic Surgeons (STS) Risk Score Assessment

B. Medical History and Physical Exam including Cardiac Medications

C. Cardiopulmonary:

1. Cardiac Catheterization (within 6 months prior to consent)
2. 3D Computed Tomography scan with contrast of chest, heart and peripheral vasculature with assessment of degree and pattern of MAC
3. Transthoracic echocardiogram (TTE)
4. 12 Lead Electrocardiogram (ECG)
5. Chest X-Ray
6. Pulmonary Function Test (PFT) within 1 year prior to consent

A. Functional Assessments:

1. 6 minute walk test (6MWT)
2. NYHA classification
3. QOL assessments: KCCQ
4. 5 meter walk test (5MWT)

B. Subject Clinical Laboratory Tests

1. Complete Blood Count (CBC) and platelet count
2. Complete metabolic panel (CMP) including Albumin
3. B-type natriuretic peptide (BNP)
4. PTT or PT/INR (if applicable)

5. A blood or urine pregnancy test will be performed at screening for females with childbearing potential. A positive pregnancy test will render the subject ineligible for study participation.

14.3 Intra-Procedure Assessments

Total procedure time is defined as the time from skin incision to the time of skin incision access closure. The following invasive hemodynamic data must be collected pre and post implant:

A. Transesophageal echocardiogram (TEE) assessments:
    1. To be collected prior to placement of valve
        i. Mitral valve gradient (peak and mean)
        ii. Quantify severity of mitral regurgitation (ERO, vena contracta width)
        iii. Left ventricular outflow tract (LVOT) width in millimeters (mm) and gradient
        iv. Presence of other valvular heart disease
        v. Left ventricular ejection fraction
    2. To be collected following placement of valve:
        i. central or paravalvular mitral regurgitation
        ii. transmitral gradient
        iii. left ventricular outflow tract (LVOT) gradients
B. Cardiac output and cardiac index
C. Adverse Event Assessment

14.4 Discharge Procedures

The following data will be collected for all study subjects within 24 hours of the date of discharge from the index hospitalization. However, subjects discharged within 48 hours of exiting the cath lab / operating room are not required to repeat tests collected during the Post Procedure period that are also required for the discharge visit. See Table 1.0. If subject is discharged over a weekend or holiday, the discharge tests may be completed on the last weekday prior to discharge.

A. **Systems:**

1. Pertinent physical examination [includes blood pressure, height, weight, major systems findings] including clinical assessment for Stroke and/or TIA;
2. Medications given for cardiovascular effect including anti-platelet/anti-thrombins;
3. Adverse Event assessment;

B. **Cardiac:**

1. Transthoracic echocardiogram (TTE).
2. NYHA classification;
3. Standard 12-lead ECG;
4. Chest X-ray examination

C. **Clinical Laboratory Tests:**

1. B-type natriuretic peptide (BNP).
2. CBC and platelet count;
3. PT/INR;
4. Metabolic Panel

14.5 Follow-Up Procedures

Follow-up procedures will be conducted at the intervals specified in Table 1.0. Blood draws will be performed at the specified intervals and according to hospital standard or medication regimen. Subjects will be informed that some of the data that are collected at scheduled follow-ups as well as at unscheduled visits, including the echocardiogram and CT scan may be sent to the respective independent core lab for analysis.

If a subject cannot be reached for a follow-up visit, the investigator will document on the follow-up data form, the efforts undertaken to contact the subject. These efforts should include 3 attempts of telephone contacts at separate dates and times, and a registered letter. If the subject cannot be reached in any way for their follow-up visits and misses the scheduled visit, new efforts will be undertaken to locate them at subsequent follow-up visits. In the event that

the subject's implanted valve is explanted, the subject needs to be continued to be followed for the duration of the study.

Follow-up visit intervals are as follows: 30 days (-7/+14 days), 6 months (±30 days), 12 months (+60 days). Additional phone follow-ups may be performed as needed to obtain up to date survival information for use in regulatory submissions.

For all subjects at all visits, the time clock starts on the date of the first implant attempt, whether or not the implant is successful and site visits will be scheduled accordingly.

14.4.1 One Month Follow-Up Visit

The following data will be collected for all study subjects at one month (within 7 days before and 14 days after the 30 days date)

A. Systems:

1. Pertinent physical examination [includes blood pressure, height, weight, major systems findings] including clinical assessment for Stroke and/or TIA;
2. Medications given for cardiovascular effect including anti-platelet/anti-thrombins;
3. Adverse Event assessment

B. Cardiac:

1. 4D Computed Tomography scan with contrast of the heart to include valve assessment
2. NYHA classification
3. Standard 12-lead ECG
4. Transthoracic echocardiogram (TTE)

C. Functional Assessments:

1. 6MWT
2. QOL: KCCQ

D. Clinical Laboratory Tests:

1. CBC and platelet count

2. Complete Metabolic Panel (CMP)
3. B-type natriuretic peptide (BNP)
4. Plasma free hemoglobin
5. Haptoglobin
6. PT/INR

E. Non-Invasive Studies:

1. Chest X-ray examination

14.4.2 Six Month Follow-Up Visit

The following data will be collected for all study subjects at 6 months: (±30 days).

A. Systems:

1. Pertinent physical examination [includes blood pressure, weight, major systems findings] including clinical assessment for Stroke and/or TIA;
2. Medications given for cardiovascular effect including anti-platelet/anti-thrombins;
3. Adverse Event assessment

B. Cardiac:

1. 4D Computed Tomography scan with contrast of heart to include valve assessment *if* any of the following have occurred:
   A. presence of thrombus on 30 day 4DCT scan
   B. Increase in mitral gradient as measured on TTE
   C. Clinical deterioration or clinical event including:
      i. neurological or peripheral embolic event
      ii. Rehospitalization for heart failure
2. NYHA classification
3. Transthoracic echocardiogram (TTE)

C. Clinical Laboratory Tests:

1. Plasma free hemoglobin
2. Haptoglobin
3. PT/INR (if applicable)

14.4.3 Twelve Month Follow-Up Visit

The following data will be collected for all study subjects at 1 year (365 days) +60 days.

A. Systems:

C. Pertinent physical examination [includes blood pressure, weight, major systems findings] including clinical assessment for Stroke and/or TIA;

D. Medications given for cardiovascular effect including anti-platelet/anti-thrombins

E. Adverse Event assessment

B. Cardiac:

F. NYHA classification

G. Standard 12-lead ECG

H. Chest X-ray examination

I. Transthoracic echocardiogram (TTE)

C. Clinical Laboratory Tests:

J. CBC and platelet count

K. Complete metabolic panel

L. B-type natriuretic peptide (BNP)

M. Plasma free hemoglobin

N. Haptoglobin.

O. PT/INR (if applicable)

D. Functional Assessments:

P. 6MWT

Q. QOL: KCCQ

15.0 STUDY DATA MONITORING AND DATA AND SAFETY MONITORING BOARD

The purpose of the monitoring plan is to facilitate compliance with GCP guidelines (GCP 5.18.1), FDA guidelines and FDA regulations (21 CFR 812). The monitoring plan for this study includes use of monitoring services and institution of a Data and Safety Monitoring Board. . A Data Safety and Monitoring Board (DSMB) will be constituted for this study to provide additional safety review. The DSMB is an independent advisory group of experts with a mandate to periodically review and evaluate safety and evaluate data for continuing validity.

The DSMB will be responsible for assuring that research subjects are not exposed to unnecessary or unreasonable risks. Ongoing responsibilities of the DSMB will be to evaluate the progress of the study, including periodic assessments of adverse events and serious adverse events. The DSMB will report on the safety and scientific progress of the study.

On site monitoring will be completed at regular intervals at each site commensurate with enrollment of the first subject and completion of the index procedure. As an electronic data capture system will be used to collect the data, the data entered into the database will be remotely reviewed to evaluate for potential safety issues such as unanticipated adverse device effects. Compliance with the study milestones for each enrolled subject will be reviewed, as well. Sites will be contacted for source information as indicated.

Reports from each monitoring visit will be provided to the site Investigator and the sponsor at completion of the monitoring.

16.0 DATA COLLECTION

All required data for this investigation are to be collected on standardized electronic case report forms (eCRFs) for individual enrolled subjects; sample eCRFs are provided. The eCRF must be electronically signed by the Principal Investigator or co-Investigator listed in the Clinical Studies Agreement and/or Delegation of Authority Log. If for any reason the eCRFs are unavailable and/or inaccessible, paper CRFs will be provided by the Sponsor to be completed, signed by the Principal Investigator or designee and submitted to the Sponsor.

Case Report Form Instructions will be provided to assist the Investigator(s) and appropriate investigational staff in the completion of the required eCRFs. Source documents are original documents, data, and records from which the subject's CRF data are obtained. These include, but are not limited to, hospital records, clinical and office charts, laboratory records, and correspondence. Electronic CRFs must be kept current to reflect enrolled subject status during the course of the investigation.

17.0 IMAGING CORE LAB

All baseline and follow-up transthoracic echocardiograms, transesophageal echocardiograms and CT scans will be evaluated at The Baylor Scott & White Research Institute Imaging Core Lab, under the direction of Paul Grayburn, M.D and Ambarish Gopal M.D.

Follow-up Doppler echocardiograms will be evaluated by the designated Echo Core Lab. A standardized written report generated by the Core Lab for each Doppler echocardiogram will be entered into an electronic database maintained by the Sponsor. The Clinical Site Manager or Sponsor designee shall notify the Investigator should there be any indication of a complication or discrepancy that the Investigator may not have noted. This will allow or an opportunity to further review the test results and clarify the findings if necessary.

18.0 SCREENING/ENROLLMENT LOG

All subjects considered for the study will be recorded on the Screening Log. A Screening Log will be provided to the investigational sites to maintain a cumulative log of all screened subjects. For subjects who are ineligible for participation in the clinical investigation, a reason supporting the disqualification of the subject must be entered on the Screening Log.

19.0 DEVIATIONS FROM THE STUDY PROTOCOL

The Investigator will not deviate from the protocol without the prior written approval of the Sponsor except in medical emergencies or in unforeseen, isolated instances where minor changes are made that will not increase the subject's risk or affect the validity of the study. Any subsequent revisions to the

protocol, including the Informed Consent Form and the Case Report Forms, other than very minor revisions, must be approved by the Sponsor, the FDA, and the IRB. In medical emergencies, prior approval for protocol deviations will not be required, but the Sponsor or its designee and IRB must be notified within 5 working days of the incident. Periodic monitoring of protocol compliance will be performed for each site. Deviations will be documented on the appropriate case report form. The sponsor has the right to suspend enrollment at sites deemed to have excessive protocol compliance issues.

20.0 INVESTIGATOR RESPONSIBILITIES

The Investigator is responsible for ensuring that this clinical study is conducted according to the Investigator Agreement, Protocol, all conditions of FDA and IRB approval and applicable FDA regulations. Written IRB approval of the protocol and ICF must be provided to the Sponsor prior to the enrollment of any subject in the clinical study at each investigational site. The Investigator is responsible for ensuring that informed consent is obtained from all subjects prior to any diagnostic tests or treatments that are outside the standard course of treatment that would be followed if this subject was not being considered for enrollment in this clinical study. Subjects must be informed that their medical records will be subject to review by the Sponsor, its authorized designee or representatives of FDA. Subjects will be informed that they are free to refuse participation in this clinical study without loss of benefits to which they are otherwise entitled, and, that if they choose to participate, they may withdraw at any time without prejudice to future care. The informed consent provided by each investigational site's IRB must be signed prior to study participation. The original signed informed consent for each subject must be retained by the Investigator and is subject to review by the Sponsor and the FDA. A copy of the informed consent will be provided to the subject.

21.0 WITHDRAWAL

Subjects may voluntarily withdraw from the study at any time. If such withdrawal occurs, or if the subject fails to return for visits, the site investigator must determine the primary reason for a subject's premature withdrawal from the study and record this information in the subject's study records.

For subjects who are lost to follow-up, the site investigator should show "due diligence" by documenting in the subject record steps taken to contact the subject, e.g., dates of telephone calls, registered letters, etc.

Subjects who are prematurely withdrawn from study treatment or from the study will not be replaced.

22.1 POTENTIAL RISKS AND BENEFITS

The risks associated with the use of the system are similar to those encountered with standard cardiac catheterization, use of anesthesia, mitral valve replacement (MVR) and the use of bioprosthetic heart valves, in addition to risks associated with study-related procedures (e.g. Transesophageal echocardiography, MSCT scan, etc.). A list of anticipated or potential adverse events is provided below.

22.2 Adverse Events

An adverse event is any undesirable clinical occurrence in a study subject, whether or not it is related to the study intervention. Any condition that was recorded as pre-existing is *not* an AE unless there is a change in the nature, severity or degree of the condition. Furthermore, for a pre-existing condition that is not protocol defined to be reported as an adverse event, a change in severity must meet the criteria for being serious (see definition below).

22.3 Serious Adverse Event

Serious adverse events are defined by FDA regulation as any experience that results in a fatality or is life threatening; results in significant or persistent disability; requires or prolongs a hospitalization; results in a congenital anomaly/birth defect; or represents other significant hazards or potentially serious harm to research subjects or others, in the opinion of the investigators. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse event when, based upon appropriate medical judgment, they may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

22.4 Unanticipated Serious Adverse Event

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

22.5 Event Recording

The following adverse events will be captured throughout the period of study participation:

A. Protocol-defined (as described below)
B. Serious unanticipated events (serious *"Other"* adverse events)

22.6 Causality

The investigator will assess the relationship of an adverse event to the surgical intervention. If possible, the investigator should distinguish the relationship between the event and (a) the surgical procedure and (b) the investigational intervention (implant of Edwards SAPIEN 3 valve). Causality will be defined as follows:

A. **Probable**

Adverse events that, after careful medical evaluation, are considered with a high degree of certainty to be related to the surgical intervention

The following characteristics will apply:

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

B. **Possible**

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

The following characteristics will apply:

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

C. **Unlikely**

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

The following characteristics will apply:

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

22.7 Reporting of Serious Adverse Events

All investigators must report both expected (protocol-defined) and unexpected serious adverse events. All serious protocol defined adverse events must be reported directly to the clinical center's IRB and the sponsor within 10 working days of knowledge of the event, or as dictated by the specific IRB policy, whichever is sooner. All unexpected serious adverse events must be reported to the sponsor within 24 hours of knowledge of the event and the clinical center's IRB as dictated by the specific IRB policy.

22.8 Eliciting adverse effect information

Investigators are responsible for preparing and submitting all reports as summarized on Table 1.0.

Case Report Forms should be entered within 10 days after the corresponding visit. Investigators are responsible for notifying the Sponsor of any changes to previously reported data. Upon request of the reviewing IRB, FDA, the Investigator must provide accurate, complete, and current information about any aspect of the study.

22.9 Table 1.0: Investigator Report Requirements

Report title/description	Requirement(s)	Submit to:
Adverse events (AE)	Immediately but no later than 10 days of becoming aware	Sponsor
Serious Adverse Event (SAE)	Report should be submitted immediately after the Investigator first learns of the event but no longer than 10 days hours	Sponsor If applicable, IRB
Unanticipated Adverse Device Effect (UADE)	Report should be submitted immediately after the Investigator first learns of the event but no longer than 10 working days	Sponsor IRB
Withdrawal of IRB approval	Report must be submitted immediately after the Investigator learns of the withdrawal but no longer than 5 working days.	Sponsor
Progress Report	Report must be submitted annually, or as required by the IRB, for the duration of the clinical study. The Sponsor may also prepare this report.	If applicable, IRB
CIP Deviations	Deviations from the investigational plan must be approved by the Sponsor prior to implementation NOTE: If the deviation affects the scientific soundness of the CIP or the rights, safety or welfare of the Subjects, the deviation must be approved by the Sponsor and IRB, if applicable.	Sponsor If Applicable IRB
	In the event that a CIP deviation occurs and the sponsor cannot be notified ahead of time (e.g., if the notification was to protect the life or physical well-being of the Subject),	Sponsor IRB

22.9 Anticipated or Potential Adverse Events

The list below provides anticipated or potential adverse events that may occur during the study. The potential adverse events are those that are expected to occur during the study because they are associated with the surgical procedure, stress-induced tests (e.g. TEE/TOE, TTE, MSCT scan, exercise tolerance, etc.), or the heart failure population over time. It is anticipated that subjects may require temporary medical and/or mechanical hemodynamic support in the peri and/or early post-op period. These events are not considered adverse events.

- Abnormal Lab values
- Allergic Reaction to Anesthetic, Anti-coagulant Therapy, Contrast or Cobalt Chromium
- Anaphylactic Shock or Toxic Reaction
- Anemia
- Angina
- Annulus Rupture/ A-V Groove Disruption
- Aortic Valve Impairment/Damage
- Arrhythmias
- Atrial Fibrillation
- Atrio-ventricular Node Block
- A-V fistula or pseudo-aneurysm
- Bleeding diathesis
- Cardiac Arrest
- Cardiac Failure or Decompensation
- Cardiac Perforation
- Cardiac Tamponade/ Pericardial Effusion
- Cardiogenic Shock
- Chordal Rupture
- Conduction System Injury (defect) which may require pacemaker
- Conversion to Open Sternotomy
- Coronary Artery Obstruction
- Death
- Dissection, Any Vessel
- Dyspnea
- Edema
- Electrolyte Imbalance
- Electro-mechanical Dissociation
- Embolization including air, particulate, calcific material, or thrombus
- Emergent PCI
- Emergent Cardiac Surgery
- Endocarditis
- Esophagus Irritation/Perforation (TEE related)
- Fever
- Frame Strut Fracture
- GI Bleeding
- Heart Failure

- Hematoma
- Hemolysis / Hemolytic Anemia
- Hemorrhage require transfusion/surgery
- Infection at the access site
- Inflammation
- Leaflet tearing
- Left Ventricle Failure
- Local and Systemic Infection
- LVOT Obstruction
- Mal-positioning of Prosthesis
- Multi-system Failure
- Myocardial Infarction
- Myocardial Ischemia
- Pacemaker Implantation
- Pannus Formation
- Papillary Muscle Damage
- Peripheral Ischemia
- Pleural effusion
- Pneumonia
- Prosthesis Dislodgement/Embolization
- Prosthesis Leaflet Entrapment
- Prosthesis Migration
- Prosthesis Paravalvular Leak
- Prosthesis Regurgitation
- Prosthetic Valvular Endocarditis
- Prosthetic Valvular Thrombosis
- Pulmonary Edema
- Pulmonary Vein Obstruction
- Reintervention or reoperation
- Renal Failure or Insufficiency
- Respiratory Failure
- Retroperitoneal Bleed
- Septicemia
- Stroke, TIA, or other Neurological Event
- Structural Deterioration
- Systolic Anterior Motion
- Thromboembolism
- Valve Stenosis
- Vascular trauma, dissection, or occlusion
- Ventricular Perforation by Frame
- Vessel Spasm
- Wound Dehiscence

22.10 Risk Minimization

Efforts to minimize risks associated with performing the procedure include the following:

A. Selection of qualified Investigators
B. Comprehensive Investigator training to insure that Investigators have a thorough knowledge of the CIP and the proper technique for implantation of the study device, including the following elements of instruction:

1. Providing CIP training to all Investigators and study staff noted on the Delegation of Authority log (DOA)
2. Clearly defining the subject inclusion and exclusion criteria
3. Monitoring echocardiographic and hemodynamic parameters during placement of the implant
4. Ensuring data collection is consistent with the CIP
5. Ensuring treatment and follow-up of subjects is consistent with the CIP and standard and current medical practice

22.11 Potential Benefits

The clinical benefits of using the SAPIEN 3 valve in subjects with mitral annular calcification (MAC) associated with mitral stenosis and/or regurgitation are not known at the present time. There are no guaranteed benefits from participation in this clinical study and being treated with the study device.

Mitral valve replacement with the SAPIEN 3 valve may result in one or more of the following benefits for subjects typically considered high risk or inoperable for surgical MVR: decrease in mitral stenosis, decrease in mitral regurgitation, acute alleviation of symptoms related to mitral insufficiency and/or stenosis, and/or improved morbidity and mortality. Information gained from the conduct of this study may be of benefit to other people with the same medical condition in the future as the indication for the system is expanded.

23.0 STATISTICAL ANALYSIS & DATA MANAGEMENT

To describe procedural success and device success at 30 days, and subject success at 12 Months descriptive statistics (e.g. percentage) and plots will be estimated.

All tasks will be performed in compliance with HIPAA regulations. Patients' identifiers will be encrypted for study data shared with other study personnel. All data for the proposed study will be stored in the

secure database we will develop and periodic back-up will protect against catastrophic loss. All hard copy materials (summary printouts) will be stored by the principal investigator in locked file cabinets; disks and other removable storage media files will be stored as per HIPAA regulations. The Principal Investigator will be responsible for the data management operations.

24.1 ROLE OF BAYLOR RESEARCH INSTITUTE AS CLINICAL AND DATA COORDINATING CENTER

Baylor Research Institute is the sponsor of this study. The Sponsor is responsible for ensuring that this study will be conducted in compliance with all applicable U.S. Federal regulations pertaining to investigational devices including but not limited to: 21 CFR Part 50, Part 54, Part 56, Part 812, Good Clinical Practice (GCP) standards, and Health and Insurance Portability and Accountability Act (HIPAA).

Baylor Research Institute Regulatory Affairs and Data Management departments have quality assurance procedures to ensure that complete, accurate and timely data are collected, that the Investigational Plan requirements are followed and that all complications and adverse events are reported in a timely manner.

Electronic CRFs are used for collecting and recording of data for enrolled subjects at all investigational sites. Investigators or their designees are responsible for the timely completion of these forms. Entered data are reviewed to identify inconsistent or missing data and adverse events. Data problems will be addressed by phone or written communication with the investigational sites and/or during site visits. All forms and data files will be secured to ensure confidentiality. Investigators are to maintain all source documents required by regulation, including diagnostic test reports, laboratory results, completed CRFs, supporting medical records and informed consents. The source documents will be referenced during regular monitoring visits to verify the information documented on the CRFs.

Pre-operative diagnostic tests will be evaluated by the Investigator and other appropriate professionals at the investigational site to determine the subject's eligibility for the clinical study.

25.0 Table of Events (Table 2.0)

	Screening/ Baseline	During Procedure	Discharge	1 Month (-7/+14 days)	6 Month (+/- 30 days)	12 Month (+ 60 days)
Informed Consent	X					
Medical History	X					
Physical Exam	X		X	X	X	X
Cardiac Medications	X		X	X	X	X
Cardiac Catheterization	X					
CT Scan with contrast	X[1]			X[4]	X[5]	
TTE	X		X	X	X	X
PFT[2]	X					
Chest X-ray	X		X	X		X
12-Lead ECG	X		X	X		X
6 Minute Walk Test	X			X		X
5 Meter Walk Test	X					
NYHA Classification	X		X	X	X	X
STS Risk Score	X					
Quality of Life (KCCQ)	X			X	X	X
Intra-Procedure assessments		X				
Adverse Event Assessment		X	X	X	X	X

Table of Events (Table 2.0) continued

Lab Measurements						
CBC and Platelet Count	X		X	X		X
CMP	X		X	X		X
BNP	X		X	X		X
PTT or PT/INR	X		X	X	X	X
Blood or urine pregnancy[3]	X					
Plasma Free Hemoglobin				X	X	X
Haptoglobin				X	X	X

1. 3D Computed Tomography scan with contrast of chest, heart and peripheral vasculature with assessment of degree and pattern of MAC
2. Pulmonary Function Test within 1 year of consent
3. A blood or urine pregnancy test will be performed at screening for females with childbearing potential. A positive pregnancy test will render the subject ineligible for study participation.
4. 4D Computed Tomography scan with contrast of the heart to include valve assessment
5. 4D Computed Tomography scan with contrast of heart to include valve assessment *if* any of the following have occurred:

    A. presence of thrombus on 30 day 4DCT scan

    B. Increase in mitral gradient as measured on TTE

    C. Clinical deterioration or clinical event including:

        i. neurological or peripheral embolic event

        ii. Rehospitalization for heart failure

Appendix 1 Informed Consent Form Template

BAYLOR RESEARCH INSTITUTE

Investigational Site Name

PARTICIPATION EXPLANATION AND CONSENT FORM

PROJECT TITLE: **S**urgical **I**mplantation of **TRA**nscatheter va**L**ves in native mitral stenosis (SITRAL) Trial

INVESTIGATORS:

TELEPHONE NUMBER:

Introduction:

Before you say that you will be in this clinical trial (a kind of research study) you need to read this form. It is important for you to understand all the information in this form. This form will tell you what the clinical trial is about and how it will be done. It will tell you about some problems that might happen during the clinical trial. It will also tell you about the good things that might happen for you during the clinical trial. When you read a paper like this to learn about a clinical trial it is called "informed consent." The people who are doing this clinical trial are giving you very important information about the clinical trial. When you give your consent for something, it is the same as giving your permission. This consent form may contain words that you do not understand. Please talk with one of the doctors or their staff if you have questions. Do not sign this consent form unless all your questions have been answered and you feel comfortable with the information you have read. You will be given a copy of the form to keep.

You are being asked to take part in this study because you have been diagnosed as having mitral stenosis and mitral annular calcification (MAC) and are high-risk or inoperable for mitral valve surgery.

Why is this study being done?

The purpose of this study is to establish the safety and feasibility of the Edwards SAPIEN 3 valve in subjects with mitral stenosis and mitral annular calcification (MAC) who are high-risk or inoperable for mitral valve surgery.

What is the Status of the Drugs (Devices or Procedures) involved in this study?

The Edwards SAPEIN 3 valve is currently approved by the US Food and Drug Administration for the treatment of aortic stenosis.

How Many People Will Take Part In The Study?

About 30 people will take part in this study at six sites worldwide. About 5 of these people will take part at this location.

What Is Involved In The Study?

The following information will be collected for all study subjects prior to procedure. Baseline assessments must be completed within 30 days of subject enrollment unless otherwise specified.

- Medical History and Physical Exam including Cardiac Medications
- Blood tests (about 2-3 teaspoons)
- Society of Thoracic Surgeons (STS) Risk Score Assessment
- Heart catheterization with an x-ray dye (contrast media) to evaluate your heart. This test will take about 2 hours.
- Computed tomography (CT) scan of chest, heart and abdomen with assessment of degree and pattern of MAC with an x-ray dye (contrast media). This test will take about 1-2 hours.
- Transthoracic echocardiogram (TTE: a probe is placed on your chest and images of your heart are recorded). The TTE does not require anesthesia and takes about 45 minutes.
- 12 Lead Electrocardiogram (ECG) (a test which measures the electrical activity of your heart)
- Chest X-Ray which will take about 15 minutes
- Pulmonary Function Test (PFT)
- 6 minute walk test (measures how far you can walk in six minutes)
- New York Heart Association classification (this is a score based on severity of your heart failure symptoms)
- Quality of Life questionnaire which will take about 10 minutes
- 5 meter walk test (this measure how fast you walk)

What Happens during the procedure?

The study doctor will perform your mitral valve surgery in a cardiac operating room (OR) under general anesthesia. An incision will be made on your right side so that the study doctor can access your heart.

You will be placed on cardiopulmonary bypass during your procedure. This is sometimes called a "heart-lung machine". The machine will remove the blood from your body through tubes and add oxygen to it. The machine then returns the blood to your body. The study doctor will try to minimize the time you spend on this machine. The study doctor will explain the entire procedure to you, including all the risks and the steps he will take to minimize those risks.

Once the study doctor has access to your mitral valve, a small portion will be removed from your valve leaflet and the study doctor will choose an Edwards Sapien 3 valve that is appropriately sized. A camera will be used to help visualize the procedure to confirm that the valve is in a good position and that there are no leaks. Once the valve is confirmed to be in a good positioned and well seated, sutures will be used to secure the valve in position and the heart will be closed.

The valve function will be assessed by transesophageal echocardiogram (TEE) during the procedure. If the valve appears to be functioning well with little to no paravalvular leak (blood flowing around the valve). The patient will be weaned from the "heart lung machine" and transferred to the ICU for further care.

The following information will be collected during you procedure:

- Transesophageal echocardiogram (TEE) assessments:
    - Mitral valve gradients
    - Quantify severity of mitral regurgitation
    - Left ventricular outflow tract (LVOT) width in millimeters (mm) and gradient
    - Presence of other valvular heart disease
    - Left ventricular ejection fraction
    - central or paravalvular mitral regurgitation
    - transmitral gradient
- Cardiac output and cardiac index

The following data will be collected within 24 hours of the date of your discharge. If you are discharged within 48 hours of leaving the operating room, the tests collected during the Post Procedure period will not be repeated at discharge. If you are discharged over a weekend or holiday, the discharge tests will be completed on the last weekday prior to your discharge.

- Physical examination
- A list of current Medicines will be collected
- Transthoracic echocardiogram
- NYHA classification
- Standard 12-lead ECG
- Chest X-ray examination
- Blood tests (about 2-3 teaspoons)

Follow-Up Procedures:

Follow-up procedures will be conducted at the intervals list below. Blood draws will be performed at the specified intervals and according to hospital standard or medicine regimen. You will be informed that some of the information collected at scheduled follow-ups as well as at unscheduled visits, including the echocardiogram, CT scan, ECG and the Quality of Life questionnaires, may be sent to the respective independent core lab for analysis.

Follow-up visit intervals are as follows: 30 days (-7, +14) days, 6 months (±30 days), 12 months (+ 60 days). Additional phone follow-ups may be performed as needed to obtain up to date survival information.

30 day Follow-Up Visit:

The following data will be collected for all study subjects at 30 days (within 7 days before and 14 days after the 30 days date)

- Physical examination
- A list of current Medicines will be collected
- Transthoracic echocardiogram
- 4D Computed tomography (CT) scan of heart with an x-ray dye (contrast media). This test will take about 1-2 hours.
- NYHA classification
- Standard 12-lead ECG
- Chest X-ray examination
- Blood tests (about 2-3 teaspoons)

- 6 minute walk test
- Quality of life questionnaire which will take about 10 minutes

Six Month Follow-up Visit:

- Physical examination
- A list of current Medicines will be collected
- Transthoracic echocardiogram
- NYHA classification
- Blood tests (about 2-3 teaspoons)
- A 4D Computed tomography (CT) scan of heart with an x-ray dye (contrast media) will be completed *if* any of the following have occurred:

    A. presence of thrombus (blood clot) on 30 day 4DCT scan

    B. Increase in mitral gradient as measured on TTE

C. Clinical deterioration or clinical event including:
   i. neurological or peripheral embolic event
   ii. Rehospitalization for heart failure

12 Month Follow-Up Visit

The following data will be collected for all study subjects at +60 days.

- Physical examination
- A list of current Medicines will be collected
- Transthoracic echocardiogram
- NYHA classification
- Standard 12-lead ECG
- Chest X-ray examination
- Blood tests (about 2-3 teaspoons)

- 6 minute walk test
- Quality of life questionnaire which will take about 10 minutes

How Long Will I Be In The Study?

You will be in the study for about 1 year or 12 months**.**

The researcher may decide to take you off the study if any of the following occur:

- He/She feels that it is in your medical best interest.
- Your condition worsens.
- New information becomes available.
- The study is stopped by the sponsor.

You can stop taking part in this study at any time. However, if you decide to stop taking part in the study, we encourage you to talk to the researcher and your regular doctor first.

What Are The Risks of The Study?

While on the study, you are at risk for these bad reactions. You should discuss these with the researcher and/or your regular doctor. There also may be other bad reactions that we cannot predict.

Risks and bad reactions related to the procedure we are studying include:

- abnormal lab values (reduced number of red blood cells, abnormal white blood cells, low platelets, elevated renal (kidney) function), hematologic dyscrasia (abnormal blood cells), hepatic enzyme changes (changes in liver lab)
- access site arteriovenous fistula or pseudoaneurysm; (hole or abnormal connection between the arteries and veins at the access site);
- allergic reaction to anesthesia or to contrast media (x-ray dye);
- anemia(reduced number of red blood cells);
- angina (chest pain);
- arrhythmia (irregular heart beat);
- bleeding (loss of blood);
- cardiovascular or vascular (involving the heart and blood vessels) injury including perforation (a hole), obstruction (blockage), or dissection (damage) of valvular structures that may require intervention, including access sites;
- conduction system (the system that controls the heart to contract and pump blood) injury (defect) which may require permanent pacemaker;
- death;
- dyspnea (e.g. orthopnea) (shortness of breath);
- electrolyte imbalance;
- embolization (obstruction) including air, particulate, calcific material (plaque); or thrombus (clot formation) ;
- exercise intolerance (unable to do exercise that is expected for one's physical condition) or weakness;
- fever;
- heart failure;
- heart murmur;
- hematoma (blood accumulation or bruising);
- hemorrhage (a rapid loss of blood) requiring transfusion or intervention;
- leaflet tearing;
- hypertension(high blood pressure)/hypotension(low blood pressure);
- infection, including septicemia (infection in the blood), and endocarditis (inflammation of the heart);
- inflammation (swelling);
- myocardial infarction (heart attack);
- pain or changes at the access site;
- paralysis;
- pericardial effusion/cardiac tamponade (bleeding into the heart sac);
- permanent disability;
- pleural effusion(fluid accumulation in the lungs);
- prosthesis nonstructural dysfunction (poor function of the study device);
- prosthesis pannus (a hanging flap of tissue from device);
- pulmonary edema(fluid in the lungs);
- renal failure (poor kidney function requiring dialysis);

- renal insufficiency (poor kidney function);
- reoperation(having another operation);
- restenosis (narrowing of the mitral valve);
- retroperitoneal bleed (bleeding into a space in the abdomen);
- syncope (fainting or brief loss of consciousness);
- systemic (body) or peripheral (arms and legs) ischemia (decreased blood flow)/nerve injury;
- thromboembolic events, stroke, transient ischemic attack (mini-strokes), clusters (type of mini stroke), or neurological (brain, spinal cord and nerves) changes.

Complications with the investigational device you may experience may include, but are not necessarily limited to, the following:

- Cardiac arrest(heart stops beating);
- cardiac dysrhythmias (irregular heart beat) requiring permanent pacemaker;
- cardiac failure/low cardiac output (poor heart function);
- cardiogenic shock (heart muscle is unable to supply blood to the body);
- cardiovascular or vascular (involving the heart and blood vessels) injury including perforation (a hole), obstruction(blockage), or dissection (damage) of valvular structures that may require intervention, including access sites;
- chordal rupture (tearing of a portion of the native valve);
- device degeneration(device breakdown);
- device explants (removal of the device);
- device migration (movement), malposition (implanted in unintended position) or embolization (obstruction) requiring intervention;
- device thrombosis (clot formation) requiring intervention;
- emergency cardiac (heart) surgery;
- hemolysis (disruption of blood cells);
- infection including endocarditis (inflammation of the heart);
- leak (transvalvular or paravalvular) (blood leakage through or around the device);
- Left Ventricular Outflow Tract obstruction (blocking the path of blood leaving the heart);
- non-emergent reoperation (need for another operation that is not an emergency);
- nonstructural Mitral THV dysfunction (poor function of the study device);
- papillary muscle damage;
- pulmonary vein obstruction (blocking the path of blood entering part of the heart);
- structural deterioration (poor function of the aortic valve) (wear, fracture, calcification, leaflet tear/tearing, leaflet retraction (valve parts stop working), stent creep, suture line disruption, thickening, stenosis, or other);
- thromboembolism (permanent or transient neurological events);
- transvalvular (across the valve) flow disturbances or aortic valve impairment/damage;

- valvular regurgitation (leakage);
- ventricular or atrial (chambers of the heart) wall damage, abrasion (injury), or perforation (hole);
- worsening of heart failure;
- worsening of valvular insufficiency (valve function).

With any investigational device there may be unforeseeable risks, which are not known at this time. Medical and / or surgical intervention may be required to correct clinical complications associated with the device and / or study procedure.

Pregnancy Risks

Women who are pregnant may not take part in this study. The effects of this treatment and follow-up requirements to an embryo or fetus are currently unknown. If you are a woman of child-bearing potential, and are not sterile, a small amount of blood or urine will be collected, to confirm you are not pregnant, before the study procedure. A urine pregnancy test is not as sensitive as a blood pregnancy test and a negative urine test does not completely rule out an early pregnancy in progress.

A serum pregnancy test will be given to if you are considered of child-bearing potential (WOCBP). To be considered as non-WOCBP, you must be post-menopausal (12 months of natural amenorrhea with an appropriate clinical profile [e.g., age appropriate, history of vasomotor symptoms] or six months of spontaneous amenorrhea with serum FSH levels > 40mIU/mL)

Other study procedure risks:

- Possible nausea and vomiting from general anaesthesia
- Possible bruising at blood draw site

If you have additional questions about these risks, ask the researcher.

Please notify the study doctor or study staff if you experience any side effects or complications during the study. You will be monitored throughout the study in order to minimize risks.

Radiation Risks:

If you take part in this study, you will undergo several medical imaging procedures involving exposure to radiation. The following lists these procedures:

- a CT scan (also known as a CAT scan) to help visualize the heart valves and blood vessels in and around your heart, done during the screening assessment as well as the 30 days and 6 month visits.

- Heart catheterization under fluoroscopy (fluoroscopy is like an x-ray "movie") during the screening assessment (standard of care that you would have likely had even if not in the study)
- Fluoroscopy during the procedure to replace your mitral value if the replacement is performed with a catheter (research only procedure)
- Chest x-ray

If you have concerns about the radiation exposure associated with this study, please speak with your doctor.

Conflict of Interest

Your doctor may be an investigator in this research study. If so, s/he is interested both in your medical care and in the conduct of this research. Before you sign up for this study or at any time during the research, you may discuss your care with another doctor who is not associated with this research project. You are not under any obligation to take part in any research study offered by your doctor.

The people working on this study may be paid for their work on this research study from money provided by the company sponsoring this research study. The people working on this study may be paid for other work that is unrelated to this research study, such as consulting with the sponsor company or speaking at educational programs at the request of the sponsor company or other companies that may have an interest in the study. The people working on this study may have public stock holdings as an investment in the company sponsoring this research study.

Are There Benefits to Taking Part in The Study?

If you agree to take part in this study, there may or may not be direct medical benefit to you. We hope that the information learned from this study will benefit other subjects with this disease in the future.

What Other Options Are There?

Instead of being in this study, you have the following options:

- You may choose to receive no therapy at this time and receive only care to help you feel more comfortable.
- You may choose not to take part in the study.

Please talk to your regular doctor about these and other options.

What About Confidentiality?

You have a right to privacy. This means that all the information about you from this study will only be shown to the people working on the study. The results of this study may be published in a scientific book or journal. If this is done, your name will not be used. All information about you from this research project will be kept in a locked office or other locked area. Information that is kept on computers will be kept safe from access by people who should not see it.

The privacy law requires that *(Insert Site Name here)* get your permission before giving any of your health information to other people. There are people who need to review your information to make sure the study is done correctly. These people may look at or copy your information while they are doing this review. When you sign this form you give permission to *(Insert Site Name here)* to give other people information about your health as needed for the research project. These groups include people who work for *(Insert Site Name here)* (including the Institutional Review Board), the US Food and Drug Administration, the Office for Human Research Protections and the Association for the Accreditation of Human Research Protection Programs. This also includes the following groups of people who are working with the sponsor of the study: Baylor Scott & White Research Institute, Baylor Scott & White Research Institute Imaging Core Lab, Edwards Lifesciences, (*list additional groups as applicable)*. Even though we usually remove your name from the information, the people who get this information may be able to figure out who you are. The kinds of health information that might be given to these people include results from lab tests or other tests like x-rays. This information might also be notes written by your doctor from your medical record or notes written by your doctor asking for tests to be done on you.

You do not have to give this permission and it is all right to refuse to sign this form. Your doctor will still treat you and your insurance company will still pay your medical bills (according to their policy) even if you do not give your permission for us to release this information. However, since it is important for the people listed above to have access to your information, if you do not sign this form, you cannot be in the research study.

If you give permission to (Insert Site Name here) to give other people information about your health and the other people are not part of the group that must obey this law, your health information will no longer be protected by the privacy law. However, we will take all reasonable measures to protect your information from being misused.

If you change your mind and later want to withdraw your permission, you may do so. You must notify (Insert appropriate name and address here) If you decide to do this, it will not apply to information that was given before you withdrew your permission and you will no longer be able to take part in the study.

Unless permission is withdrawn, this permission will not expire at the end of the study.

What Are the Costs?

Taking part in the study may lead to added costs to you or your insurance company. Please ask about any expected added costs or insurance problems.

- You or your insurance company will be required to pay for all expenses related to the implantation procedure and your other hospital care.

The sponsor of this study is paying *(Insert Site Name here)* a specific amount of money for each person who agrees to take part in the study. This money is to cover the cost of doing the study and pay for such things as study supplies, staff salaries, etc.

Will I Be Paid For Taking part in This Study?

You will not be paid for being in this study.

What if I am Injured or Become Ill While Taking part in this Study?

The people doing this research project will do everything they can to make sure you do not get hurt during the project. If you do get hurt, there are some things that you need to know:

- The people doing the research project have not set funds aside to pay you money if you are hurt.
- Baylor Health Care System, Baylor Research Institute and The Heart Hospital at Baylor Hospital have not set funds aside to pay you money if you are hurt.
- The sponsor, Baylor Scott & White Research Institute, has not set funds aside to pay you money if you are hurt.
- If you have an emergency illness during the project, the people working with you will provide emergency care. You or your insurance company may need to pay for the emergency care if that happens.
- You have not given up any of your legal rights by signing this form.

What are My Rights As a Participant?

Taking part in this study is voluntary. You may choose not to take part or may leave the study at any time. If you agree to take part and then decide against it, you can withdraw for any reason. Deciding not to be in the study, or leaving the study early, will not result in any penalty or loss of benefits that you would otherwise receive.

We will tell you about any new information that may affect your health, welfare, or willingness to stay in this study.

All of the people working on the project must be careful not to carelessly harm you. If you are hurt during this project, you have the right to seek legal counsel. Nothing in this consent form takes away that right if you are hurt during this research.

Whom Do I Call If I have Questions or Problems?

If you have concerns, complaints or questions about the study or have a research-related injury, contact the Principal Investigator,_____at_____.

For concerns, complaints or questions about your rights as a research subject or if you simply wish to speak with someone who is not a part of the research staff, contact_____, M.D., IRB Chair, at _____.

Statement of Person Obtaining Consent:

I have explained to_____the purpose of the research project, the procedures required and the possible risks and benefits to the best of my ability. They have been encouraged to ask questions related to taking part.

_____ _____ _____

Signature of Person Obtaining Consent Date Time

Confirmation of Consent by Research Subject:

You are making a decision about being in this research study. You will be asked to give your written consent if you want to be in the study. Giving consent is like giving permission. You should not give your permission to be in this study until you have read and understood all the pages in this form. If you cannot read, then someone can read the form to you. Make sure that all your questions about this research project have been answered before you sign this form. When you sign this form, you are giving your permission to be in the study. By signing this form, you have not given up any of your legal rights or released anyone from liability for negligence.

_____has explained to me the purpose of the research project, the study procedures that I will have, and the possible risks and discomforts that may happen. I have read (or have been read) this consent form. I have been given a chance to ask questions about the research study and the procedures involved. I believe that I have enough information to make my decision. I have also been told my other options. To the best of my knowledge, I am not in any other medical research. Therefore, I agree to give my consent to take part as a subject in this research project.

_____ _____ _____

Signature of Subject Date Time

Appendix 2: VALVE ACADEMIC RESEARCH CONSORTIUM DEFINITIONS

TERM	DESCRIPTION
Cardiovascular Mortality (M-VARC)	**Any of the following criteria:** • Death due to proximate cardiac cause (e.g., myocardial infarction, cardiac tamponade, worsening heart failure) • Death caused by non-coronary vascular conditions such as neurological events, pulmonary embolism, ruptured aortic aneurysm, dissecting aneurysm, or other vascular disease • ***All procedure-related deaths***, including those related to a complication of the procedure or treatment for a complication of the procedure • Sudden or unwitnessed death • Death of unknown cause
Procedure-related death (M-VARC)	Procedure-related death is defined by any intra-procedural events that result in immediate or consequent death (***within 48 hours***).
Non-cardiovascular mortality (M-VARC)	Any death in which the primary cause of death is clearly

related to another condition (e.g., trauma, cancer, suicide).

Myocardial Infarction (M-VARC)

Peri-procedural MI (≤ 72 hours after the index procedure):

New ischemic symptoms (e.g. chest pain or shortness of breath)***, or new ischemic signs*** (e.g. ventricular arrhythmias, new or worsening heart failure, new ST-segment changes, hemodynamic instability, new pathological Q waves in at least two contiguous leads, imaging evidence of new loss of viable myocardium or new wall motion abnormality),

AND

Elevated cardiac biomarkers **within 72 h** after the index procedure consisting of at least one sample post-procedure ***with a peak value exceeding 15x upper reference limit (troponin) or 5x for CK-MB.***
If cardiac biomarkers are increased at baseline (>99th percentile), a further increase ***of at least 50% post-procedure is required*** AND the peak value must exceed the previously stated limit.

Spontaneous MI (> 72 hours after the index procedure):

Any one of the following criteria:

1) Detection of ***rise and/or fall of cardiac biomarkers*** (preferably troponin) with at least one value above the 99th percentile 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)]
– New pathological Q waves in at least two contiguous leads
– Imaging evidence of new loss of viable myocardium or new wall motion abnormality

2) ***Sudden, unexpected cardiac death***, involving cardiac arrest, often with symptoms suggestive of myocardial ischemia, and ***accompanied by presumably new ST elevation, or new LBBB, and/or evidence of fresh thrombus by coronary angiography and/or at autopsy***, but death occurring before blood samples could be obtained, or at a time before the appearance of cardiac biomarkers in the blood.

3) ***Pathological findings*** of an acute myocardial infarction.

Bleeding (M-VARC)

Life-threatening Bleeding:
• Fatal bleeding (BARC type 5) OR
• Bleeding in a critical organ, such as intracranial, intraspinal, intraocular, or pericardial necessitating pericardiocentesis, or intramuscular with compartment syndrome (BARC type 3b and 3c) OR
• Bleeding causing hypovolemic shock or severe hypotension requiring vasopressors or surgery (BARC type 3b) OR
• Overt source of bleeding with drop in hemoglobin of ≥ 5 g/dL

	or whole blood or packed red blood cells (RBCs) transfusion ≥ 4 units* (BARC type 3b) Major Bleeding: • Over bleeding either associated with a drop in the hemoglobin level of at least 3.0 g/dL or requiring transfusion of 2 or 3 units of whole blood/RBC AND • Does not meet criteria of life-threatening or disabling bleeding Minor Bleeding: • Any bleeding worthy of clinical mention (e.g. access site hematoma) that does not qualify as life-threatening, disabling, or major.
Acute Kidney Injury (M-VARC)	Change in serum creatinine (up to 7 days) compared with baseline • Stage 1 Increase in serum creatinine to 150–200% (1.5–2.0 × increase compared with baseline) or increase of ≥0.3 mg/dL (≥26.4 mmol/L) within 48 hours. • Stage 2 Increase in serum creatinine to 200–300% (2.0–3.0 × increase compared with baseline) • Stage 3* Increase in serum creatinine to ≥300% (>3x increase compared with baseline) or serum creatinine of ≥4.0 mg/dL (≥354 mmol/L) with an acute increase of at least 0.5 mg/dL (44 mmol/L) *Subjects receiving renal replacement therapy are considered to meet Stage 3 criteria irrespective of other criteria

Vascular access site and site related complications **(M-VARC)**	**Major Vascular Complications:** • Any thoracic aortic dissection, aortic rupture, annulus rupture, left ventricle perforation, or new apical aneurysm/pseudo-aneurysm • Access site or access-related vascular injury (dissection, stenosis, perforation, rupture, arterio-venous fistula, pseudoaneurysm, hematoma, irreversible nerve injury, compartment syndrome, percutaneous closure device failure) leading to death, major bleeding*, visceral ischemia or neurological impairment • Distal embolization (non-cerebral) from a vascular source requiring surgery or resulting in amputation or irreversible end-organ damage • The use of unplanned endovascular or surgical intervention associated with death, major bleeding, visceral ischemia or neurological impairment **Minor Vascular Complications:** • Access site or access-related vascular injury (dissection, stenosis, perforation, rupture, arterio-venous fistula, pseudoaneurysm, hematomas, percutaneous closure device failure) not leading to death, major bleeding*, visceral ischemia or neurological impairment • Distal embolization treated with embolectomy and/or thrombectomy and not resulting in amputation or irreversible end-organ damage • Any unplanned endovascular stenting or unplanned surgical intervention not meeting the criteria for a major vascular complication

Percutaneous Closure Device Failure:

• Access site or access-related vascular injury (dissection, stenosis, perforation, rupture, arterio-venous fistula, pseudoaneurysm, hematomas, percutaneous closure device failure) not leading to death, major bleeding*, visceral ischemia or neurological impairment

• Distal embolization treated with embolectomy and/or thrombectomy and not resulting in amputation or irreversible end-organ damage

• Any unplanned endovascular stenting or unplanned surgical intervention not meeting the criteria for a major vascular complication

Vascular Complications:

• Major vascular complications:

– Hematoma at the access site > 6 cm;

– Retroperitoneal hematoma;

– Arterio-venous fistula;

– Symptomatic peripheral ischemia/nerve injury with clinical signs or symptoms and lasting > 24 hours;

– Vascular surgical repair at catheter access sites;

– Ipsilateral deep vein thrombus; or

– Access site-related infection requiring intravenous antibiotics and/or extended hospitalization.

Device Failure

Device failure, defined as the absence of device success, is subclassified as:

- Delivery failure (i.e., technical failure)
- Structural failure: the device does not perform as intended due to a complication related to the device (e.g., fracture,

migration or embolization, frozen leaflet, device detachment, and so on)

- Functional failure: the device performs as intended without complication but does not adequately reduce the degree of MR (MR . moderate [2+], or fails to relieve or creates new mitral stenosis [EROA ,1.5 cm2 or transmitral gradient .5 mm Hg]).

Specific device-related technical failure issues and complications Paravalvular leak

Paravalvular leak

- Major: moderate or severe (2+, 3+, or 4+), or associated with haemolysis, or requiring intervention or surgery
- Minor: trace or mild (1+), without haemolysis

Iatrogenic atrial septal defect

- Major: significant left-to-right shunt (Qp:Qs ≥2:1) or symptomatic requiring the need for closure
- Minor: nonsignificant shunt that is still present at ≥6 months

Coronary vessel compression or obstruction

- Angiographic evidence of any reduction in coronary artery luminal diameter or coronary sinus diameter due to either external compression, thrombosis, embolism, dissection, or other cause, subclassified as:
    - Major (≥50% diameter stenosis) or minor (<50%)
    - Symptomatic or not
    - Requiring treatment or not
    - Transient (intraprocedural only, resolved at procedure end) or persistent

Pericardial effusion

- Major: leading to cardiac tamponade or requiring intervention
- Minor: not leading to cardiac tamponade and not requiring intervention

Conversion to open mitral valve surgery during a transcatheter procedure, subclassified as

- Secondary to mitral valve apparatus damage or dysfunction, requiring surgical valve repair or replacement, or
- Secondary to procedural complications (such as cardiac perforation, removal of an embolized device, and so on)

Device malpositioning

- Ectopic device placement: permanent deployment of a device in a location other than intended
- Device migration: after initial correct positioning, the device moves within its initial position but not leading to device embolization
- Device embolization: the device moves during or after deployment such that it loses contact with its initial position

Device detachment

- Partial: detachment of part of the device from the initial position without embolization
- Complete: detachment leading to device embolization or ectopic device placement

Device fracture

- Major: a break, tear, perforation, or other structural defect in the device (stent, housing, leaflet, arm, and so on) resulting in device failure, resulting in recurrent symptoms, or requiring reintervention, or
- Minor: a break, tear, perforation, or other structural defect in the device (stent, housing, leaflet, arm, and so on) not resulting in device failure, not resulting in recurrent symptoms, and not requiring reintervention

Damage to the native mitral valve apparatus

- Chords
- Papillary muscles
- Leaflets
- Mitral annulus

Interaction with non-mitral valve intracardiac structures

- Left ventricular outflow tract obstruction (gradient increase ≥10 mm Hg from baseline)
- Aortic valve regurgitation (≥ moderate or 2+)
- Other

Device thrombosis, defined as any thrombus attached to or near an implanted valve, subclassified as:

- Major: occludes part of the blood flow path, interferes with valve function (e.g., immobility of 1 or more leaflets), is symptomatic, or is sufficiently large to warrant treatment, or
- Minor: incidental finding on echocardiography or other

imaging test that is not major

Endocarditis

Any 1 of the following:

- Fulfilment of the modified Duke endocarditis criteria[11], or
  - Evidence of abscess, paravalvular leak, pus, or vegetation confirmed as secondary to infection by histological or bacteriological studies during an operation or autopsy.
    - Should be further subclassified by organism, and early (<1 yr) vs. late (≥1 yr)

Haemolysis

- The presence of a paravalvular leak on transoesophageal or transthoracic echocardiography plus anaemia requiring transfusion plus increased haptoglobin and/or LDH levels; should be confirmed by a haematologist

Other device-specific endpoints

- The number of devices (e.g., clips, neochords) used by intent to achieve the desired reduction in MR
- The need for unplanned use of additional devices (e.g., valves, clips, neochords) as a result of failed device delivery, device detachment, device fracture, or other device system failure
- If surgery is required, inability to perform mitral valve repair because of the presence of or anatomic changes from the device

Appendix 3: NYHA FUNCTIONAL CLASSIFICATION

The Criteria Committee of the New York Heart Association.[10]

NYHA FUNCTIONAL CLASSIFICATION	
Class I:	Subjects with cardiac disease but without resulting limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnea, or anginal pain.
Class II:	Subjects with cardiac disease resulting in slight limitation of physical activity. They are comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnea, or anginal pain.
Class III:	Subjects with cardiac disease resulting in marked limitation of physical activity. They are comfortable at rest. Less than ordinary activity causes fatigue, palpitation, dyspnea, or anginal pain.
Class IV	Subjects with cardiac disease resulting in inability to carry on any physical activity without discomfort. Symptoms of heart failure or the anginal syndrome may be present even at rest. If any physical activity is undertaken, discomfort is increased.

Kansas City Cardiomyopathy Questionnaire (KCCQ-12)

The following questions refer to your **heart failure** and how it may affect your life. Please read and complete the following questions. There are no right or wrong answers. Please mark the answer that best applies to you.

1. **Heart failure** affects different people in different ways. Some feel shortness of breath while others feel fatigue. Please indicate how much you are limited by **heart failure** (shortness of breath or fatigue) in your ability to do the following activities over the past 2 weeks.

Activity	**Extremely** Limited	**Quite a bit** Limited	**Moderately** Limited	**Slightly** Limited	**Not at all** Limited	Limited for other reasons or did not do the activity
a. Showering/bathing	O	O	O	O	O	O
b. Walking 1 block on level ground	O	O	O	O	O	O
c. Hurrying or jogging (as if to catch a bus)	O	O	O	O	O	O
	1	2	3	4	5	6

2. Over the past 2 weeks, how many times did you have **swelling** in your feet, ankles or legs when you woke up in the morning?

Every morning	3 or more times per week but not every day	1-2 times per week	Less than once a week	Never over the past 2 weeks
O	O	O	O	O
1	2	3	4	5

3. Over the past 2 weeks, on average, how many times has **fatigue** limited your ability to do what you wanted?

All of the time	Several times per day	At least once a day	3 or more times per week but not every day	1-2 times per week	Less than once a week	Never over the past 2 weeks
O	O	O	O	O	O	O
1	2	3	4	5	6	7

4. Over the past 2 weeks, on average, how many times has **shortness of breath** limited your ability to do what you wanted?

All of the time	Several times per day	At least once a day	3 or more times per week but not every day	1-2 times per week	Less than once a week	Never over the past 2 weeks
O	O	O	O	O	O	O
1	2	3	4	5	6	7

5. Over the past 2 weeks, on average, how many times have you been forced to sleep sitting up in a chair or with at least 3 pillows to prop you up because of **shortness of breath**?

Every night	3 or more times per week but not every day	1-2 times per week	Less than once a week	Never over the past 2 weeks
O	O	O	O	O
1	2	3	4	5

6. Over the past 2 weeks, how much has your **heart failure** limited your enjoyment of life?

It has **extremely** limited my enjoyment of life	It has limited my enjoyment of life **quite a bit**	It has **moderately** limited my enjoyment of life	It has **slightly** limited my enjoyment of life	It has **not limited** my enjoyment of life at all
O	O	O	O	O
1	2	3	4	5

7. If you had to spend the rest of your life with your **heart failure** the way it is right now, how would you feel about this?

Not at all satisfied	Mostly dissatisfied	Somewhat satisfied	Mostly satisfied	Completely satisfied
O	O	O	O	O
1	2	3	4	5

8. How much does your **heart failure** affect your lifestyle? Please indicate how your **heart failure** may have limited your participation in the following activities over the past 2 weeks.

Activity	**Severely** Limited	Limited **quite a bit**	**Moderately** limited	**Slightly** limited	**Did not** limit at all	Does not apply or did not do for other reasons
a. Hobbies, recreational activities	O	O	O	O	O	O
b. Working or doing household chores	O	O	O	O	O	O
c. Visiting family or friends out of your home	O	O	O	O	O	O
	1	2	3	4	5	6

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