BAYLOR SCOTT & WHITE RESEARCH INSTITUTE
Baylor Scott & White the Heart Hospital Plano
Cardiac Surgery Specialists Clinic

PARTICIPATION EXPLANATION AND CONSENT FORM

PROJECT TITLE: Surgical Implantation of **TRA**ns catheter va**L**ve in native mitral annular calcification (SITRAL) Study

PRINICIPAL INVESTIGATOR (PI): Robert Smith, MD

TELEPHONE NUMBER: 469-800-6200

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 this study is about and how it will be done. It will tell you about some problems that might happen during this study. It will also tell you about the good things that might happen for you during this study. When you read and sign a paper like this to learn about a study it is called "informed consent." The people who are doing this study 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 annular calcification (MAC – is a common deterioration or decline of the valve) with mitral stenosis (is a narrowing of your valve opening) and/or regurgitation (a leaky valve) 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 annular calcification (MAC) associated with mitral stenosis and/or regurgitation who are at high-risk for mitral valve surgery or deemed inoperable due to the extent of calcification.

What is the Status of the Devices Involved in This Study?

The Edwards SAPIEN 3 valve is currently approved by the US Food and Drug Administration for other treatments, but is not approved for the disease in this study, so it is considered investigational in this study.

IRB NUMBER: 016-100
IRB APPROVAL DATE: 10/21/2021
IRB EXPIRATION DATE: 10/20/2022

How Many People Will Take Part In This Study?

About 30 people will take part in this study at seven sites nationwide. About 10 of these people will take part at this location.

What Is Involved In This Study?

The following information will be collected for all study subjects prior to procedure.

- Medical History and Physical Exam including Cardiac Medications
- Blood tests (about 2-3 teaspoons)
- Society of Thoracic Surgeons (STS) Risk Score Assessment
- Heart catheterization (this procedure uses a flexible tube put into a blood vessel in your arm, upper thigh or neck and passed to your heart to diagnose and treat some heart conditions) 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) (this is a test that measures how well your lungs breathe in and breathe out air). If you have a history of lung disease.
- 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)
- A serum pregnancy test will be done on women of child bearing age to confirm that they are not pregnant

What Happens During This 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 or the middle of your chest 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 (the part of your valve that opens and closes to allow blood flow) and the study doctor will choose a 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 leaking around the valve), you will be weaned from the "heart lung machine" and transferred to the ICU for further care.

Total procedure time is defined as the time from skin incision to the time of skin incision access closure. The following invasive hemodynamic (continuous monitoring of the movement of blood and the pressures being exerted in the veins, arteries, and chambers of the heart) data will be collected pre and post implant:

- Transesophageal echocardiogram assessments (TEE - a flexible tube about ½ inch is guided down your throat to look at your heart valves and chambers, this takes about 40 minutes):
    - Mitral valve gradients (this assesses the overall function of your heart and will take about 40 minutes)
    - Quantify severity of mitral regurgitation (how bad is your heart valve leaking)
    - Left ventricular outflow tract (LVOT) width in millimeters (mm) and gradient
    - Presence of other valvular heart disease
    - Left ventricular ejection fraction (measurement of your heart pump)
    - central or paravalvular mitral regurgitation
    - transmitral gradient
- Cardiac output (blood flow) 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 listed 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 data that are 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.

Additionally, your doctor may put you on a blood thinning medication for at least 3 months after your valve surgery. You may require frequent lab testing (may be as often as once per week) with this medication to make sure it is appropriately thinning your blood.

Thirty 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 day 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:

The following data will be collected for all study subjects at 6 months (within 30 days before or after the 6 month date)

- 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

Twelve Month Follow-Up Visit

The following data will be collected for all study subjects at 12 months (or up to 60 days after the 12 month date)

- 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 This 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 this study, we encourage you to talk to the researcher and your regular doctor first.

What Are The Risks of This Study?

While on this 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. There also may be other reactions that we cannot predict. These unknown reactions could also be to your unborn child if you are pregnant or become pregnant while on this study.

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);
- increased risk of bleeding related to administration of blood thinning medication
- 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)

Or

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 your reproductive status has been confirmed by a follow-up hormone level assessment.

Other research study procedure risks:

- Possible nausea and vomiting from general anesthesia
- 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 this study. You will be monitored throughout the study in order to minimize risks.

Radiation Risks

While in this study, you will receive several diagnostic imaging procedures that involve exposure to radiation. Some of these procedures are research indicated. This means that you may not have had these procedures if you were not enrolled in this study. Over the course of this study, you may receive:

- up to 3 chest CTs (also known as CAT scans)
- Up to 4 Chest X-ray exams
- Fluoroscopy (movie-like x-ray imaging of your body) during your right heart catheterization

You may be wondering if this amount of radiation exposure carries any additional risk of cancer in the future.

- The State and Federal government has established yearly limits of radiation exposure for people (radiation workers) who work around radiation every day. There has been no increased rate of cancer for radiation workers compared to others.
- If enrolled in this study, the additional radiation exposure from the tests will result in you receiving up to slightly more than one third of the annual radiation exposure limit for a radiation worker.
- At this level of radiation exposure, your increased risk of cancer due to the radiation is very low.
- Please also note that this is a long-term risk. That is, cancers that are known to be caused by radiation generally do not appear for 5 to 50 years after the exposure.

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 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 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 This 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 this 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 Baylor Scott & White Research Institute (BSWRI) and your doctors and other health care providers and facilities that have provided services to you, which could include physicians that work for the Scott & White Clinic, HealthTexas Provider Network or Texas Oncology, P.A., Baylor University Medical Center, Scott & White Medical Center – Temple and other health care providers depending on where you have received care (collectively, "Your Health Care Providers") 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 this 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 BSWRI and Your Health Care Providers to give other people information about your health as needed for the research project. These groups include people who work for BSWRI (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 this sponsor of this study: Baylor Scott & White Research Institute, Baylor Scott & White Research Institute Imaging Core Lab, and Edwards Life Sciences. 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 include notes and other information in your medical records from Your Health Care Providers. We may ask for these notes and other information in your medical records from Your Health Care Providers. This means that the records of your care and information about you maintained by Your Health Care Providers may be given to the people mentioned above and, by signing this form, you are agreeing that Your Health Care Providers may release this information to these people.

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 BSWRI and Your Health Care Providers 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 this research study.

If you give permission to BSWRI and Your Health Care Providers to give other people information about your health and the other people are not part of the group that must obey the privacy 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 BSWRI in writing at 3434 Live Oak St, Dallas, TX 75204. Please be sure to tell us the name of this study and the PI for this study for which you are withdrawing permission. BSWRI will provide your withdrawal notice to Your Health Care Providers promptly after BSWRI receives your withdrawal notice. While not required, you should also talk with your PI and Your Health Care Providers and make sure they are aware you are withdrawing your permission. If you decide to do this, it will not apply to information that was given to others by BSWRI before you withdrew or to information given to others by Your Health Care Providers before Your Health Care Providers receive your notice of withdrawing your permission. If you withdraw your permission and you will no longer be able to take part in this study.

You may not be allowed to look at your health information during this study. However, at a later time, you will be able to look at this information. This later time will be sometime after this study is completed.

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

A description of this clinical trial will be available on www.ClinicalTrials.gov, as required by U.S. Law. This Web site will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this Web site at any time.

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 Baylor Research Institute 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, Edwards Life Sciences 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, Robert Smith, MD at (469) 800-6200.

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 Lawrence R. Schiller, M.D., IRB Chair, at 214-820-2687.

Statement of Person Obtaining Consent:

I have explained to [redacted] 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.

[redacted] [redacted] [redacted]

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.

[redacted] 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.

[redacted] [redacted] [redacted]

Signature of Subject Date Time