ON-X LIFE TECHNOLOGIES, INCORPORATED

INVESTIGATIONAL PLAN

ON-X® PROSTHETIC HEART VALVE

17mm AORTIC

23mm MITRAL

CONFIDENTIAL

SPONSOR

ON-X LIFE TECHNOLOGIES, INC.

1300 EAST ANDERSON LN, BLDG. B

AUSTIN, TEXAS 78752

September 29, 2017

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1.0 PURPOSE

The purpose of the proposed study is to assess the safety and efficacy of the 17mm On-X Aortic Prosthetic Heart Valve when used to replace diseased aortic valves and the 23mm On-X Mitral Prosthetic Heart Valve when used to replace diseased mitral valves in human subjects.

The On-X 17mm aortic valve will be implanted in approximately 20 and at least 15 patients and will be followed for 1 year. Enrollment of On-X 23mm mitral valve patients has been discontinued due to low enrollment potential. Follow-up of enrolled patients will continue according to the protocol for 1 year.

2.0 PROTOCOL

This study is prospective. All centers will follow a common protocol in which eligible patients will be asked to participate in the 1-year follow-up of the On-X valve. The objective of the trial is to establish the clinical safety and effectiveness of the size 17mm aortic valve. It is expected that 20 centers from both within and outside the United States implanting between 1 to 2 valves will be involved. The number enrolled at a single center will depend entirely on the study as a whole reaching the required 15 patients. A copy of the investigator's agreement for the trial is contained in Appendix D.

Valve safety:

- Although sample size will limit the value of event rate calculations, early (30-day) and late time-related incidence and associated rate of all deaths and each valve related cardiovascular complication will be determined. Adverse events are those defined by the STS/AATS definitions[(1)], as well as all other cardiovascular complications. Rates of valve thrombosis, thromboembolism, hemorrhage (both all and major), endocarditis, hemolysis, hemolytic anemia, mortality, reoperation, valve explantation and prosthetic valve dysfunction (structural, non-structural and paravalvular leak (both all and major)) are primary safety endpoints to be evaluated using both linearized and actuarial statistical methods.
- Hemolytic potential of the valve will be measured using a CBC, reticulocyte count, serum haptoglobin, serum lactate dehydrogenase and plasma free hemoglobin.

Valve effectiveness:

- Functional status changes will be assessed using classification nomenclature developed by the New York Heart Association (NYHA). The assessment

shall include proportions within class and cross tabulation of changes over time.

- Hemodynamic performance of the valve will be determined by echocardiography. The following specific parameters will be evaluated using standard descriptive statistics: peak and mean pressure gradients, effective orifice area (EOA), cardiac output (CO), valvular regurgitation and indices of EOA and CO to body surface area (BSA), and performance index of EOA to geometric orifice area (GOA).

Valve safety and effectiveness will be compared by valve position to corresponding historical controls contained in the clinical results presented in the original PMA for other size On-X valves (P000037 and P000037/S001). The trial is designed specifically to meet the criteria established by ISO[(2)] and recognized by FDA for clinical trials of a single size of a prosthetic heart valve. The data will be used to obtain and maintain appropriate regulatory approvals where needed.

2.1 STUDY DESIGN (SAMPLE SIZE)

Patients meeting all the appropriate criteria will be recruited for clinical trial participation. Enrollment is non-randomized, and continues until the sample size requirement is met, unless the sponsor terminates the clinical trial early for unforeseen reasons.

Submission for premarket approval in the U.S. will occur after international standards criterion of at least 15 patients will be followed for one year. This follow-up will include echocardiography, blood damage, NYHA status and any adverse events.

2.2 PATIENT POPULATION AND SELECTION CRITERIA

The indications for replacement of a patient's natural or prosthetic valve will be those which the principal investigator follows in his routine practice of cardiovascular surgery.

The following are criteria for <u>inclusion</u> of patients in this study:

1. Patients of any age; unless waived by local IRB assent of the patient and in all cases consent of parent or legally authorized representative is required if a patient is under the age of majority and not legally emancipated.
2. Patients who are sufficiently ill to warrant replacement of their diseased natural or prosthetic valve, based on standard cardiovascular diagnostic workups.
3. Patients who are in sufficient satisfactory condition, based on the physical exam and investigator's experience, to be an average or better operative risk, (i.e., likely to survive one year postoperatively).
4. Patients who require an isolated aortic valve replacement size 17 mm.
5. Patients who are geographically stable and willing to return to the implanting center for follow-up visits.

6. Patients or legally authorized representatives who are adequately informed of their participation in the clinical study and what will be required of them in order to comply with the protocol.
7. Patients requiring concomitant cardiovascular surgery, such as coronary bypass may be included in the study.

The following are criteria for exclusion of patients from this study:

1. Patients who are pregnant, planning to become pregnant or are lactating.
2. Patients who have a noncardiac progressive disease, which in the investigator's experience produces an unacceptable increased risk to the patient.
3. Patients who have a documented history of substance (drug or alcohol) abuser or are prison inmates.
4. Patients with a previous prosthetic valve, where it is not being replaced by a study valve, or patients requiring multiple valve replacement.
5. Patients with active endocarditis or active myocarditis.
6. Patients who require mitral, tricuspid or pulmonic valve replacement.
7. Patients who have not agreed to return for the required number of follow-up visits or who are geographically unavailable for follow-up.
8. Patients who cannot be maintained on long-term anticoagulant therapy.
9. Patients with non-cardiac illness resulting in a life expectancy of less than 1-year.
10. Patients previously enrolled and implanted in this trial may not re-enter after withdrawal.
11. Patients already enrolled in another investigational device or drug study (nor can enrolled patients be enrolled in other studies).
12. Patients with acute preoperative neurological deficit, myocardial infarction, or cardiac event who have not returned to baseline for at least 30-days prior to enrollment.
13. Patients with aortic aneurysm or other medical condition that creates a higher than usual risk of surgical complication.
14. Patients who are prisoners or mentally ill, and pediatric patients of assent age who are incapable of understanding their assent as judged by the principal investigator.

Patients are free to withdraw from the study at any time for any reason without prejudicing their medical care. Surviving patients who have their valve explanted for any reason will also be considered withdrawn. There are no other anticipated reasons for withdrawal from the study.

At each center, patient recruitment will occur in the following manner. Determine whether or not the patient is eligible to receive the On-X valve by assessing if the patient meets the selection criteria. If the patient is eligible, discuss all aspects of the On-X clinical trial requirements and invite the patient or patient's legally authorized representative to participate. If the patient or representative agrees to participate, obtain informed consent and enroll the patient in the clinical trial. All patients who might receive a small valve should be consented even though a larger valve may be used based on findings during surgery. This may create some screen failures but will avoid losing potential patients in what is expected to be a small patient group overall.

Recruitment will continue until the overall study has reached its patient enrollment requirements.

2.2.1. Screen Failures

The principal investigator will select patients to approach for enrollment based on his professional judgment using all available preoperative data. It is not expected that large patients (body surface area (BSA) >1.8M^2) or patients with echo finding of native valve diameters greater than 19mm aortic will be screened as candidates, but those with small body size <1.5M^2 or smaller than the above valve diameters by echo will be screened. All patients approached or evaluated for enrollment will be entered on the screening log contained in the case report forms in Appendix B. If prior to surgery the patient is dropped from consideration or during surgery a different valve is implanted, then the screen failure will be noted in the log with sufficient explanation to allow assessment of the cause of the screen failure and determination of affect on the study.

2.3 INSTITUTIONAL REVIEW AND INFORMED CONSENT

Institutional review through the appropriate standing committee of the clinical center (either Ethics Committee or Institutional Review Board) must be obtained as required by local rules, and a copy of the approval document must be supplied to the sponsor. A list is contained in Appendix F.

Informed consent must be obtained for each patient prior to participation in the clinical trial in accordance with local rules. As this study includes some pediatric patients, consent shall include assent of the patient as well as consent of his/her parent or legally authorized representative whenever such patient is recruited. Assent may be waived by the local IRB if the patient is incapable due to age, maturity or psychological state. Local IRB rules or individual case review can be used to determine if waiver is appropriate, which if not addressed in the IRB approval document must be obtained case-by-case. It is the responsibility of the principal investigator to obtain such waiver prospectively as needed. A copy of the informed consent should be provided to the patient or representative and they should be encouraged to review it. It is recommended that the informed consent be reviewed as part of the preoperative procedures with prospective enrollment. An example informed consent document is in Appendix C.

Each clinical center must have a staff echocardiologist responsible for conduction of the echocardiographic portions of this study. Additionally, coagulation profiles are to be reported as the international normalized ratio (INR), and hemolysis study blood samples must be sent to a local laboratory and the laboratory normal ranges must be supplied to the sponsor.

This study also requires that copies of all echocardiography electronic recordings be sent to the sponsor for review.

2.3.1 Collaborating Parties

Core cardiology laboratory and cardiologist – Department of Echocardiography, Guy's and St. Thomas' Hospital Trust, London, England – Dr. John Chambers.
Duties: Echo consulting, review and calculations.

Core pathology laboratory and pathologist – Clinical Pathology Laboratories, Austin, Texas – Dr. Mark Silberman.
Duties: Explant pathology analysis and report.

Data Safety Monitoring Board –
Surgeons: Dr. Sidney Levitsky, Harvard University, Dr. Richard Engelman, University of Massachusetts
Cardiologist: Dr. Karen Hamilton, University of Florida
Statistician: Dr. Jay Herson, Johns Hopkins University

Duties: Review of study progress, adjudication of adverse events, recommendations about study continuation or termination. Meetings to be held at least annually by conferencing methods or in person.

2.4 INVESTIGATIONAL PROCEDURES

The sponsor will provide case report forms (CRFs) to each principal investigator for the purpose of recording patient data. Assessments will be obtained for the preoperative, operative/discharge period and postoperatively at three to six months and one year from the date of implant (Table 2.4.1 summarizes the required information at each visit).

Table 2.4.1 - Patient Progress and Data Record

Form/Data	Preoperation	Operation	Interval of Early/discharge	Follow-up 3-6 Month	1 Year
Preoperative Form CRF 1	X				
Echocardiography CRF 2	X		X	X	X
Echo Recordings	X		X	X	X
Blood Sample to Lab	O			X	X
Implantation Data Card		X			
Operative Form CRF 3		X			
Early Follow-up CRF 4			X		
Late Follow-up CRF 4				X	X
Complication CRF 5		O	O	O	O
Reoperative CRF 6		O	O	O	O
Death Summary/ Autopsy		O	O	O	O
Explant Summary		O	O	O	O

X	Required	Data
O	Required	only if needed
	Not	applicable

All appropriate sections of the CRFs must be filled out accurately and completely. Echocardiography recordings are to be forwarded to the sponsor for eventual assessment by a core cardiologist. All case report forms must be reviewed, signed and dated by the investigator(s). The CRFs should be sent expeditiously to the sponsor, when completed, and be kept in the patient record notebooks. Blood samples for hemolysis assessment are to be properly forwarded to the laboratory, per its protocol.

To protect patient confidentiality, the sponsor will use the information from the CRF's for statistical and device tracking purposes only and will treat medical records as confidential. For this reason, the sponsor is not routinely collecting patient names, but using patient initials for patient identification; thus better protecting patient confidentiality. A representative of the U.S. Food & Drug Administration or other appropriate regulatory authority may look at, and perhaps copy, some of the medical records; these organizations also have rules for protection of patient privacy that they must follow.

2.4.1. Preoperative Procedures

The investigator will determine and document on CRFs whether each patient meets the selection criteria previously outlined before enrollment into the study. He will also obtain informed consent for study participation from each patient prior to enrollment. A copy of the informed consent form will be kept by the investigator in the patient's study notebook. Patients not meeting the selection criteria or not receiving informed consent **should not** be enrolled in the study.

The investigator will determine and record on CRF1 each patient's demographics and relevant medical history, i.e., New York Heart Association (NYHA) functional class, cardiac rhythm, preoperative conditions, and diagnosis for valve replacement, etc. A preoperative echo/Doppler evaluation of the valve(s) being replaced is required according to the procedures of this study; a cardiac catheterization is not requested.

Blood studies on each patient will include: white blood cell count, red blood cell count, hemoglobin, hematocrit, serum lactate dehydrogenase (with fractionation by isoenzymes if above normal), plasma free hemoglobin, reticulocyte count, and haptoglobin. This will be recorded preoperatively, if possible, and at both follow-up intervals. The laboratory report including normal ranges will suffice as a CRF for these tests.

Specific Instructions for Form CRF1

These instructions are made to assist the study coordinator in filling out the form. Complete all items on the form. If information is unavailable to answer any item, make a note on the form. When asked to specify a particular answer, use a short description. On all check off lists, the space to be checked is either in front of, or below the answer. Please check any and all items that apply to the patient.

For patient study ID use patient initials. NYHA functional class uses the generally familiar nomenclature of that association. For the purposes of this study the commonly used classes of IIa and IIb are not used, either subgroup is considered class II. For infants and toddlers the Ross Scale functional classification can be substituted for NYHA classification anytime this data element is requested.

Previous cardiovascular surgery, and for pediatric patients pediatric comorbidities, should be noted with a one or two word name of surgery and the date performed (page 2 of CRF1). Room is given for three prior procedures. Attach a separate explanation if more prior surgery was done. For coronary artery bypass surgery, please note the number of grafts by the following notation: CABG x 2 = double graft; CABG x 3 = triple graft; and so on.

If the patient has been maintained on any permanent, preoperative anticoagulant therapy, the most recent available preoperative INR should be measured and recorded.

2.4.2 Operative Procedures

The surgical technique employed is that developed and perfected by the principal investigator in his normal practice of cardiac surgery. Operative details such as cardioplegia are not specified in the protocol.

An echo/Doppler assessment of the study valve(s) is required on each patient just prior to discharge (CRF2). The echocardiography tapes will also be provided to the sponsor, each echo exam on each patient will be recorded on a separate tape.

The investigator will record on CRF3 information regarding the particular valve(s) implanted and other details concerning the surgery such as suture technique and any concomitant procedures. The implantation data card contained in the valve package will be provided to the distributor within 24 hours of the surgery.

Specific Instructions for Form CRF3

Use the patient study ID assigned on the preoperative form (CRF1) to identify the patient. Check any and all of the items that apply to this patient. Where explanations are needed, print a brief description of the required data.

Carefully record the valve position, size and serial number. For concomitant procedures, there are spaces for these additional procedures. Write in the name of the procedure done. For coronary artery bypass grafting, also note the number of grafts (i.e., CABG x 2 = double graft, CABG x 3 = triple graft, and so on).

Where requested, attach additional CRFs or reports. Also any appropriate intraoperative hemodynamic evaluation form, or complication form is required.

2.4.3 Early Postoperative/Discharge Procedures

The investigator will record the date of the patient's discharge from the hospital and the date of the early follow-up examination on CRF4. The discharge follow-up exam records the patient's status at the time of discharge or at 30 days, whichever comes

first. The patient's NYHA and cardiac rhythm status and any complications will be noted along with the patient's antithromboembolic therapy. It is important to record the international normalized ratio (INR) at the time of the exam. Wherever possible this value should be within the therapeutic range described below **before** a patient is discharged from the hospital.

Mechanical heart valve recipients should be maintained continuously on anticoagulant therapy, except where contraindicated. Postoperatively, the continuous warfarin (tradename Coumadin®) therapy shall maintain the following therapeutic levels of INR: 2.0 to 3.0 for aortic valves. These procedures generally follow guidelines published by various medical societies.

Preoperative echocardiograms on the dysfunctional valve being replaced, predischarge, 3-6 month and one year postoperative Doppler echocardiograms on the study valve are required for each patient. At each postoperative assessment, the investigator will need to determine the patient's availability for future follow-up. If any patient needs to be seen at other than a regularly scheduled follow-up visit, the same follow-up information as required at regular times will be documented by the investigator on the follow-up form, and that follow-up will be indicated as an interim visit.

2.4.4 Late Follow-up Reporting

Late follow-up is required in the 3-6 month postoperative interval, and at 1-year (between 11 and 14 months postoperatively). Follow-up must be in person; telephone or questionnaire follow-up is unacceptable. A late follow-up form (CRF4) is due at each follow-up on each patient whether or not follow-up has occurred.

Late follow-up information includes in all cases the patient ID, cardiac rhythm (from electrocardiogram or echocardiogram), NYHA classification, and anticoagulant therapy information, including INR. Blood samples shall be drawn and forwarded to the local laboratory at each regularly scheduled late follow-up. These samples are the same as the preoperative tests and are handled in the same manner. Echocardiography studies are required at the 3-6 month and 1-year follow-up. Those data should be included at that time, but should also be added when done optionally at any other follow-up. For any new complication, a complication report (CRF5) must be completed and attached. All complications that have occurred between follow-up examinations must be reported on the appropriate form.

2.4.5 Complication Reporting

All complications should be recorded by the investigator on the proper complication form, CRF5. Start and stop dates and etiology should be noted. The investigator will attempt to evaluate the relationship of all deaths, reoperations, explants, or cardiovascular complications to the study valve as presented in the AATS/STS guidelines[1] and will provide pertinent details of the event on the CRF. Copies of autopsy report and/or death summary must be included where applicable. Every effort should be made to return any explanted valve(s) (at autopsy or reoperation) to the

sponsor, see section 2.4.8. Please complete CRF6. Return kits for explanted valves can be provided by the sponsor.

The investigator will report any serious or unexpected complication occurring during the investigation to the monitor within 24 hours, followed by a written report in ten working days, after the investigator first learns of the event. A serious or unexpected complication would include those complications not generally expected in a heart valve patient.

Adverse events are defined by the United States FDA as complications, meaning:

"Operative mortality, morbid events, and consequences of morbid events. Complications may or may not be device related."

According to the European EN 540, an adverse event is defined as:

"Any undesirable clinical occurrence in a subject whether it is considered to be device related or not."

This study uses the term "complication" to mean any adverse event or adverse device effect (a device-related adverse event), which may be mild, moderate, or severe. If as a result of a complication during a clinical investigation a subject has to be hospitalized, if hospitalization is unduly prolonged because of potential disability, if hospitalization is unduly prolonged because of potential danger to life, if a reoperative intervention has been necessary, or if the event is terminal, the complication is regarded as severe.

The definitions which appear in the following sections will be used to report complications associated with the use of the On-X prosthesis. Complications will be recorded and dated when they are observed or estimated to have occurred and treatment(s) documented. An event will be recorded once unless there are multiple occurrences of that event. For example, a cerebrovascular accident (CVA) reported once with sequelae still present at subsequent follow-visits will not be reported again. If another CVA occurs that is unrelated to the initial episode, then it is reported as a separate incident.

When determining whether a complication is valve related this study will use the definitions of the AATS/STS guidelines[1]. More specific guidance on these determinations is contained in the following discussions of the various types of complications. In any case, adequate documentation must be supplied to support the contention that a complication generally regarded as valve-related is not valve related. Information that pertains to reoperation, explant, and death must be recorded on the appropriate sections of CRF5 and/or 6. For death, the cause of death must be established, and an autopsy performed when possible. An explant analysis must be conducted in all cases when a valve is explanted whether by reoperation or autopsy. Attach supporting hospital reports when appropriate. Following completion of the information, the investigator must review, date, and sign the CRF.

Specific Instructions for Completing CRF5.

The complication form (CRF5) allows the identification of event type, and how each event was diagnosed and treated; what the outcome of the complication was; and what the patient's status at the time of the event was. Death from unrelated causes is also reported on CRF5. Details of any reoperation are given on a separate form (CRF6), which also asks for a description of any explant (from reoperation or autopsy). A separate CRF5 should be completed for each independent complication.

Study valve related reoperation is defined as any operation that repairs, alters or replaces a previously implanted study prosthesis, also included are operations that treat other valve related complications but do not involve surgery on this valve, i.e., surgery to resolve a hemorrhagic complication. This category also includes incidental replacement of the prosthesis, e.g., the patient undergoes surgery for a different cardiovascular procedure and the surgeon decides to remove the study valve. Cardiovascular surgical procedures other than repair or replacement of the study valve will also be recorded on the CRF5.

Death will be recorded as cardiac or not, and valve related or not. Valve related deaths include deaths from the following causes:

- thrombosis or thromboembolism;
- endocarditis;
- prosthetic valve dysfunction;
- anticoagulant related hemorrhage;
- hemolysis; and
- congestive heart failure, where documentation of a cause other than the valve cannot be given; and sudden unexplained death without autopsy which can definitely assign other causes than the valve.

Deaths caused by heart failure in patients with advanced myocardial disease and satisfactorily functioning prosthetic valves are not considered valve related. Any death that occurs within 30 days of reoperation for a valve related complication is considered valve related.

Classification of each complication is described in the sections that follow.

<u>Thromboembolism</u>

Thromboembolism is defined as any valve thromboembolus exclusive of infection. This includes any new focal or global neurological deficit (transient or permanent), myocardial infarction, prosthetic thrombosis, or peripheral arterial embolus.

A thromboembolic cerebrovascular accident (CVA) is an infarction of the central nervous system determined or suspected to be due to thromboembolism as diagnosed by imaging study with or without clinical symptoms.

A transient neurological event is defined as an abrupt onset of a focal neurological dysfunction caused by brain, spinal cord or retinal ischemia without acute infarction lasting at least one minute and no longer than 72 hours.

Intraoperative myocardial infarctions are not counted. Postoperative myocardial infarction is also not counted unless the infarction is caused by coronary embolus detected by operation, autopsy or clinical imaging. Emboli caused by non-thrombotic material (atherosclerosis, myxoma) are not counted.

Thrombi that are secondary to another primary complication; i.e., endocarditis, are recorded but also noted to be a secondary event by stating so in their etiology.

Excluded from the thromboembolism category are:

- Events which occur intraoperatively or within 24 hours of surgery due to myocardial infarction or stroke.
- Any peripheral arterial emboli proven to have originated from another cause, e.g., atrial myxoma.
- Failure to awaken from the surgical procedure.
- Pulmonary emboli.
- Events due to proven ischemic disease of the extremities.

However, if any of these complications occur, document the events anyway in the Complications Form.

For any thromboembolic event it is important to determine the INR of the patient at the time of the event, if possible. Every attempt should be made to do so.

Thrombosis

Thrombosis is any premortem thrombus adhering to or near the study valve that occludes part of the blood flow path or that affects valve function. This is listed as its own category and should be confirmed by reoperation (explant) or autopsy. Thrombolytic therapy, other than that used to stabilize a patient prior to surgery, is not recommended as a treatment for thrombosed valves. In this study suspected thrombosed valves are to be replaced through reoperation, wherever possible. Clinical judgment can be used to diagnose the presence of thrombosis (lack of normal prosthetic valve sound, prolonged lowered blood pressure, loss of consciousness, cardiovascular shock) if the clinical diagnosis is accompanied by a confirming medical test (echocardiography, cineradiography or angiography).

Bleeding Event

Bleeding Event is defined as any episode of internal or external bleeding in patients. Episodes immediately related to this surgery will be recorded as perioperative. This also includes any episode of hemorrhagic tamponade. The INR at the time of hemorrhage should be determined, if possible. These events will be classified as major or minor, and are defined as follows.

- Major: An episode of internal or external bleeding that causes death, permanent injury, operation, hospitalization, or requires transfusion or pericardiocentesis. Examples include nosebleeds that require outpatient transfusion, cerebral bleeding that results in neurological damage and/or death, and gastrointestinal bleeding that requires hospitalization.

- Minor: All other episodes of internal or external loss of blood. Examples include nosebleeds that do not require transfusion, hematomas due to trauma or surgery that do not require transfusion, and ocular hemorrhage. Bleeding or bruising from traumatic wounds are excluded, unless the bleeding goes uncontrolled enough to require intervention that would place the event in the major category.

Prosthetic Valve Endocarditis

Prosthetic valve endocarditis is defined as documented evidence of infection of the prosthesis based on histopathological evidence in a surgical or autopsy specimen and/or customary clinical criteria, including an appropriate combination of clinical signs (fever, new/altered cardiac murmurs, splenomegaly, systemic emboli, immunopathological lesions) and possibly positive blood cultures as available. The organism(s) involved should be identified whenever possible.

Prosthetic Valve Dysfunction

Prosthetic valve dysfunction is defined as any change in valve performance which results from intrinsic or extrinsic abnormalities that cause stenosis or regurgitation. Prosthetic valve dysfunction can be classified as structural deterioration, nonstructural dysfunction, or paravalvular leak.

a. Structural Valve Deterioration

Structural valve deterioration is any change in function of the prosthesis which results from an intrinsic abnormality that causes stenosis or regurgitation. The diagnosis can be based on an examination of the explanted or damaged valve or clinical investigation. Examples include excessive wear, leaflet escape, leaflet fracture, housing crack, leaflet pitting, or sewing ring deterioration. Excluded from this category is structural deterioration which results from endocarditis, paravalvular leak, and thrombosis.

b. Nonstructural Valve Dysfunction

Nonstructural dysfunction of the valve is any change in function of the prosthesis that results in stenosis or regurgitation which is not intrinsic to the valve. Examples

include patient-prosthesis mismatch, inappropriate positioning or sizing, leaflet entrapment by suture or pannus, paravalvular leak and hemolysis. The diagnosis should be based on examination of the damaged or explanted valve, or clinical investigation. Events to be excluded are those associated with endocarditis and thrombosis.

c. Paravalvular Leak

Any evidence of leakage of blood around the prosthesis between the sewing ring and native annulus. Diagnosis of paravalvular leak may be obtained from echocardiography; however, definitive diagnosis will be obtained at reoperation, explant, or autopsy. Indicate severity of the leak.

Indicate if the event is secondary to another valve-related complication, e.g., endocarditis, hemolysis, thromboembolism, thrombosis. Such events will be classified as major (required surgical or percutaneous intervention) or minor (does not require surgical or percutaneous intervention).

Hemolytic Anemia

Hemolytic anemia will be recorded as a complication in all cases of hemolytic anemia that are attributable to the valve, based on usual clinical criteria, such as easy fatigability, dyspnea, faintness, pallor, rapid pulse, low blood pressure or other common signs of anemia, and which require intervention: such as long-term iron supplement, transfusion, prosthesis replacement, etc. Indicate if hemolytic anemia is primary or secondary to another valve related adverse event (e.g., paravalvular leak). Events that are not considered valve-related are those due to liver disease, myocardial infarction, or systemic infection, where these causes are confirmed by other clinical evidence.

Hemolytic anemia that requires intervention will be considered to be clinically significant hemolytic anemia. Hemolytic anemia that does not require intervention will be considered to be clinically insignificant hemolytic anemia and will be reported. Hemolytic anemia should be distinguished from compensated hemolysis or compensated hemolytic state, where the hematocrit is stable and there is no anemia because increased red blood cell production is able to keep up with accelerated red blood cell destruction from hemolysis.

For purposes of this clinical trial, hemolysis is defined from blood studies alone by the following inclusive criteria, but is not reported as a complication until associated with anemia that is treated medically or surgically (i.e. clinically significant hemolytic anemia). Thus, hemolysis and clinically significant hemolytic anemia are analyzed separately.

Ongoing hemolysis:

- Serum lactate dehydrogenase greater than 200% of the upper normal limit;
- Reticulocyte count of at least 4.0%;

- Plasma free hemoglobin above upper limit of laboratory normal;
- Reduction of 20% in haptoglobin below normal range; and
- Untreated clinical sequelae (once treated this becomes hemolytic anemia).

Hemolytic anemia by laboratory test additionally requires:

- Hematocrit below laboratory normal range;
- Hemoglobin below the laboratory normal range;

Unanticipated Valve-Related Event

It is unknown what kind of event would qualify, but in case any unknown valve-related complication should arise that does not meet any other defined criterion, pleased record on the Complications Form. Should this happen this event must be reported to the monitor immediately, since it is likely to create immediate regulatory reporting requirements. An occurrence of an unknown negative effect is very serious and must not be left unreported for any length of time.

Congestive Heart Failure

Congestive heart failure will be considered valve related if the event is new and is not continued from a preoperative heart failure condition, and is caused by one of the following prosthesis-related events: Anticoagulant-related hemorrhage, endocarditis, hemolysis, nonstructural dysfunction, paravalvular leak, structural deterioration, thromboembolism, thrombosis, or reoperation.

The most common causes of non-valve related congestive heart failure are coronary artery disease, hypertension, valvular heart disease (due to a valve other than the study valve), cardiomyopathy, cor pulmonale, congenital heart disease, or unknown causes. When an event is considered not valve related the reasons for that decision must be recorded.

Other Cardiovascular and Pulmonary Complications

Other cardiovascular and pulmonary complications are defined as a complication or any new diagnosis that is not related to the prosthesis, but is important to subsequent morbidity and mortality of the patient, e.g., cardiomyopathy, aortic aneurysm, chronic obstructive pulmonary disease, pulmonary embolism. These events may be characterized by the following factors: necessity for intervention, new or unduly prolonged hospitalization, or death. Minor events of no importance to the patient's valve related morbidity or mortality, such as acute upper respiratory infections, should not be reported.

Other Non-Cardiovascular Complications

Neurological, gastrointestinal, hepatic, renal, and other complications are defined as a complication or any new diagnosis that is not related to the prosthesis but is important to subsequent morbidity and mortality of the patient, e.g., cerebrovascular accident,

transient ischemic attack, ulcer bleeding, hepatic disease, coagulopathy, kidney failure, infection. These events may be characterized by the following factors: necessity for intervention, new or unduly prolonged hospitalization, or death. Minor events of no importance to the patient's valve related morbidity or mortality, such as acute intestinal virus infections, should not be reported.

2.4.6 Echocardiography Procedures

In addition to preoperative echoes, echocardiographic evaluation of the study prosthesis **is required** when the patient is stable during the early postoperative follow-up (prior to discharge or 30 days, whichever occurs first); at 3-6 months and at the 1-year follow-up (between 11 and 14 months). Regurgitation and stenosis information is required for all remaining heart valves as these results may impact the study valve.

Preoperative echocardiography of the valves being replaced is required in this study. For preoperative echocardiographic data, the best available examination information will be used.

Record only one patient echocardiography examination per recording. Attach the following information to each recording:

- Patient study ID
- Name of the institution and investigator
- Date of the echocardiography examination

The echocardiography protocol used will generally follow that developed by FDA guidelines or ISO standards (Appendix A contains summary of the protocol), however, to provide a uniform method whereby data collection will be common to all echocardiography centers only one method will be used to derive the echo study output data. The derived data will conform to ISO standards. Additionally, only directly measured data will be provided by the center, and all calculated data will be derived centrally by the core lab. Regurgitation will be assessed by the investigator's echocardiographer and reassessed by the study cardiologist to provide for consistency across the centers.

Transthoracic echocardiographic examinations will follow a step-by-step progression of the following interrogation regions: left parasternal, apical and periapical, right parasternal, subcostal, and suprasternal. For each interrogation include 2D and M-mode recording for structure, function and timing data, and color Doppler for flow pattern to guide the pulsed (PW) and continuous (CW) Doppler measurements. It is understood that the right parasternal view is difficult to get in the immediate post-operative period. If needed, this view can be dropped from the early post-operative exam.

Specific Instructions for Completing CRF2

Provide the patient study ID and other basic information listed at the beginning of the form.

Using the echocardiography report from your center, provide the anatomical data collected from 2D or M-mode studies. Valve hemodynamics are to be gathered from the position giving the best signal. If the position used is different from those listed in the progressions noted in the previous section, then note the position used for either pressure or regurgitation measurement.

Provide the hemodynamic data requested on the form from the view that provides the best signal. Summarize the results of the echocardiography exam and forward the recording of the session to the monitor.

For the purposes of this study regurgitation will be graded as none, trivial, 1+ = mild, 2+ = moderate, 3+ = moderately severe, or 4+ = severe.

Subaortic diameter measurement should be made from the trailing edge of the left septal echo to the leading edge of the anterior mitral leaflet echo. If severe left ventricular hypertrophy or bowing of the anterior mitral leaflet exist, this measure should not be made and the space should be left blank on the CRF. If in pediatric patients this dimension cannot be reliably measured as judged by the core echocardiographer, the nominal valve tissue annulus diameter (i.e. 17mm for the aortic valve) will be used for aortic orifice area calculations and the orifice area calculation by continuity equation will be skipped for the mitral valve.

Diastolic filling period in this study is arbitrarily defined as the time from the onset of flow to when flow falls below 10 cm/sec. This allows calculation of transmitral flow.

2.4.7 Blood Studies for Hemolysis

Preoperatively and at each scheduled late follow-up the study protocol calls for blood studies to determine the level of hemolysis in the patient. The specific tests required are red cell count, white cell count, hemoglobin, hematocrit, plasma free hemoglobin, serum lactate dehydrogenase (SLDH), reticulocyte count, and serum haptoglobin. When SLDH is elevated above the upper end of normal, it is to be fractioned and quantified by its five isoenzymes.

Blood tests must be processed according to local requirements. Local laboratory normal ranges for all tests must be provided.

2.4.8 Explants

Whenever a valve reoperation occurs whether or not as a result of one of the complications described in Section 2.4.5 above complete and return CRF 6. Explants are requested at autopsy whenever practical. Reoperative explants may also occur. Return of explanted valves within the study is required.

Specific explant analysis requirements are included in this plan. An explanted mechanical valve prosthesis refers to a study valve that has been removed from the patient at reoperation or autopsy. The recommended procedures have been developed to ensure accuracy, consistency and completeness of the analysis of explanted valves. This section outlines in detail the procedures for explanting, recording data and returning the explanted valves.

Explanting the Valve

When explanting a valve at reoperation or autopsy:

1. Inspect the mechanical valve prosthesis prior to removal including the condition of the annulus for evidence of dysfunction such as thrombi, paravalvular leak, vegetations, pannus overgrowth. Culture of pertinent areas of the valve when appropriate is mandatory.
2. Examine the lining of the chambers of the heart, both proximal and distal to the valve for possible jet lesions or endocardial fibrosis.
3. Special attention should be paid to the possibility of extrinsic interference with the valve function, particularly by retained mitral valve leaflet tissue or sutures.
4. If possible, photograph the mechanical valve prosthesis *in situ*. For valves obtained at autopsy, photograph both the inflow and outflow aspects.
5. DO NOT rinse the valve.
6. Request an explant kit from the sponsor and place the valve in the jar provided in the explant kit.
7. If no explant kit is available, place the valve in either 1% glutaraldehyde solution or 10% buffered formalin until a kit is obtained.
8. Record observations on CRF6 in the appropriate locations.

Data and Shipping Requirements

To send the data and return the valve to study sponsor:

1) Attach a copy of the reoperative or autopsy report to the appropriate CRF6.
2) Attach any *in situ* photographs to CRF6.
3) Ship the valve as instructed in the explant kit, clearly marked as an explant, and inform the monitor by telephone or telefax of its shipment.
4) Notify your clinical research monitor if the valve cannot be returned.
5) If the valve is examined by a pathologist at the hospital where it was explanted, send that report to the monitor as well.

Each returned heart valve received by the sponsor (or monitor) will be tracked and analysis information compiled and stored. Each explant will be analyzed by the independent study pathologist and his/her report will be provided to the investigator and monitor.

2.4.9 Monitoring Procedures

The monitor of the study shall be a professional staff member of the Clinical Studies Department of the sponsor or a consulting Clinical Research Organization. Monitoring of the clinical trial will be a continuous process to ensure that high quality data are obtained through compliance with the investigational plan. Case report forms

or electronic data will be reviewed for accuracy, completeness, and conformity with requirements. Particular attention will be paid to blood damage studies, echocardiography and complication reporting. Frequent communication will be maintained with each clinical center to keep both the center and the sponsor informed and aware of the clinical trial progress.

On-site monitoring of all study centers will occur at least annually to ensure continued acceptability of the center by assessing compliance to the investigational plan, adherence to data collection procedures, verification of the accuracy of submitted clinical data to the patient's source documents, maintenance of clinical trial records, verification of informed consent, and verification of control of test articles. Reports of each center's visits will be provided to the investigator and sponsor, and if necessary, appropriate corrective action will be taken to ensure compliance to the investigation plan.

Preinvestigation Visit:

Preinvestigation visits will be conducted by the sponsor or sponsor representative to review the investigational plan and discuss the report of previous investigations with the investigator and staff to assure that they:

- Understand the investigation of the device and the requirements for its accountability.
- Understand the nature of the investigational plan including record, reports and recruitment of patients.
- Understand the requirement for an adequate, well controlled clinical trial.
- Understand and accept the obligation to conduct the clinical investigation in accordance with applicable national regulations.
- Understand and accept the obligation to obtain Ethics Committee or Institutional Review Board (IRB) review and approval before the clinical trial may be initiated, ensure continuing review of the trail by the Ethics Committee or IRB and keep the sponsor informed of any actions by the Ethics Committee or IRB that concern the clinical trial.
- Have access to an adequate number of suitable patients to conduct the investigation.
- Have adequate facilities and staffing to conduct the investigation.
- Have sufficient time from other obligations to fulfill the responsibilities of the investigation.
- Particular attention will be given complication reporting.

Annual Center Monitoring Visit:

Following the preinvestigation visit, on-site monitoring visits will be conducted at least annually.

On-site monitoring visits will assess the progress of the clinical trial and identify any concerns that result from device performance and review of the investigator's clinical trial records, study management documents and patient consent forms. This review includes adherence to the investigational plan, Ethics Committee or IRB review of the clinical trial and its progress and maintenance of records and reports.

To assure the integrity of the clinical trial data, individual patient records and other source documents are compared to reports from the investigator to determine that:

- The information recorded in the case report forms and/or reports is accurate, complete and legible.
- There are no omissions in the case report forms of specific data (e.g., development of an intercurrent illness)
- Missing follow-up visits are documented in the reports.
- Patients failing to complete the clinical trial and the reason for failure are noted in the reports.
- Informed consent has been documented.

A record of the monitor's findings will be maintained by the sponsor and investigator and will contain the following information:

- The date(s) of the visit.
- The name(s) of the monitor(s) who conducted the visit.
- The name(s) and address of the investigator(s) and other center staff who were visited.
- A statement of the findings, conclusions and any actions taken to correct deficiencies observed during the visit.

Resolution of concerns and completion of assigned tasks will be documented by the monitor.

2.4.10 Statistical Analyses

Descriptive statistics will be calculated for all hemodynamic or hemolytic measures taken in the trial. These will be compared by t-test or chi square test as appropriate to PMA results at equivalent time periods. Demographic data will also be summarized using descriptive statistics and compared to PMA data where practical. Limited sample size may limit the power of these comparisons. Adverse event data will be evaluated both early and late in accordance with the AATS/STS guidelines on reporting valve studies. Again, limited sample size may make comparisons to PMA data inappropriate and may make rate calculations unreliable. However, calculations will be done and comparisons will be made to the PMA data; and an assessment of the power of these comparisons will be made.

Screen failures will also be examined for potential biasing effects on the trial. Analysis will be dictated by the information available, if any.

2.5 CASE REPORT FORMS

Example Case Report Forms are provided in Appendix B. A forms notebook for each patient will be provided by the sponsor. The notebook is designed to make keeping the records for the study more organized and to reduce the potential for mixing up data. Extra forms will be provided on request, or as needed.

3.0 DEVICE DESCRIPTION AND RISK ANALYSIS (17mm aortic and 23mm mitral)

The On-X™ prosthesis is a bileaflet mechanical heart valve prosthesis. The housing consists of On-X® pyrolytic carbon coating on a graphite substrate. In other sizes the On-X valve has been in clinical use since 1996 and has been approved for commercial distribution in the US since 2001 (aortic valves) and 2002 (mitral valves).

Two radiopaque leaflets are constrained by pivots in the housing walls. The leaflets are On-X® pyrolytic carbon deposited on a graphite substrate which is mixed with 10 weight % tungsten to allow for radiographic visualization. In the closed position, the occluders rest at 40° within the valve orifice. The valve design permits maximum leaflet opening angles of 90° from the plane of the housing, a position that follows flow. The pivot design includes features that enhance and ensure closure response to reverse flow and opening response to forward flow.

The rotatable sewing ring is made from polytetrafluoroethylene (PTFE) fabric attached to the valve housing by means of titanium retaining rings and 5-0 suture material. The retaining rings positively attach the sewing ring to the valve housing by straddling a flange on the housing OD. They also provide the means for radiographic visualization and identification. There are no coatings or treatments on the fabric, although black orientation marks are included on the ring fabric. The sewing rings are supra-annular and allow the tissue annulus to abut the pyrolytic carbon housing

directly, except in sizes larger than 25 mm, where the sewing rings become intra-annular to allow the 25 mm housing (largest size made) to fit properly into larger tissue annuli.

Valves are packaged on a valve holder /rotator with a separately packaged, removable handle to facilitate insertion and in situ orientation, and to provide protection during shipment and handling. The package is designed for shipment protection as well as handling ease. Valves are surgically clean and have been sterilized. The instructions for use packaged with the valve describe the handling of the valve during surgery in detail. Adhere to all instructions, warnings and precautions in the labeling. Reusable valve sizers, rotators, handles and leaflet motion probes are provided non-sterile in a separate accessory kit. These devices are designed to aid the proper selection and implantation of the On-X® valve, and should be cleaned and sterilized in accordance with their instructions prior to each use.

The subjects for whom this device is intended are those seriously or critically ill patients whose prognosis without surgery for replacement or repair of the diseased natural or prosthetic valve is unacceptably poor in terms of survival, quality of life, or both in the opinion of the attending physicians, based upon the patient's disease history and physical and laboratory findings from standard cardiovascular diagnostic workups and who require a smaller than currently available valve size. For this special subset of patients there are a number of widely accepted prosthetic heart valves in common use. All prosthetic heart valve implants carry risks of serious complications, and/or death, related to thrombogenicity, hemodynamics and durability, among other causes. Valvular reconstruction is also an option for this patient population, but not for all cases or conditions.

The purpose of this investigation is to establish the hemodynamics, hemolytic potential and valve-related complication rates of a smaller On-X® prosthetic heart valve. The use of the valve is not expected, based on existing clinical and preclinical study results, to carry any increased risk over those of other mechanical heart valves. All diagnostic procedures included in the investigation are standard to the postoperative care of heart valve patients. The normal diagnostic procedures used include blood tests from standard venipuncture draws, and physical examination, which are either non-invasive or minimally invasive with little or no risk to the patient. Hazardous invasive techniques, such as cardiac catheterization, are not generally used, and are not expected to occur. Reoperations will be conducted only when a complication creates a need for such action, and these events cause the same intervention for presently available prostheses.

The use of modern cardiopulmonary bypass techniques; including cold cardioplegia, are expected to minimize operative risk consistent with the standards of practice for open heart surgery. The use of properly balanced anticoagulant therapy along with explicit instructions to patients regarding the importance of their drug therapy, are expected to bring about an optimal balance between thrombotic and hemorrhagic

complications. Additional instructions to patients and their referring physicians are useful in minimizing complications, such as prosthetic endocarditis.

Because the On-X® valve in a small size has demonstrated performance meeting or exceeding standards requirements in preclinical studies and in its clinical history in larger sizes has established reasonable safety and effectiveness, it is reasonable to continue to investigate this device to expand the size range available for human subjects under the controlled conditions described in the protocol, and within the patient population also described.

4.0 LABELING

A copy of the device label is contained in Appendix E. The labeling consists of the standard box label for the On-X valve used in production units with the investigational device label added. The IFU in the box is also the standard production IFU with an insert sheet for the 17mm aortic valve and the investigational label added. This size valve has been used internationally for over 15 years, but is not available in the US due to lack of hemodynamic or blood damage data.

5.0 REFERENCES

1. Akins CW, Miller DC, Turina MI, et al. Guidelines for reporting mortality and morbidity after cardiac valve interventions. J Thorac Cardiovasc Surg 2008; 135:732-8.
2. ISO 5840, Standard for Cardiovascular Implants - Cardiac Valve Prostheses; 2005.

APPENDIX A

COMPLETE ECHOCARDIOGRAPHY PROTOCOL

ON-X LIFE TECHNOLOGIES

On-X® 17mm AORTIC/23mm MITRAL STUDY

ECHOCARDIOGRAPHIC PROCEDURES

1. General – interobserver and intraobserver variability

1.1 At each center, no more than two operators should perform studies.

1.2 At each center, one or at most two machines will be used for the study. Velocity data will be calibrated using a string phantom or equivalent device.

2. Exclusions

2.1 Poor echocardiographic window

3. Recording studies

3.1 Unless impossible, every study will include the following standard imaging views: parasternal long-axis, parasternal short-axis, apical 4-chamber, apical 2-chamber, apical long-axis and subcostal. Off-axis views as appropriate will also be necessary particularly to look for paraprosthetic regurgitation.

3.2 Doppler recordings will be made with a stand-alone continuous wave probe from apical views and for valves in the aortic position from additional right intercostals or suprasternal views. Both orthograde waveforms and, if present, regurgitant jets will be recorded.

3.3 Subaortic pulsed recordings will be made in the apical 5-chamber view with the sample placed just below the level at which significant flow acceleration occurs.

3.4 Recordings should be made with the scale set to maximize signal size and with the maximum available sweep speed.

3.5 All images and waveforms used for calculating information will be recorded on electronic media.

4. Data collected

4.1 Heart rate (BPM), height (cm) and weight (kg) are collected by the most convenient measure at the time of the echo exam. Body surface area (BSA) is determined from the standard nomogram or standard equation below. Geometric orifice area (GOA) is given by valve size in Table 8 of the On-X valve instructions for use. BSA (m^2) = ($Wt(kg)^{0.425}$ X $Ht(cm)^{0.725}$) X 0.007184.

4.2 Diameter of the left ventricular outflow tract measured on three parasternal long-axis frames frozen in systole. Diameters will be measured from the trailing edge of the left septal echo to the leading edge of the anterior mitral leaflet echo. The maximum dimension will be taken. **If there is reverberation artifact from calcium, the leading edge to leading edge convention will be used; if this artifact is excessive, the measurement will not be made. The best measurement (usually at the preoperative examination) will be assumed to remain constant throughout the study. If measurement is not practical for pediatric patients the aortic tissue annulus diameter of the valve will be used, and the measurement will not be made for the mitral valve.**

4.3 From the subaortic waveform (for prostheses in mitral or aortic positions): **peak velocity (v_1), mean pressure (ΔP_1) calculated by echo machine software, velocity integral (VTI_1).**

4.4 From the transaortic waveform (prostheses in the aortic position only): p**eak velocity (v_2), mean pressure (ΔP_2) calculated by echo machine software, velocity integral (VTI_2)**.

4.5 From the mitral waveform (prostheses in the mitral position only): **Pressure half-time (PHT), mean pressure drop (ΔP_m), peak instantaneous early velocity (v_m), diastolic velocity integral (DVI)**.

4.6 **Doppler measurements will be made over 3 cycles in sinus rhythm or over 5 to 10 cycles in atrial fibrillation (depending on clinical judgment). These will then be averaged.**

5. Calculations

The data collected will be entered on a database and the following calculations will be performed at the central laboratory:

5.1 **Effective area by the continuity equation (EOA) in the aortic position:**

$$EOA = CSA \times VTI_1 / VTI_2 \qquad [1]$$

where CSA is left ventricular outflow cross-sectional area in cm^2 calculated from the diameter assuming circular cross-section; VTI_1 is subaortic velocity integral in cm and VTI_2 is aortic velocity integral in cm.

5.2 **Effective area by the continuity equation (MOA) in the mitral position:**

$$MOA = CSA \times VTI_1 / DVI \qquad [2]$$

where DVI is diastolic velocity integral in cm

5.3 Effective area by the pressure half-time method (MOA1/2) in the mitral position:

MOA1/2 = 220/PHT [3]

5.4 **Peak pressure drop across the aortic valve:**

Peak $\Delta P = 4 (v_2^2 - v_1^2)$ [4]

5.5 **Mean pressure difference across the aortic valve (per ISO requirement):**

Mean $\Delta P = \Delta \mathbf{P_2} - \Delta \mathbf{P_1}$ [5] (Per ISO 5840 – mean ΔP = aortic ΔP – subaortic ΔP)

5.6 Peak pressure drop across the mitral valve:

Peak $\Delta P = 4v_m^2$ [6]

5.7 Cardiac Output:

$CO = CSA \times VTI_1 \times BPM$ [7]

5.8 Indexed effective orifice areas (EOAI), and cardiac index (CI):

EOAI = EOA/BSA [8]; CI = CO/BSA [9]

5.9 Performance Index (PI):

PI = EOA/GOA [10]

6. Other analyses

6.1 For valves in the aortic position, mean and standard deviation values will be calculated for the following parameters: peak transaortic velocity, mean transaortic velocity, mean pressure difference, peak pressure difference, effective orifice area, cardiac output and all indices.

6.2 For valves in the mitral position, mean and standard deviation values will be calculated for the following parameters: peak transmitral velocity, peak transmitral pressure difference, mean transmitral pressure difference, effective orifice area by continuity equation, pressure half-time and effective orifice area by pressure half-time, cardiac output and all indices.

6.3 The site and severity of aortic regurgitation and mitral regurgitation will be assessed.

6.4 The presence, site and size of any thrombus will be assessed.

APPENDIX B

CASE REPORT FORMS

Institution: Investigator:	ON-X LIFE TECHNOLOGIES On-X® 17mm Aortic/23mm Mitral Study Screening Log	Page ___ of ___ 2010-01, Rev H

Patient Initials	Screen Date	Consent Date	Drop-out Date	Explanation of Timing and Cause

Institution: Investigator:	ON-X LIFE TECHNOLOGIES On-X® 17mm Aortic/23mm Mitral Study CRF 1 Preoperative Data	Patient Initials _____ 2010-01, Rev H

Visit Date (m/d/y): _____/_____/_____

Date of Birth (m/d/y): _____/_____/_____ Sex: ☐ Male ☐ Female

1. Patient has met Inclusion/Exclusion criteria. ☐ Yes ☐ No (If No, attach explanation)

2. Informed Consent has been given. ☐ Yes ☐ No (If No, follow notification procedure.)

   Date (m/d/y): _____/_____/_____ (Keep signed Informed Consent in patient study file.)

3. NYHA Functional Class: ☐ I ☐ II ☐ III ☐ IV ☐ Unknown

4. Cardiac Rhythm: ☐ Sinus ☐ Atrial Fibrillation ☐ Paced ☐ Other, specify: _____

5. Disease Etiology: ☐ Rheumatic ☐ Calcific ☐ Pros. Valve Dysfunction ☐ Congenital ☐ Endocarditis ☐ Degenerative/Myxomatous ☐ Other, specify: _____

6. Valvular Lesions:

	Mitral	Aortic
Stenosis	☐	☐
Regurgitation	☐	☐
Mixed	☐	☐
Other, specify: _____	☐	☐

7. Previous cardiac surgery: ☐ Yes ☐ No _____
   or pediatric comorbidity: (If yes, specify) _____
   _____

8. Pre-operative Anticoagulation ☐ Yes ☐ No

   ☐ Heparin ☐ Warfarin/Coumadin ☐ Clopidogrel ☐ Aspirin ☐ Indandione derivatives

   INR: _____ INR Target Range:_____ Date (m/d/y): _____

Investigator Signature: _____ Date (m/d/y):_____/_____/_____

Institution: Investigator:	ON-X LIFE TECHNOLOGIES On-X® 17mm Aortic/23mm Mitral Study CRF 2 (p1 of 2) Echocardiographic Data	Patient Initials _____ 2010-01, Rev H

1. ECHO DATE (m/d/y): _____/_____/_____

2. VALVE Position _____, Size _____ Serial Number _____

3. PHYSICAL ASSESSMENT: _____ bpm heart rate

_____ cm height

_____ kg weight

_____ m^2 BSA

4. CARDIAC RHYTHM: Normal sinus

☐ Atrial fibrillation

☐ Atrial flutter

☐ Heart block: degree _____

☐ Paced

☐ Other: _____

5. IMAGING: _____ cm LVOT diameter systole

6. SUBAORTIC WAVEFORM: _____ m/s Peak velocity

_____ mmHg Mean gradient

_____ cm Velocity time integral

7. TRANSAORTIC WAVEFORM (FOR AVR): _____ m/s Peak velocity

_____ mmHg Mean gradient

_____ cm Velocity time integral

(continues to next page)

Institution: Investigator:	ON-X LIFE TECHNOLOGIES On-X® 17mm Aortic/23mm Mitral Study CRF 2 (p2 of 2) Echocardiographic Data	Patient Initials _____ 2010-01, Rev H

Date of Echo (m/d/y) _____

8. TRANSMITRAL WAVEFORM (FOR MVR): _____ m/s Peak velocity

_____ mmHg Mean gradient

_____ cm Velocity time integral

_____ ms Pressure half-time

9. REGURGITATION: ☐ No ☐ Yes, please complete amount and location below:

Location: ☐ Through ☐ Paravalvular ☐ Uncertain

Amount:

None ☐

+1 Mild/Trivial ☐

+2 Moderate ☐

+3 Moderately severe ☐

+4 Severe ☐

10. LEFT VENTRICULAR FUNCTION:

☐ Normal (EF>50%)

☐ Mild impairment (EF40-50%)

☐ Moderate impairment (EF30-<40%)

☐ Severe impairment (EF<30%)

11. VALVE THROMBUS: _____ No _____ Yes. If yes, specify location and amount: _____

12. OTHER ABNORMALITIES: Describe: _____

Investigator's Signature: _____ Date (m/d/y):____/_____/_____

Institution: Investigator:	ON-X LIFE TECHNOLOGIES On-X® 17mm Aortic/23mm Mitral Study CRF 3 Operative Data	Patient Initials _____ 2010-01, Rev H

Surgery Date (m/d/y): _____/_____/_____ Surgeon:_____Emergency: ☐ Yes ☐ No

Valve Information: Type _____ Size: _____ Serial #: _____

Concomitant Cardiovascular Procedures: ☐ CAB ☐ Valve ☐ A ☐ M ☐ T ☐ P ☐ ASD ☐ VSD ☐ Aneurysm ☐ Aortic ☐ Abdominal ☐ Ventricular ☐ Arch ☐ Other, specify:_____ _____ ☐ None

Suture Technique: ☐ Interrupted ☐ Pledgeted ☐ Everting Mattress ☐ Noneverting ☐ Continuous ☐ Other, specify: _____

Crossclamp time: _____Minutes

Cardioplegia:	☐ Cold ☐ Warm ☐ Both
	☐ Antegrade ☐ Retrograde ☐ Both
Intraoperative Drugs:	Heparin ☐ Yes ☐ No

Intraoperative Adverse Events: ☐ Yes ☐ No (If Yes, complete below.)

Prolonged Hypotension	☐ Yes	☐ No	Difficulty Restarting Rhythm	☐ Yes	☐ No
Excessive Bleeding	☐ Yes	☐ No	Difficulty Weaning from Bypass	☐ Yes	☐ No
Cardiac Tamponade	☐ Yes	☐ No	Study Valve Explanted	☐ Yes	☐ No
Cardiac Arrest	☐ Yes	☐ No	Death	☐ Yes	☐ No
Other	☐ Yes	☐ No			

Other, if Yes, explain:_____

Valve Orientation: Check the most accurate valve orientation description below based upon the direction of the valve axis.
Aortic: ☐ LC/RC Commissure ☐ RC/NC Commissure ☐ NC/LC Commissure ☐ Other, describe:_____
Mitral: ☐ Anatomical ☐ Anti-anatomical ☐ Other, describe: _____

Investigator Signature: _____ Date (m/d/y): _____/_____/_____

Institution: Investigator:	ON-X LIFE TECHNOLOGIES On-X® 17mm Aortic/23mm Mitral Study CRF 4 Follow Up	Patient Initials _____ 2010-01, Rev H

Visit Date (m/d/y) _____/_____/_____

☐ PostOperative/Discharge

☐ Early (3 to 6 months)

☐ 1-Year (11 to 14 months)

☐ Off Schedule

Patient Status (If follow up Off Schedule)

☐ Missed Follow Up Visit. Reason, _____

☐ Lost to Follow Up:
Efforts to Contact and Results:_____

☐ Adverse Event (Complete Complications Form CRF 5)

Type of Examination: ☐ Office/Outpatient ☐ Hospital ☐ Telephone ☐ Other _____

NYHA Class: ☐ I ☐ II ☐ III ☐ IV ☐ Unknown

Cardiac Rhythm:

☐ Sinus
☐ Paced
☐ Atrial Fibrillation
☐ Regular
☐ Irregular
☐ Other, specify:_____

Anticoagulant Therapy:

☐ None
☐ Clopidogrel
☐ Aspirin
☐ Warfarin/Coumadin
☐ Heparin
☐ Other _____

INR _____ Blood Collection Date (m/d/y): _____/_____/_____ (closest to date of visit)

New Complications: (Since last follow up) ☐ Yes ☐ No (Complete complication form, CRF 5)

Echo Completed (m/d/y)_____ Attach CRF 2 and send echo, applicable at discharge, 3-6 months and 1 yr follow-up.

Investigator Signature: _____ Date (m/d/y): _____/_____/_____

Institution: Investigator:	ON-X LIFE TECHNOLOGIES On-X® 17mm Aortic/23mm Mitral Study CRF 5 Complications 1 of 2	Patient Initials _____ 2010-01, Rev H

Start Date (m/d/y): _____/_____/_____ Stop Date (m/d/y): _____/_____/_____ or ☐ Ongoing

Duration: _____ ☐ Weeks ☐ Days ☐ Hours ☐ Minutes

Etiology:

_____

Complication Type (complete 1 form for each event) Complication number: _____

1. ☐ Thromboembolism ☐ Neurologic: ☐ TIA ☐ Peripheral: ☐ Major ☐ Cardiac: MI
   ☐ CVA ☐ Minor
   ☐ Fatal
2. ☐ Valve Thrombosis
3. ☐ Bleeding Event ☐ Major ☐ Minor
   ☐ Cerebral ☐ Cardiac ☐ Ocular ☐ GI ☐ Nosebleed ☐ Hematoma ☐ Other
   ☐ Anticoagulant related ☐ Antiplatelet related ☐ Not drug related
4. ☐ Prosthetic Endocarditis (Organism: _____)
   Risk Factor: ☐ Dental Work ☐ IV Drug Use ☐ Recent Infection ☐ Other
5. ☐ Prosthetic Valve Dysfunction
   ☐ Nonstructural (Type: _____)
   ☐ Structural (Type: _____)
   ☐ Paravalvular Leak (☐ Minor ☐ Major)
6. ☐ Hemolytic Anemia (conduct blood tests) ☐ Primary ☐ Secondary to: _____
   ☐ Clinically significant ☐ Insignificant
7. ☐ Congestive Heart Failure ☐ Valve Related ☐ Not Valve Related
8. ☐ Reoperation ☐ Repair ☐ Explant
9. ☐ Other Valve Related Explain: _____
10. ☐ Death - Primary Cause: ☐ Valve related ☐ Other cardiac ☐ Other ☐ Unknown

(continues next page……..)

Institution: Investigator:	ON-X LIFE TECHNOLOGIES On-X® 17mm Aortic/23mm Mitral Study CRF 5 Complications 2 of 2	Patient Initials _____ 2010-01, Rev H

Complication number: _____

Treatment: ☐ None ☐ Medication ☐ Hospitalization ☐ Surgery (Complete CRF6)

Patient Condition at Time of Event

Cardiac Rhythm ☐ Sinus ☐ Paced ☐ Atrial Fibrillation ☐ Other

NYHA Class ☐ I ☐ II ☐ III ☐ IV ☐ Unknown

Anticoagulant Therapy ☐ Warfarin ☐ Clopidogrel ☐ Heparin

INR: _____ ☐ Aspirin ☐ None ☐ Other _____

Outcome:

☐ Event Fully Resolved

☐ Permanent Impairment (Specify: _____)

☐ Event Ongoing

☐ Death Date (d/m/y): _____/_____/_____

Autopsy ☐ Yes ☐ No

Explant ☐ Yes ☐ No (If yes, complete CRF-6)

Relationship to Device:

Valve Related: ☐ Yes ☐ No

Investigator Signature: _____ Date (m/d/y): _____/_____/_____

Institution: Investigator:	ON-X LIFE TECHNOLOGIES On-X® 17mm Aortic/23mm Mitral Study CRF 6 Reoperative Data	Patient Initials _____ 2010-01, Rev H

Reoperative Procedure: Procedure Date (m/d/y): _____/_____/_____

☐ Study Valve Replacement (complete Explant data below)
☐ Aortic Replacement Valve Mfg: _____ Size: _____mm Type: _____
☐ Mitral Size: _____mm Type: _____

☐ Study Valve Repair Specify: _____

☐ CABG

☐ Pacer Implantation

☐ Aneurysm Repair

☐ Non Study Valve
☐ Replacement Procedure: _____
☐ Repair Replacement Valve Mfg: _____
Size: _____mm Type:_____

Explant Condition: (check all that apply) ☐ Reop ☐ Autopsy Explant Date (m/d/y): _____/_____/_____

☐ Pannus Overgrowth
☐ PVL
☐ Thrombus
☐ Vegetation Organism: _____
☐ Other Specify: _____

Valves Returned: ☐ Yes Date Returned (m/d/y): _____/_____/_____
☐ No If No, Explain, _____

Investigator Signature: _____ Date (m/d/y): _____/_____/_____

APPENDIX C

Example Informed Consent

On-X® Prosthetic Heart Valve Size 17mm Aortic Clinical Investigation

Patient Informed Consent/Assent Form

Statement of Research

You are being invited to participate in a clinical trial (research study) as described below.

Please Read the following explanation before agreeing to participate in this study which will involve the On- X Prosthetic Heart Valve size 17mm aortic.

Information about the Research

The On-X® mechanical heart valve consists of an On-X® pyrolytic carbon housing and two leaflets with a titanium alloy ring around the housing. There is a sewing ring made of knitted plastic cloth (polytetrafluoroethylene) attached to the housing with two titanium rings and suture material. I understand these materials have a long history of use in cardiac valves. The larger sizes of this valve have also been available for patients for more than 15 years.

The On-X® heart valve, (the Prosthesis), is intended for treatment of patients who have been diagnosed with disease of a heart valve, and require replacement of their natural aortic valve, or previously implanted mechanical or tissue aortic valve.

The purpose of this study is to show that the smaller size Prosthesis is safe and effective, and will perform in a manner comparable to the larger size On-X heart valves. Your surgeon has determined that you will likely require the 17mm aortic valve if your aortic valve is being replaced. If in surgery your surgeon finds you do not need this size valve, a different valve will be used and you will be told after surgery.

The smaller size of the On-X Prosthesis is an investigational device, meaning that government regulatory authorities require clinical studies to establish the safety and effectiveness of this size heart valve, and that the device safety and effectiveness has not been established to allow commercial marketing for these sizes. This clinical study will involve approximately 15 patients from up to 40 selected sites from both within and outside the United States. All patients will follow the same procedures and follow-up schedule. When the information has been collected, it will be submitted to the appropriate regulatory authorities for possible approval to sell this size of the valve without further study.

Patients who have valvular heart disease, are of the proper body size and require replacement of their heart valve are being invited to participate in this study. Your treatment will be similar to that provided to patients who have their heart valves replaced with the larger size On-X prosthetic heart valves.

Before surgery, you will have routine diagnostic tests to assess the status of your heart valves. You will then have surgery with implantation of the Prosthesis. Your progress will be closely

monitored and recorded at the following times: discharge (or within 30 days following surgery), three to six months after surgery, and 11 to 14 months following surgery. Total duration of the study is expected to be 3 years.

Laboratory blood samples will be drawn and other procedures and diagnostic tests (history and physical examination and echocardiography – a diagnostic machine that creates images of your heart with sound waves) will be done according to the requirements of the protocol during the appropriate follow-up visits. The Prosthesis tests will allow your doctor to assess the status and function of your heart and the Prosthesis. In addition, you will need life-long anticoagulant medication therapy which will require frequent laboratory blood tests. Long-term baby aspirin therapy (unless you have a medical condition that does not allow it) is also recommended. The understanding of the use of these medications is important to your overall care. If the Prosthesis is explanted for some reason, it must be returned to the study sponsor, as a requirement of the study protocol. Also, autopsies are requested should death occur during the study period to retrieve the prosthesis for evaluation.

Risks and Discomforts

Certain risks are associated with any surgical procedure. General surgical risks include anesthesia complications, drug reactions, and infection. General risks of heart surgery include disturbances of the heart beat, chest pain, heart attack, and potential damage to heart structures that are not directly part of the surgery, that is, other valves and blood vessels. The primary risk associated with the Prosthesis is similar to that of all commercially available heart valves, that is, failure to restore function. Specifically, this might involve breakage of the valve, blood leak around the valve, clotting on or around the valve which can move from the valve as well and cause injury – including stroke – from blockage of blood vessels, tissue growth on the valve could interfere with its function, blood damage which may lead to anemia or infection of the valve. Use of blood thinners as necessary with mechanical valves carries the risk of excessive bleeding. As a heart valve patient you are also subject to the continuous risk of heart failure. As with any other prosthetic valve, the complications that may occur with the Prosthesis can result in minor to severe consequences, including permanent disability, reoperation, explants of the valve or death.

Foreseeable risks and discomforts will be minimized by thorough preoperative evaluation and close intraoperative and postoperative monitoring of your condition. There may be risks or discomforts that are not yet known.

Benefits

Expected benefits from use of the Prosthesis are similar to those associated with commercially available heart valves with two moving flaps (bileaflet valves). The primary benefit is restoration of heart function by replacement of the diseased heart valve. Another benefit will be that your progress and health status will be carefully monitored. Any complication that might arise may be detected and treated (if necessary) at an early stage, decreasing the potential for more serious problems. Also, knowledge that is gained by your participation may be of potential benefit to other patients.

Alternative Methods of Treatment

Alternatives to heart valve replacement with the Prosthesis include replacement of your aortic valve with a different mechanical or tissue heart valve; or repair of your native heart valve. Another alternative is that you may decide not to undergo any surgical treatment, and remain cared for with medications.

Confidentiality

Confidentiality of your medical records will be maintained at all times by those associated with this research study. Regulatory authorities (those responsible for the well-being of patients involved in research studies) and the sponsor (On-X Life Technologies, Inc.) and monitor of the study may inspect and perhaps copy the medical research records, if necessary, to ensure the validity of the information. Knowledge that is gained from the study may be published in scientific journals; however, no patient will be identified.

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.

Research Related Injuries

If physical injury occurs due to involvement in the research, medical treatment will be available, but you (or your insurance company) should be responsible for payment for the cost of treatment. Compensation for lost wages and/or direct or indirect losses will not be available. Further information about research-related injuries is available from the hospital (telephone: _____-_____-_____).

Your participation in this study does not waive any legal rights or release the hospital or its agents from liability for negligence.

Questions about the Research

Nothing in this document is intended to limit the authority of the doctor to provide emergency medical care to the extent that the doctor is permitted to do so under applicable local laws.

If you have questions about the research or develop a study-related problem, you should contact Dr. _____ at the following telephone number: _____- _____ - _____. During non-business hours, you should contact the on-call doctor at _____ - _____ - _____.

If you have any questions about your rights as a research subject, you should contact the Ethics Committee Chairperson (Name): _____ at _____ - _____ - _____.

Voluntary Participation

Your participation in this research study is voluntary. Your refusal to participate will not jeopardize your future treatment or benefits at (Name of Hospital or Institution). _____ _____.

You are free to discontinue participation for any reason in this study at any time without fear of penalty or loss of medical care. Your doctor may withdraw you from the study for just cause without your permission.

Progress of the Study

As the study progresses and information is collected, your doctor will inform you of any new and significant findings related to the Prosthesis or the procedures associated with its use which may affect your willingness to continue in the study.

Costs

There will be no additional cost to you beyond the usual customary costs associated with heart valve replacement. However, neither On-X Life Technologies, Inc. nor (Name of Hospital or Institution) is responsible for compensation in the event of any physical injury that might occur as a result of your participation in this study. Information (tests, physical examination, x-rays, etc.) that is gathered purely for the purposes of this research study (that is, not part of the usual medical intervention for heart valve replacement) will be provided to you free of charge.

Signatures

You are making a decision whether or not to participate in this study. Your signature indicates that you have read the information provided, have discussed this study with your doctor and his or her staff, and have decided to take part. Again, you may withdraw from the study at any time, or choose not to participate without any prejudice to you. You will receive a copy of this form for your personal records.

Assent

_____ _____

Date Signature of minor patient, if applicable

Assent waived

_____ _____

Date Investigator Signature

Consent

_____ _____

Date Patient or Legal Representative Signature

Reason, if patient or legal representative did not sign:

_____

_____

_____

_____ _____

Date Witness Signature

I have fully explained this research study to the participant, and in my opinion, and his/hers, there was sufficient information regarding the risks and benefits to make an informed decision. I will inform the participant in a timely manner of any changes in the procedure or the risks and benefits if any occur.

_____ _____

Date Investigator Signature

APPENDIX D

Investigators Agreement

INVESTIGATOR AGREEMENT FOR ON-X® PROSTHETIC HEART VALVE SIZE 17MM AORTIC AND 23MM MITRAL CLINICAL INVESTIGATION

I wish to participate in the supplemental clinical investigation of the On-X ® Prosthetic Heart Valve, Aortic and Mitral Models. I understand that this is a new prosthesis which is manufactured by ON-X LIFE TECHNOLOGIES and is planned for testing in a clinical trial.

I am familiar with the intent of the investigation of this product, including the objective of the proposed clinical trial and the proposed trial procedures. I believe that, because of my training and experience and available patient population, I am qualified to investigate the product performance under the proposed Clinical Investigation Plan. I agree to conduct the clinical investigation under the purview of an appropriate Institutional Review Board (IRB) or Ethics Committee.

I specifically, and further, agree that:

1. I will conduct the clinical investigation and explant procedure in accordance with the Investigator Agreement, the Clinical Investigation Plan, any applicable regulations and any condition of approval imposed by any hospital or other reviewing authority. I will obtain all preoperative and operative data and complete follow-up data for each valve implant, as defined in the Clinical Investigation Plan.
2. All use of the product involving human subjects will be under my direct supervision. I will not release the prosthesis or its components to anyone other than another physician responsible to me without written consent from ON-X LIFE TECHNOLOGIES.
3. Information concerning the product and the study must be provided to each patient participating in this clinical investigation. Written informed consent must be obtained from each patient who participates in this clinical investigation.
4. All information which I hereafter obtain from ON-X LIFE TECHNOLOGIES or any other person acting on behalf of ON-X LIFE TECHNOLOGIES about or relating to the prosthesis, including its components, which is the subject of this study and all information which I have or will obtain under or concerning this study is considered by ON-X LIFE TECHNOLOGIES to be proprietary and confidential to ON-X LIFE TECHNOLOGIES. I will maintain all such information in confidence and will not use such confidential information, or release, reveal or disclose such confidential information to anyone without the written consent of ON-X LIFE TECHNOLOGIES or prior public disclosure by ON-X LIFE TECHNOLOGIES. I will also assure that any and all co-investigators listed here and reporting to me will maintain confidentiality as described above.
5. I will notify ON-X LIFE TECHNOLOGIES, in writing, when approval for this investigational study is obtained from the Institutional Review Board (IRB) or Ethics Committee.

6. I have never participated in an investigational study which has been terminated for reasons of noncompliance.
7. Additional investigators (including echocardiologist) participating in this study and reporting to me are:

Name (Surgeon)	Address
Name (Surgeon)	Address
Name (Surgeon)	Address
Name (Surgeon)	Address
Name (Surgeon)	Address
Name (Surgeon)	Address
Name (Surgeon)	Address

8. The study coordinator currently participating in the study under my direct supervision is:

Name	Address

Signature of Investigator	Type or Print Name
Institution	Address
City/State/Country	Telephone
FAX	Date

APPENDIX E

LABELING

APPENDIX F

INVESTIGATOR LIST

The following principal investigators have agreed to participate in this clinical investigation and the respective committees have reviewed and approved this investigational plan before commencement.

Active Sites

STUDY ID*	CENTER	INVESTIGATOR and ADDRESS
005	**Mayaguez Medical Center**	**Raul Garcia-Rinaldi Western Cardiovascular Surgery Mayaguez Medical Center P.O. Box 6684 Marina Station Mayaguez, PR 00681-6684**
006	**Maine Medical Center**	**Reed Quinn Maine Medical Center Department of Surgery 22 Bramhall Street Portland, ME 04102-3175**
007	**UT Southwestern Medical Center**	**Timothy Pirolli UT Southwestern Medical Center Children's Medical Center 1935 Medical District Drive – MC B3.10 Dallas, TX 75235**
008	**University of Oklahoma**	**Harold Burkhart University of Oklahoma Children's Hospital Section of Thoracic & Cardiovascular Surgery 920 Stanton L. Young Blvd., WP-2230 Oklahoma City, OK 73104**
009	**Children's Heart Center of Nevada**	**Michael Ciccolo Children's Heart Center of Nevada 3006 S. Maryland Pkwy., Suite 690 Las Vegas, NV 89109**
010	**Cincinnati Children's Hospital**	**David Luís Simón Morales Chief of Pediatric Cardiovascular Surgery The Heart Institute Cincinnati Children's Hospital Medical Center The University of Cincinnati College of Medicine 3333 Burnet Avenue – MLC 2013 Cincinnati, OH 45229**

012	**MultiCare Health System**	**Dennis Nichols** **MultiCare CT Surgical Associates** **314 Martin Luther King, Jr. Way, Ste. 202** **Tacoma, WA 98405**
013	**University of Virginia**	**James Gangemi** **University of Virginia** **P.O. Box 800679** **Room 4054, University Expansion** **Charlottesville, VA 22908**
014	**University of Michigan**	**Ming-Sing Si** **Michigan Congenital Heart Center** **11-735 C.S. Mott Children's Hospital** **1540 E. Hospital Dr. SPC 4204** **Ann Arbor MI 48109**
015	**El Camino Hospital**	**Vincent Gaudiani, MD** **Taft Center for Clinical Research** **El Camino Hospital** **2500 Grant Road** **Mountain View, Ca 94040** **Palo Alto Medical Foundation** **2490 Hospital Drive** **Suite 109** **Mountain View, California 94040**
016	**Nationwide Children's Hospital**	**Patrick McConnell, MD** **Cardiothoracic Surgery** **Nationwide Children's Hospital** **700 Children's Drive** **Columbus, OH 43205-2664**

*Study IDs are not sequential.

Closed Sites

STUDY ID	CENTER	INVESTIGATOR and ADDRESS
001	**Hospital Clinico Provincial**	**Jose Luis Pomar** **Chief – Dept. of Cardiovascular Surgery** **Hospital Clinico Provincial** **Carrer de Villaroel, 170** **University of Barcelona** **08036 Barcelona, Spain**
002	**University Hospital Salamanca**	**Jose Gonzalez Santos** **Chief – Dept. of Cardiac Surgery** **Hospital Universitario de Salamanca** **Paseo de San Vincente 58-182** **37007 Salamanca, Spain**

This list will be updated as needed and whenever a change occurs. CVs of principal investigators are kept in a separate file.