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Clinical Trial of the On-X® Valve Using Low Dose Anticoagulation

(also known as PROACT: Prospective Randomized On-X Anticoagulation Clinical Trial)

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Study Protocol - Rev. N, March 3, 2014

Investigational Plan

Clinical Trial of the On-X® Valve Using Low Dose Anticoagulation

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MVR Arm Late Enrollment Only

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I. Hypothesis

Various patient groups with the On-X Valve can be maintained safely on lower doses of Coumadin® or on antiplatelet drugs only rather than the standard dose of Coumadin and aspirin presently recommended by ACC/AHA or ACCP professional societies.

II. Study Design

This is a longitudinal, randomized (randomization to occur at the 3 month follow-up) study comparing the On-X valve on low dose anticoagulation (test group) to concomitant control groups of On-X valves receiving standard Coumadin/aspirin therapy, and also to FDA objective performance criteria (OPC)[1]. It is a multicenter study consisting of up to 50 centers in the United States, Canada and Italy enrolling and randomizing no more than 1200 patients as described in Section II.D. A list of participating centers is included in Appendix E with updates available upon request or as required by the FDA approval order.

A. Patient Inclusion

1. Patients requiring isolated aortic valve replacement (AVR), or isolated mitral valve replacement (MVR).
2. AVR patients receiving low dose or antiplatelet only anticoagulation will be divided into groups at low risk and high risk for thromboembolism with all patients being in the low risk group except for patients with the following conditions which place a patient in the high risk group:
   - Chronic atrial fibrillation (see definition below)
   - Left ventricular ejection fraction < 30 %
   - Enlarged left atrium >50mm diameter
   - Spontaneous echo contrasts in the left atrium
   - Vascular pathology (see definition below)
   - Neurological events (see definition below)
   - Hypercoagulability (see definition below)
   - Left or right ventricular aneurysm
   - Lack of platelet response to aspirin or clopidogrel (see definition below)
   - Women receiving estrogen replacement therapy
3. Concomitant cardiac surgery is allowed
4. Adult patients

B. Patient Exclusion

1. Right side valve replacement
2. Double (aortic plus mitral) valve replacement
3. Patients with active endocarditis at the time of implant

4. Previous confirmed or suspected thromboembolic event or thrombophlebitis occurring or resolving within the last year prior to enrollment
5. Other terminal illness
6. Patients who are in an emergency state
7. Inability to return for required follow-ups
8. Patients with an On-X valve implanted within the study and subsequently explanted
9. Patients who are known to be pregnant, plan to become pregnant or are lactating
10. Patients with acquired immunodeficiency syndrome or know to be HIV positive
11. Patients who are prison inmates or known drug or alcohol abusers
12. Patients unable to give adequate informed consent.

All patients meeting the criteria will be invited to participate.

Definitions –

Anticoagulation or anticoagulant –
For the purposes of this study anticoagulation shall mean any drug therapy that interferes with the coagulation of the blood whether by inhibition of vitamin K (Coumadin) or inhibition of platelet aggregation (aspirin or clopidogrel). Anticoagulant regime shall be specified whenever discussed.

Chronic Atrial Fibrillation –
Atrial fibrillation that is unresponsive to medical or cardioversion therapy and that has become the primary heart rhythm of the patient, also called persistent atrial fibrillation, having been present in the patient for at least 1 month.

Hypercoagulability –
Hypercoagulability in AVR patients will be defined by the following blood tests and results done preoperatively with the patient not on Coumadin:

1. APC resistance (Factor-V-Leiden mutation) – heterozygous or homozygous
2. Prothrombin mutation – heterozygous or homozygous
3. AT-III activity – below normal
4. Protein C activity – below normal
5. Protein S activity - below normal
6. Factor VIII activity – elevated above 250%.
7. Lipoprotein – above normal

Antiplatelet Resistance (Treatment Failure) –
Resistance to aspirin or clopidogrel in AVR patients will be defined by clinical laboratory tests and results done preoperatively or postoperatively after patients have been taking aspirin and clopidogrel for at least 1 week (see section III C page 12 for enrollment processes):

1. Urine 11 dehydro thromboxane B2 – not reduced after aspirin treatment
2. P2Y 12 not reduced

Vascular Pathology –
For the purposes of determining AVR risk in this study, vascular pathology shall include any historical evidence of carotid or peripheral artery occlusion of at least 50% by ultrasound or angiography, arterial aneurysms, claudication and/or ischemic ulcers of the lower extremities.
Neurological events –
For the purposes of determining AVR risk in this study, neurological events shall include any historical evidence of transient ischemic attack (TIA), stroke or cerebral aneurysm.

C. Test and Control Group Drug Therapies

Isolated Aortic Valve Replacement –
Test Group I (high risk AVR) – First 3-months postoperation, Coumadin at an INR target of 2.0 to 3.0 with 81 mg/day aspirin will be used. After 3-months, Coumadin dose will be reduced to an INR target of 1.5 to 2.0 with 81 mg/day of aspirin continued. Enrollment in this arm has ceased.

Test Group II (low risk AVR) – First 3-months postoperation, Coumadin at an INR target of 2.0 to 3.0 with 81 mg/day aspirin will be used. After 3-months, Coumadin dose will be removed and clopidogrel will be added using a loading dose of 300 mg followed by 75 mg/day with aspirin at 325 mg/day. AVR low risk patients who do not pass hypercoagulability or drug response tests will no longer be moved to the high risk group. This arm has been closed. See Addendum A for close out process for this test group and its control.

Control Groups – Postoperatively Coumadin with an INR target of 2.0 to 3.0 with 81 mg/day aspirin throughout the study. A separate control group will be used for each test group above.

Mitral Valve Replacement –
Test Group III, (regardless of risk) – First 3-months postoperation, Coumadin at an INR target of 2.5 to 3.5 with 81 mg/day (75 mg/day in Italy) aspirin will be used. After 3-months, Coumadin dose will be reduced to an INR target of 2.0 to 2.5 with 81 mg/day (75 mg/day in Italy) of aspirin continued.

Control Group – Postoperatively Coumadin with an INR target on 2.5 to 3.5 with 81 mg/day (75 mg/day in Italy) aspirin throughout the study.

D. Sample Size

A sample size estimate was conducted based on FDA OPC criteria [1]. The study is expected to test the safety of low dose (LD) therapy for anticoagulant therapy in On-X valve patients with LD therapy consisting of the use of Coumadin in combination with aspirin or the use of antiplatelet therapy alone. This study is designed as a non-inferiority study requiring only that LD therapy is not inferior to standard

Coumadin/aspirin treatment. Testing the superiority of LD therapy with adverse event rates as low as expected would require exposure of a prohibitively large patient group. It was necessary for the sample size calculation to assume an acceptable event rate for the primary endpoints of thromboembolism, thrombosis and bleeding events derived by summing the FDA OPC's. The incident rate of the sum of these three events needs to be at least as low as the OPC sum, 7.3%. Table 1 gives the resulting sample size requirements based on a variety of outcomes.

The number of patients to be enrolled in the clinical trial is based first on the ability to show that linearized adverse event rates for the primary endpoints in the test groups are not inferior to the corresponding control groups and second on the ability to show that all valve related adverse event rates in the test groups do not equal or exceed 2 times the rates determined to be acceptable for mechanical valves.

For the first criterion above, the test group will need to have less than 6%/ptyr cumulative rate of the three events for the study to reach significance with a randomized patient population of between 150 and 250 per group followed for between 5 and 6.7 years at a statistical power of 80% with type I error of 0.05 and a maximum allowable difference between groups of 1.5%. It is expected that each of 50 centers will be able to enroll an average of 30 patients into the study balanced to provide adequate population in each sub-group, providing sufficient patient-years to test the hypothesis, which under the above conditions is around 1000 as shown in Table 1. Thus the study has 200 patients per group in AVR high risk with an average of 5 years of follow-up, or alternatively 150 patients in AVR low risk averaging 6.7 years of follow-up and and up to 250 MVR averaging 4 years of follow-up, providing the approximately 1000 patient-years per group estimated to meet hypothesis.

For the second criterion above, the established rates are the objective performance criteria (OPC) given in the FDA guidance document [(1)]. The adverse event rates for which OPCs are established include the primary endpoints of thrombosis, thromboembolism and bleeding and the secondary endpoints of paravalvular leak and endocarditis as listed below:

Adverse Event	% per valve year (R_A)
Thrombosis	0.8
Thromboembolism	3.0
All Bleeding	3.5
Major Bleeding	1.5
Paravalvular Leak	1.2
Endocarditis	1.2

In the comparison to OPCs for each adverse event, the null hypothesis being tested is that the true adverse event rate for each test group is equal to or greater than twice the acceptable rate. Rejecting the null hypothesis would conclude that the rate for the test groups is less than two times the acceptable rate. The null and alternative hypotheses can be written as:

Null hypothesis: $R \geq 2R_A$

Alternative hypothesis: $R < 2R_A$

Table 1
Sample Size Estimation for On-X Trial
LD Therapy vs. Control

The sample size estimation is based on one-sided proportion test, which tests that the incidence rate of thrombosis, thromboembolism and hemorrhage in the LD therapy groups are at least as low as the control groups.

Type I Error (One-sided Test)	Statistical Power	Expected Proportion In Control Group	Expected Proportion In Low Dose Group	Maximum Allowable Difference between Two Groups to Declare Non-inferiority	Needed Patient Years
0.05	80%	7.3%	4.5%	2.0%	309
			5.0%	2.0%	398
			6.0%	2.0%	719
			7.3%	2.0%	2112
			4.5%	1.5%	381
			5.0%	1.5%	504
			6.0%	**1.5%**	**992**
			7.3%	1.5%	3739
			4.5%	1.0%	483
			5.0%	1.0%	663
			6.0%	1.0%	1461
			7.3%	1.0%	8388
0.025	80%	7.3%	4.5%	2.0%	393
			5.0%	2.0%	506
			6.0%	2.0%	914
			7.3%	2.0%	2682
			4.5%	1.5%	484
			5.0%	1.5%	641
			6.0%	1.5%	1260
			7.3%	1.5%	4748
			4.5%	1.0%	613
			5.0%	1.0%	842
			6.0%	1.0%	1856
			7.3%	1.0%	10650

Where R is the observed event rate and R_A is the corresponding OPC. FDA's guidance document estimates that 800 patient years are required to test this hypothesis assuming 95% confidence, 80% power and an annual attrition of 5%. This amount of trial experience is consistent with the requirements of the first criterion shown in Table 1 indicating that a patient group of 200 followed for 5 years average or 150 followed for 6.7 years average will be adequate for both purposes.

E. Center Participation

The principal investigators selected will be responsible for fulfilling the clinical trial requirements that are outlined in this investigational plan. The investigational center should have the necessary resources to allow the investigator to adhere to all clinical trial requirements. The following criteria will be used to select centers and investigators for participation in this clinical trial:

- Expertise in clinical areas relevant to the On-X heart valve LD therapy clinical trial. This includes an extensive background in cardiovascular surgery and management of patients with prosthetic heart valves, and prior experience in conducting clinical studies on prosthetic heart valves.
- Appropriate and sufficient personnel should be available to obtain and report data as required by the investigational plan. There should be an investigational group at each center consisting of at least: the investigator (a cardiovascular surgeon); co-investigators, who will also implant the study valve; and a center study coordinator to manage, organize and coordinate the routine activities of the clinical trial.
- Appropriate and sufficient patient population should be available to meet the implant schedule requirements for aortic and mitral prostheses.
- Access to a hospital and/or clinic having the equipment necessary to perform the clinical trial.
- Willingness to comply with all aspects of the clinical trial as described in the investigational plan. This includes collection of complete and accurate data in a timely manner according to the prescribed patient follow-up schedule. Additionally, investigators should be accessible to their support staff, and sponsor and monitor personnel.

A visit by the sponsor and/or monitor will be scheduled with the investigator and members of the investigational group to provide in-depth training and discussion of the investigational plan and clinical trial requirements prior to the first implant.

Topics to be covered at the pre-study visit will include:

- Review of the study protocol requirements - particularly patient selection and informed consent;
- Review of proper data management;
- Review of follow-up requirements and monitoring procedures;

- Review of anticoagulant regime;
- Review of complication definitions and reporting;
- Review of explant procedures; and
- Review of reporting requirements.

F. Study Responsibilities (Records And Reports)

Sponsor –

The sponsor shall be responsible for the following activities:

a) selection and training of investigators;

b) ensuring that all information within the study is properly distributed;

c) providing all study materials, such as preclinical data and documentation, valves, case report forms, etc.;

d) obtaining and keeping records of all approvals, and agreements;

e) selection of monitors;

f) ensuring that provisions for compensation in the event of injury are made;

g) ensuring compliance (through the monitor) with the investigational plan;

h) maintaining all correspondence pertaining to the investigation;

i) obtaining, keeping and reporting adverse device effects per the protocol and all rules and regulations;

j) reporting any approval withdrawals, and if necessary, terminating the study;

k) keeping a current investigator list;

l) filing appropriate progress and final reports; and

m) reporting any failure to obtain prior informed consent.

Monitor –

The monitor shall be responsible for the following activities:

a) secure compliance with the investigational plan;

b) evaluate and report adverse effects (expected or unanticipated);

c) if necessary, assist in termination of the study;

d) identify protocol deviations or problems;

e) audit data from case reports;

f) confirm informed consent;

g) help train centers in conduct of the study;

h) maintain sponsor to investigator communications;

i) determine cause of plan deviations and work to remedy those deviations; and

j) document any patient withdrawals.

The monitor must establish a good working relationship with the administrator (study coordinator) at each clinical center.

Investigator –

The principal investigator at each center is responsible for the following activities:

a) ensures that the investigation is conducted in accordance with the plan;

b) ensures protection of patient rights and welfare;

c) works to achieve adequate patient enrollment;

d) obtains and maintains local institutional approval;

e) supervises the use of the device by any co-investigator;

f) maintains accurate and complete records on each patient within the study, including and especially informed consent, and forwards these records on a timely basis;

g) keeps records of all communications regarding the study;

h) properly reports any deviation from the protocol, especially failure to obtain informed consent, any withdrawal of local approval, and any unanticipated adverse event;

i) reports regularly on the progress of the study;

j) reviews and approves, by signature, the data forwarded to the sponsor; and

k) reviews and approves any final report of the study.

The investigator should use a member of his/her staff as a study coordinator, whose functions are to conduct the day-to-day administrative activities of the study, such as completion of case report forms, scheduling of follow-up, maintenance of records and filing of reports. The investigator must sign the agreement contained in Appendix B.

Other participating investigators –

INR monitoring and home testing:
Michael Fine, National Sales Manager
Quality Assured Services, Inc. (QAS) (now Alere Home Monitoring)
1506 N. Orange Blossom Trail
Orlando, Florida 32804-6103

Blood testing services:

Marilyn Johnston, President
Hemostasis Reference Centre
Henderson Research Centre
711 Concession Street
Hamilton, ON L8V 1C3
Canada

Core echocardiographer and laboratory:

Dr. Karen Hamilton

Department of Cardiology

University of Florida

1600 SW Archer Rd.

Gainesville, FL 32610

Study pathologist:

Dr. Mark Silberman

Clinical Pathology Laboratories

9200 Wall Street

Austin, Texas 78754

Web-Based Data Management:

Chris Porter, Vice President of Operations

Clinipace, Inc.

3200 Chapel Hill-Nelson Boulevard, Suite 100

Research Triangle Park, North Carolina 27709

III. Patient Follow-up

A. Endpoints

Safety –
The primary study endpoints are the rates of occurrence of valve thrombosis, thromboembolism, all major and minor bleeding events whether or not related to drug therapy, reoperation, explant and death. Other valve related adverse events including endocarditis, hemolysis, hemolytic anemia, paravalvular leak and structural and non-structural dysfunction are secondary endpoints. All events shall be as defined by the AATS/STS guidelines [2] for reporting valve study results.

Effectiveness –
Effectiveness endpoints are also secondary endpoints and shall be New York Heart Association (NYHA) functional classification and the echocardiographic hemodynamic parameters of peak and mean gradient and effective orifice area (EOA). Echocardiographic exams shall also evaluate indexed EOA, performance index, cardiac output, cardiac index and amount and location of any valvular regurgitation.

B. Follow-up Regime and Intervals

The intent of the study design is to treat mechanical valve patients with less aggressive anticoagulation. The control group drug regimes are those from the recommendations for mechanical valves of the ACCP[3] and the AHA/ACC[4], while test group regimes are either a clopidogrel/aspirin mix for low risk aortic patients or reduced Coumadin to just below the present recommendations but with aspirin added. Patients will be maintained on Coumadin/aspirin beginning immediately postoperatively, with heparin used from operation until INR target is reached. Randomization and transfer to test group will occur at the 3-month visit. INR control will be accomplished using home monitoring with the system provided by QAS or in Italy with systems as provided within the processes used in medical care there. The patient in consultation with his/her physician will also make drug dosage adjustments.

Patients will be followed at 3 months, 6 months and 1-year, then annually thereafter until the study is completed when the patient groups reach sufficient patient-years experience at up to 8-years of follow-up for any individual patient and at least 1-year follow-up for all patients. Visits will be scheduled within 1-month of the appropriate anniversary. Follow-up will be conducted by physician visit.

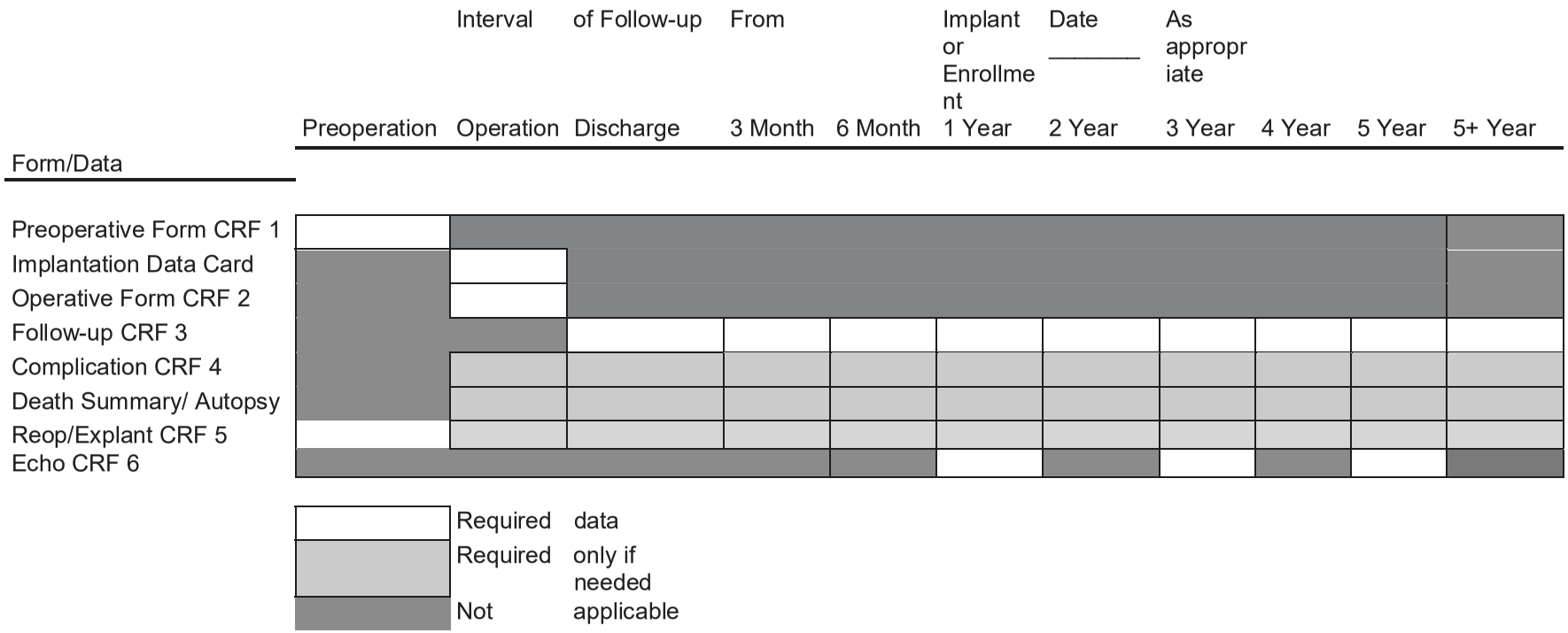
C. Investigational Procedures

The sponsor will provide case report forms (CRFs) or equivalent electronic data management tools to each principal investigator for the purpose of recording patient data. Assessments will be obtained for the preoperative, operative and discharge period and postoperatively at three and six months and annually to 5 years from the date of implant (Table 2 summarizes the required information at each visit). A follow-up schedule will be provided for each patient based on the implant date.

This protocol is designed to be used within the normal daily practice of each center. No specific instructions other than those in the labeling are given on valve orientation or concomitant drug therapies. This will result in a study that defines complication rates under the various drug therapies.

The investigator will make every attempt to follow the patients and will document the information gathered during the follow-up visits on the CRFs. Follow-up

Table 2 - Patient Progress and Data Record



visits should be made in person; telephone or questionnaire follow-up is not allowed. The patients will be encouraged by the investigator to report any address or telephone number changes. They will also be informed of the importance of returning for scheduled follow-up visits even if they are not having any problems. All dates within the study will be recorded as month/day/year using numeric designators for months. If additional space is needed on any form for any data, the data can be placed on a separate sheet and attached to the form.

The study coordinator should submit preoperative, operative and discharge case report forms within 30 days of the implant. As an exception, these CRFs may be forwarded within 30 days of discharge, if discharge is delayed by patient complication.

All appropriate sections of the CRFs must be filled out accurately and completely. All case reports form must be reviewed, signed and dated by the investigator. The CRFs should be sent expeditiously to the monitor, when completed, and be kept in the patient record notebooks or electronic files provided by the sponsor.

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 as required by United States law and regulation. For this reason, the sponsor is not routinely collecting patient names, but using a study number or initials, if necessary, 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.

Enrollment Process and Options -

The following procedures may be used for enrolling patients into the study:

AVR High Risk and MVR Patients

- From review of patient charts determine the patient's eligibility for inclusion in either of these two groups.
- Patients that eventually qualify for high risk AVR based solely on hypercoagulability testing, which must be done preoperatively off warfarin, must be recruited preoperatively as described below under low risk AVR.
- All other patients can be approached for consent either preoperatively or postoperatively up to 60 days at the discretion of the investigative site. MVR patients may be enrolled up to 1 year postoperatively.
- Once a patient has consented initiate the patient in the Clinipace database by starting a preoperative form which will automatically assign the patient number for the study. Do not assign numbers manually.
- In North America then complete the home monitoring prescription paperwork and forward to QAS right away so the insurance qualification process can begin.
- In North America randomize the patient 2 weeks prior to their 3 month visit postoperative or for MVR patients at enrollment visit if greater than 3 months postoperative and provide QAS with the study INR target range for the patient

and the home test machine order. Use Italian home monitoring procedures elsewhere, and randomize as above.

- Conduct the 3 month visit which will start the study for the patient. Change drug therapy per the protocol and randomization result.

Low Risk AVR Patients (No longer active arm of trial)

Determine the patient's potential eligibility for the low risk AVR group understanding that the group may change to high risk AVR pending the results of the hypercoagulability and drug response testing described below.

Completely Preoperative Testing Option

- Approach all eligible patients for informed consent, and once consent is given, start the laboratory testing program. At this time also enter the patient into the Clinipace database for the assignment of the patient number.

- Order clopidogrel through Canada Drug or the local VA pharmacy as appropriate. This order is for 10 – 75mg tablets to be shipped to the patient's home overnight. The prescription should prescribe a 300 mg loading dose on day 1 and 75mg/day for 1 week. Instruct the patient to take the drug in this manner. Also instruct the patient to buy and take 325 mg aspirin once daily.

- Have the patient return for testing at least 5 days later. Confirm that they are taking their antiplatelet medications. Draw the appropriate blood samples per the Accumetrics and HRL instructions and also get the required urine sample. Process all the samples for HRL per the HRL instructions and the Accumetrics P2Y12 test within 4 hours. Regardless of the Accumetrics test result, freeze and ship all other samples per the HRL instructions. Clopidogrel can be stopped as soon as the P2Y12 test is successfully done. A P2Y12 result of <35% inhibition disqualifies the patient but the full testing should still be done. A urine thromboxane result of >298 pg/mg disqualifies the patient.

- Enter the shipment information into the Clinipace database and wait 24 hours for the lab to respond that the samples have arrived properly. Hint: arrange the testing and shipment schedule to occur early in the work week to avoid any overnight sample arriving at the lab on the weekend.

- If samples arrived in good condition, instruct the patient to stop taking the drugs and schedule the operation for at least 5 days later.

- Complete the home monitoring prescription paperwork and forward to QAS right away so the insurance qualification process can begin in case it is needed after randomization.

- Randomize the patient 2 weeks prior to their 3 month visit and either order clopidogrel for test group patients or provide QAS with the study INR target range for the control group patients and the home test machine order. The clopidogrel prescription is for a 90 day supply with 7 refills the dosing regime is 300mg loading dose on day 1 and 75mg/day thereafter.

- Conduct the 3 month visit which will start the study for the patient. Change drug therapy per the protocol and randomization result.

Preoperative Hypercoagulability and Postoperative Drug Response Option -

- Approach all eligible patients for informed consent, and once consent is given, start the laboratory testing program. At this time also enter the patient into the Clinipace database for the assignment of the patient number.
- Draw the appropriate hypercoagulability blood samples per the HRL instructions. The patient must be off warfarin for this testing. Process all the samples for HRL per their instructions.
- Enter the shipment information into the Clinipace database. Hint: arrange the shipment schedule to occur early in the work week to avoid any overnight sample arriving at the lab on the weekend, so keep any frozen samples until Monday if drawn on Friday for example.
- Complete the home monitoring prescription paperwork and forward to QAS right away so the insurance qualification process can begin in case it is needed after randomization.
- The patient's surgery can proceed under normal scheduling plans.
- At 50 days postoperatively, call the patient to determine that the patient's INR is stable and in target range then order clopidogrel through Canada Drug, or the local VA pharmacy as appropriate. This order is for 10 – 75mg tablets to be shipped to the patient's home overnight. The prescription should prescribe 75mg/day for 1 week to 10 days (no loading dose). Instruct the patient to take the drug in this manner. Also instruct the patient to buy and take 325mg aspirin daily. If the patient's INR is high adjust the Coumadin dose to bring the INR in range before starting clopidogrel. Also confirm that the patient is taking his/her antiplatelet medications. It is also recommended that a CBC be done locally to make certain that the patient is not clinically anemic, which could create an inaccurate P2Y12 measurement.
- At 60 days bring the patient into the office for their drug response testing. Draw the appropriate blood samples per the Accumetrics instructions and get the required urine sample for HRL. Process the blood sample for the Accumetrics P2Y12 test within 4 hours. Also freeze and ship the urine per the HRL instructions regardless of the P2Y12 result. A P2Y12 result of <35% inhibition disqualifies the patient but the full testing should still be done. A urine thromboxane result of >298 pg/mg disqualifies the patient.
- Enter the shipment information into the Clinipace database. In 24 hours the lab should respond that the sample has arrived properly. Hint: arrange the testing and shipment schedule to occur early in the work week to avoid any overnight sample arriving at the lab on the weekend.
- Randomize the patient 2 weeks prior to their 3 month visit and either order clopidogrel for test group patients or provide QAS with the study INR target range for the control group patients and the home test machine order. The clopidogrel prescription is for a 90 day supply with 7 refills the dosing regime is 300mg loading dose on day 1 and 75mg/day thereafter.

- Conduct the 3 month visit which will start the study for the patient. Change drug therapy per the protocol and randomization result.

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 implantation of the study device. 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., age at implant, gender, New York Heart Association (NYHA) functional class, cardiac rhythm, disease etiology, previous cardiac surgery, relevant information to determine thromboembolic risk group and valve lesion (i.e., stenosis, regurgitation or mixed stenosis/regurgitation).

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 and attach an explanation, as appropriate. When asked to specify a particular answer, use a short description. Please check any and all items that apply to the patient.

For patient study number, use a 6 digit code. The first two digits are your center number, as assigned by the sponsor. The third number represents the position of the implant; 1 for aortics, and 2 for mitrals. The last three digits are assigned sequentially to each patient. For example, if your center number is 99, your first aortic patient study number is 991001, your first mitral patient study number is 992001, and so forth. Once the patient study number is assigned on CRF1, use of the patient study number is required to identify the patient on subsequent forms.

NYHA functional class uses the 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.

Any failure to obtain prior informed consent must be reported to the sponsor, and the institution within 5 working days.

Previous cardiovascular surgery 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 or long-term preoperative Coumadin therapy, the preoperative INR should be measured and recorded within 72 hours prior to surgery.

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, but must be documented on CRF2.

The investigator will record on CRF2 information regarding the particular valve(s) implanted and other details concerning the surgery such as suture technique and any concomitant procedures. Carefully record the valve position, size and serial number.

Use the patient study number 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.

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.

The Implant Registration Card is included with the valve packaging and is used for tracking valves within the study. It must be completed and returned to the sponsor within 24 hours of the surgery. Sending a copy of the card to the sponsor by facsimile or e-mail is adequate to fulfill this requirement.

There is also a permanent patient record card included in the package labeling. This card is to be completed and given to the patient as a form of permanent medical identification.

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 CRF3. The early 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 amticoagulation 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 required by this protocol in section II C.

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 off schedule visit.

Late Follow-up Reporting –

Late follow-up is required in at 3 and 6 months postoperative intervals, and annually postoperatively through at least 1 but no more than 8 years. For MVR patients enrolled greater than 60 days postoperatively, follow-up will be at 3-months post enrollment then annually on the anniversary of implant. This is also done on CRF3. Follow-up must be in person; telephone or questionnaire follow-up is not allowed. If a patient misses a scheduled follow-up visit, the investigator must make an effort to contact the patient to determine the reason for the missed visit. A new visit should be scheduled, but if the patient refuses to return for follow-up or otherwise cannot be

contacted, the patient is then recorded as lost or withdrawn from the study. The efforts to maintain contact will be documented on the follow-up form, and every effort will be made to minimize the number of patients lost (zero being preferable). Thus, a follow-up form (CRF3) is due annually on each patient whether or not follow-up has occurred.

At the 3 month follow-up each patient shall be randomized into treatment group. The investigator will log into the data management system to be assigned the random (test or control) group for the patient per the web-based procedure briefly described below. If any patient has suffered a thrombotic or bleeding event during the initial 3 month period, he/she shall not be randomized into a group and shall be considered a screening failure and the event shall not be analyzed with any group under an intent-to-treat classification.

The randomization module implements a standard randomization algorithm, Marsenne Twister that is implemented in Java. (Matsumoto M. and Nishimura T., "Marsenne Twister: A 623-Dimensionally Equidistributed Uniform Pseudo-Random Number Generator", ACM Transactions on Modeling and Computer Simulation, 1998;8:3-30.) The patented randomization module can provide block and stratified randomization results.

The procedure automatically executes upon eligibility documentation for a study subject. The randomization result is presented on the screen instantaneously upon eligibility documentation using sponsor provided language and is also stored in the study database. The Tempo electronic randomization process ensures only eligible subjects are randomized and no errors are made in storing the correct result of randomization. The Tempo system audit trail documents the randomization results and time of execution.

Late follow-up information includes in all cases the patient initials or ID, cardiac rhythm, NYHA classification, and anticoagulant therapy information, including where applicable the most recent INR provided by the patient or QAS. For any new complication, the complication report (CRF4) must be completed and attached. All complications that have occurred between follow-up examinations must be reported on the form. Echocardiography per section III D is required at 1, 3 and 5 years.

Complication Reporting –

All complications should be recorded by the investigator on CRF4. 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 [(2)] and will provide pertinent details of the event on CRF4. Copies of autopsy report and/or death summary must be included where applicable.

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 expected, or those occurring at a greater rate than expected when compared to the review requirements of this study (see section III F).

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."

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 [(2)]. 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 and death must be recorded on the appropriate sections of CRF4. For death, the cause of death must be established, and an autopsy performed when possible. Attach supporting hospital reports when appropriate. Following completion of the information, the investigator must review, date, and sign the CRF.

Specific Instructions for Completing CRF4 –

The complication form (CRF4) is designed to allow the identification of event type, then to note how each event was 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 CRF4.

Study valve related reoperation is defined as any operation that repairs, alters or replaces an 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 CRF4.

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 sections that follow.

Thromboembolism

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

A transient neurological event is defined as an abrupt onset of a focal neurological deficit lasting at least one minute but resolving without permanent sequelae.

Acute myocardial infarction (MI) is included as a thromboembolic complication when coronary anatomy was normal at the time of implant and there is no angiographic or other clinical evidence that the MI was due to coronary artery spasm or newly-developed coronary artery disease.

Thrombosis is any thrombus not caused by infection attached to or near an operated valve that occludes part of the blood flow path, interferes with valve function or is sufficiently large to warrant treatment. This is listed as a subcategory of thromboembolism and should be confirmed by imaging study, reoperation (explant) or autopsy. Any patient with confirmed prosthetic valve thrombosis is to be treated with surgery, thrombolysis and/or heparin based on the clinical assessment of the particular patient and on what is considered best and most appropriate treatment for the patient. 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).

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 on the complication form (CRF4).

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.

Bleeding Events

Hemorrhage is defined as any episode of internal or external bleeding in patients whether or not they are receiving anticoagulant therapy. This also includes any episode of hemorrhagic tamponade. Any anticoagulants used and 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, stroke, 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 from open traumatic wounds (cuts, abrasions, etc.) 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 positive blood cultures, clinical signs (fever, new/altered cardiac murmurs, splenomegaly, systemic emboli, and immunopathological lesions). 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 should be based on an examination of the explanted or damaged valve. 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, leaflet entrapment by suture or pannus, paravalvular leak and hemolytic anemia. The diagnosis should be confirmed by examination of the damaged or explanted valve. Events to be excluded are those associated with endocarditis, paravalvular leak, 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 intervention) or minor (does not require surgical intervention).

Hemolytic Anemia

Hemolytic anemia will be recorded as a complication in all cases of anemia that are attributable to the valve, based on usual clinical criteria. Indicate if hemolytic anemia is primary or secondary to another valve related adverse event (e.g., paravalvular leak). Events that are excluded are those due to liver disease, myocardial infarction, or systemic infection, where these causes are confirmed by other clinical evidence.

Hemolysis

On going hemolysis shall be defined by plasma free hemoglobin elevated to 125% of laboratory upper normal and serum lactate dehydrogenase (SLDH) values at greater than twice (200%) the laboratory upper normal unless the cellular source of the SLDH can be determined to be other than the red blood cell as evidenced by isoenzyme elevation of LD3, LD4 or LD5, and/or clinical evidence of recent myocardial infarction. Plasma free hemoglobin, serum haptoglobin, reticulocyte count and SLDH shall be tested whenever hemolysis is suspected in any patient and SLDH isoenzymes shall be fractionated whenever the SLDH test value is above 175% of upper normal.

Unanticipated Valve-Related Event

It is unknown what kind of event would qualify for the use of this form, but it is supplied in case any unknown valve-related complication should arise that does not meet any other defined criterion. 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.

D. Echocardiography Procedures

Echocardiographic evaluation of the study prosthesis **is required** by transthoracic methods, and at the first, third and fifth annual follow-ups. For MVR patients enrolled late postoperatively the 1-year echo will occur at the visit closest to 1-year after surgery and 3-year and 5-year echoes at 3 and 5 years post surgery.

The echo technician shall ensure that all views have been obtained and that all data are reviewed for accuracy before the patient has left the facility.

The echocardiography protocol used will generally follow that developed by FDA in its guidelines[(1)], but specifically shall follow the steps given in Appendix F. Echo reports along with an electronic copy of the echo shall be sent to the monitor for eventual review by the core cardiologist. Only directly measured data will be provided by the center, and all calculated data will be derived at the core center. The core cardiologist will reassess thrombus and regurgitation as well.

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. The progression of interrogation regions is transgastric, esophagogastric, and mid-esophageal. 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. All data reported on CRF 6 should be the average from a minimum of three cycles for patients in sinus rhythm or a minimum of five cycles for patients in atrial fibrillation or other arrhythmic states.

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

Valve hemodynamics are to be gathered from the view giving the best signal. If the view used is different from those listed in the progressions noted in the previous section, then note the view used for either pressure or regurgitation measurement.

Provide the hemodynamic data requested on the form from the view that provides the best signal.

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 noted as unavailable on the CRF.

E. Reoperation and/or Explant Procedures

Whenever a valve reoperation occurs whether or not as a result of one of the complications described in Section C above complete and return CRF 5.

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. 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 CRF5 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 CRF5.
2) Attach any *in situ* photographs to CRF5.
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.

F. Adverse Events

If a test group patient suffers a thrombotic event during the trial, he/she will be removed from the cohort and returned to standard Coumadin therapy. If a test group patient suffers a bleeding event during the trial, he/she may continue with the LD therapy regime or may be removed from the study depending upon the principal investigator's clinical judgment. In any case such patients shall be followed and remain in the test group for analysis purposes based on an intent-to-treat classification.

G. Study review

At least 3 independent advisors, including at least one each from cardiology, cardiac surgery and statistics, will act as the Data Safety Monitoring Committee. The Committee will examine reports of adverse events and their rates of occurrence on a regular basis, no less often than annually. The Committee will also review the occurrence of any thrombotic event as early as feasible after it occurs. The Committee shall have the power and authority to direct changes in, or termination of, the study. The study shall be terminated, if at anytime, while patients are maintained on LD therapy, the rates of thrombotic and bleeding events exceed either the rate in the control group, the expected rate from the sample size calculation, or twice the aggregate rate of such events reported for other bileaflet valves in the peer reviewed literature, as determined by meta-analysis.

Changes to the plan can only occur with concurrence of the Data Safety Monitoring Committee and ethics committees.

The committee shall initially consist of:

1. Dr. Sidney Levitsky
   Professor of Surgery
   Beth Israel Deaconess Hospital
   Harvard University
   Boston, Massachusetts
2. Dr. Jean Dumesnil

Professor of Cardiology
Hopital Laval,
Ste-Foy, Quebec, Canada

3. Dr. A. Graham Turpie
   Professor of Hematology
   McMaster University
   Hamilton, Ontario, Canada
4. Jay Herson, Ph.D.
   Adjunct Faculty, Biostatistics
   Johns Hopkins University
   Baltimore, Maryland

H. Data Analysis

Data will be analyzed using Kaplan-Meier life tables and linearized rates. Although randomization does not occur until month 3, early postoperative data (≤ 3 months postoperative) will be analyzed to examine potential differences between test and control groups using regular percentage comparisons. Data will be stratified by risk factors including age and others as appropriate. Data forms will be completed preoperatively, operatively and at each follow-up. This can be done on paper or electronically at the mutual choice of the center and the study monitor.

Case Report Forms –

Example Case Report Forms are provided in Appendix A. A forms notebook or electronic database 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. An electronic database may also be used for this purpose. Extra forms will be provided on request, or as needed.

I. Reports

Summary reports of the study shall be produced annually by the sponsor and monitor, and be provided to each investigator, Data Safety Monitoring Committee member and ethics committee chairperson.

IV. Device Description and Risk Analysis

The On-X prosthesis is a bileaflet mechanical heart valve prosthesis. The housing consists of On-X pyrolytic carbon coating on a graphite substrate.

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 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.

A review of the literature on Coumadin anticoagulation of mechanical heart valve prostheses is inconclusive on the preferable therapy for various valves. Various groups have struggled with the lack of information on the subject of anticoagulation; yet have crafted recommendations based on information available. These include the ACCP [(3)] and AHA/ACC [(4)] recommendations. Butchart[(5)] in a review of embolism in prosthetic heart valves concluded that valves vary in susceptibility to thrombosis due to subtle design differences, that optimal INR range is often uncertain, and that further research is needed.

Many studies of various mechanical valves have attempted to examine low intensity Coumadin therapy, Coumadin plus aspirin, aspirin alone and even no anticoagulation. These studies have had mixed results. Horstkotte [(6)] suggested that INR levels of 3.0 to 4.5 are too high for the St. Jude valve, but that a prospective trial is needed to show the proper level. Cannegieter [(7)] in the first detailed study of optimum anticoagulation suggested the target of 3.0 to 4.5 initially.

Others have studied and suggested lower INR targets [(8-12)] in the range of 2.0 to 3.0. These studies resulted in the lower recommendation of ACCP and ACC.
Still other groups have examined lower Coumadin in combination with antiplatelet agents, such as aspirin or dipyridamole. Starting with the work of Turpie, et al [(13)] various groups have shown a benefit of adding aspirin or dipyridamole, to Coumadin [(14-15)]. But some mixed results indicating a possible increase in bleeding occurred with addition of aspirin [(16-17)]. Three separate meta-analyses [(18-20)] support the addition of low-dose aspirin or dipyridamole to Coumadin.

Another strategy for reducing thrombotic and bleeding events from Coumadin therapy is to control the therapy better with clinic or home monitoring. These studies have uniformly shown better results with better control [(21-23)]. Yet still bleeding and thrombosis rates are considered suboptimal for mechanical valves, even though a background rate for these events exists that becomes about 2% per year at 80 years old [(24)].

As mechanical valves have long been known for their durability, they have also been thought to require long-term Coumadin anticoagulation to prevent thrombotic events. This requirement subjects patients to an increased risk of bleeding events and has been

the major shortcoming in the performance of mechanical valves. It is, therefore, desirable to reduce or eliminate Coumadin anticoagulation.

The valve selected for this trial must also be shown to perform better than existing mechanical valves in terms of adverse events and other surrogate endpoints that indicate possible reduction of events based on the effects of valve design. These endpoints include adverse event rates, (especially in relation to the degree of anticoagulation actually achieved in a study), hemodynamics and hemolysis.

The On-X aortic valve has been shown to achieve low adverse event rates [25,26], especially in the face of sporadic anticoagulation [27]. This is true also when compared to a similar contemporary study [28]. The hemodynamics of the valve are superior to other mechanical valves [26,29] indicating a reduction in turbulence which can effect blood damage and thrombotic events. The valve also produces very little hemolysis in the aortic or mitral position [30], which also indicates a potential for reduced thrombotic complications.

A study of the valve in sheep in a model designed to predict resistance to thrombosis, performed by Flameng (31), found that the On-X valve statistically outperformed both the SJM and CMI valves. The first thrombosis of an On-X valve occurred at 6 weeks compared to 2 weeks for the others. Additionally, 2 of 6 test valves survived the test without thrombosis compared to 0 of 7 for the others.

In an ongoing clinical trial in South Africa (32), 200 On-X valves have been implanted with 100% follow-up out to about 3 years. About 40% of these patients are not anticoagulated due to the social conditions in South Africa, yet there has been only one thrombosis event in the mitral position in the study. Given the valve's clinical performance to date, it is an ideal candidate for a study using lower dose Coumadin.

V. Monitoring Procedures

The monitor of the study shall be a professional staff member of the Clinical Studies Department of the sponsor. 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 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 audits 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 clinical trial monitor 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 Visit and Audit:

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 audit.

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

Interim Visits:

Interim visits to the study centers will be conducted as deemed to be necessary, typically only when circumstances require additional training or assistance as determined by the monitor.

Final Center Visit:

A final visit to the study center may be made by the monitor, if necessary. Any ongoing responsibilities that will continue after the final visit will be discussed with the investigator and the study center coordinator. A final monitoring report, which includes device inventory verification and disposition of unused devices, will be prepared by the monitor.

Regular Reports:

The monitor will provide regular at least quarterly summary reports of the clinical investigation to all investigators and the sponsor. The contents of these reports will be determined by the monitor and sponsor jointly.

The sponsor or monitor will provide reports to each investigator based on individual requests for data. Each investigator will also get at least a quarterly update of the required activities for the study at his/her center.

VI. Legal/Ethical Considerations

The study will be conducted under the rules of the local country or the Declaration of Helsinki whichever provides more patient protection. Where governmental approval is required (FDA, competent authority or Health Canada), it will be obtained prior to starting the study at any center in such country. All centers will have the approval of their local ethics committee before beginning patient enrollment. All patients will be given adequate written informed consent. The patient must agree to, and understand, the drug therapy regime and the follow-up requirements. Informed consent shall include all elements of information required by international standards, and shall notify the patient that data will be shared with government regulatory bodies as needed. See the example in Appendix C.

Sponsors must be able to verify to regulatory agencies, e.g., the Food and Drug Administration, that this clinical investigation has been conducted in accordance with

ethical principles. The Investigational Device Exemption (IDE) regulation applies to the United States. At each center investigators are required to:

- Obtain informed consent from patients involved in the clinical trial
- Obtain Institutional Review Board approval prior to starting the clinical trial at their institution.

Copies of the presently approved labeling for the device are contained in Appendix D. A list of all IRB and Investigator Information in included in Appendix E.

VII. References

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Appendix A

Case Report Forms

Institution: Investigator:	MCRI On-X® Low Dose Anticoagulation Study CRF 1 (p1 of 2) Preoperative Data	Patient Initials ☐☐☐ Patient No. ☐☐ - ☐☐☐☐

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:

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

7. Previous cardiac surgery: ☐ Yes ☐ No (If yes, specify)
   ☐ CAB
   ☐ Valve ☐ A ☐ M ☐ T ☐ P
   ☐ ASD
   ☐ VSD
   ☐ PPM /ICD
   ☐ PTCA/Stent
   ☐ Other: _____

8. Pre-operative Anticoagulation Yes ☐ No ☐
   ☐ Heparin ☐ Warfarin/Coumadin ☐ Clopidogrel ☐ Aspirin ☐ Indandione derivatives
   INR: _____ INR Target Range:_____ Date (m/d/y): _____

Institution: Investigator:	MCRI On-X® Low Dose Anticoagulation Study CRF 1 (p2 of 2) Preoperative Data	Patient Initials ☐☐☐ Patient No. ☐☐ - ☐☐☐☐

9. Preoperative risk characteristics
   Ejection fraction (%0 _____
   Left atrial systolic dimension (mm) _____
   Spontaneous echo contrasts ____Yes ____No
   Ventricular aneurysm ____Yes ____No
   Vascular pathology ____Yes ____No
   Neurological events ____Yes ____No
   Estrogen replacement therapy ____Yes ____No

10. Preoperative blood test results (AVR only)

    Factor V Leiden Mutation _____

    Prothrombin Mutation _____

    AT-III Activity _____

    Protein C Activity _____

    Protein S Activity _____

    Factor VIII Activity _____

    Lipoproteins _____

    Serum Thromboxane B2 _____

    Urine Thromboxane B2 _____

    Endogenous Thrombin Potential _____

    P2Y 12 _____

11. Patient Qualifies for Group - I) Low Risk Aortic _____, II) High Risk Aortic _____, III) Mitral _____

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

Institution: Investigator:	MCRI On-X® Low Dose Anticoagulation Study CRF 2 Operative Data	Patient Initials ☐☐☐ Patient No. ☐☐ - ☐☐☐☐

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

Valve Information: Aortic Size: _____mm Serial #: _____

Mitral Size: _____mm 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
	Aprotinin ☐ 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	If Yes, explain:_____	

Valve Orientation: Check the most accurate valve orientation description below based upon the direction of the valve axis.
Mitral: ☐Anatomical ☐ Antanatomical ☐ Other, describe: _____

Aortic: ☐ LC/RC commissure ☐ RC/NC commissure ☐ NC/LC commissure
☐ Other, describe: _____

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

Institution: Investigator:	MCRI On-X® Low Dose Anticoagulation Study CRF 3 Follow Up	Patient Initials ☐☐☐ Patient No. ☐☐ - ☐☐☐☐

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

☐ Early PostOperative/Discharge

☐ Interim (3___ or 6___ month)

☐ Annual (_____year) (12 + 2 month interval)

☐ Off Schedule

Group:_____ Randomized to: Treatment _____ Control _____

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 4)
Type of Examination: ☐ Office/Outpatient ☐ Hospital ☐ Telephone ☐ Other _____	
NYHA Class: ☐ I ☐ II ☐ III ☐ IV ☐ Unknown	
Cardiac Rhythm:	☐ Sinus ☐ Regular ☐ Paced ☐ Irregular ☐ Atrial Fibrillation ☐ Other, specify:_____
Anticoagulant Therapy:	☐ None ☐ Warfarin/Coumadin ☐ Clopidogrel ☐ Heparin ☐ Aspirin ☐ 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 4)	

Echo Completed (m/d/y)_____ Attach CRF 6 and send echo, applicable only at 1, 3 and 5 yr follow-up.

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

Institution: Investigator:	MCRI On-X® Low Dose Anticoagulation Study CRF 4 Complications 1 of 2	Patient Initials ☐☐☐ Patient No. ☐☐ - ☐☐☐☐

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

Duration: _____ ☐ Weeks ☐ Days ☐ Hours ☐ Minutes

Etiology: _____

Complication Type (check all that apply) Complication number: _____

1. ☐ Thromboembolism ☐ Neurologic: ☐ TIA ☐ Peripheral: ☐ Major ☐ Cardiac: MI ☐ Unknown
   ☐ RIND ☐ Minor
   ☐ CVA ☐ Fatal
2. ☐ Valve Thrombosis
3. ☐ Bleeding Event ☐ Major ☐ Minor
   ☐ Cerebral ☐ Cardiac ☐ Ocular ☐ GI ☐ Nosebleed ☐ Hematoma ☐ Other
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. ☐ Hemolysis (conduct blood tests)
7. ☐ Hemolytic Anemia (conduct blood tests) ☐ Primary ☐ Secondary to: _____
8. ☐ Congestive Heart Failure ☐ Valve Related ☐ Not Valve Related
9. ☐ Reoperation ☐ Repair ☐ Explant
10. ☐ Other Valve Related Explain: _____
11. ☐ Death - Primary Cause: ☐ Valve related ☐ Other cardiac ☐ Other ☐ Unknown

(continues next page……..)

Institution: Investigator:	MCRI On-X® Low Dose Anticoagulation Study CRF 4 Complications 2 of 2	Patient Initials ☐☐☐ Patient No. ☐☐ - ☐☐☐☐

Complication number: _____

Treatment: ☐ None ☐ Medication ☐ Hospitalization ☐ Surgery (Complete CRF5)

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-5)

Relationship to Device:

Valve Related: ☐ Yes ☐ No

Lab Test Results for Hemolysis, as needed:

Plasma Free Hemoglobin _____ Lab Upper Normal _____

SLDH _____ Lab Upper Normal _____ (LD1 ____, LD2 _____, LD3 _____, LD4 _____, LD5 _____)

Reticulocyte Count _____ Lab Upper Normal _____

Serum Haptoglobin _____ Lab Lower Normal _____

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

Institution: Investigator:	MCRI On-X® Low Dose Anticoagulation Study CRF 5 Reoperative Data	Patient Initials ☐☐☐ Patient No. ☐☐ - ☐☐☐☐

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

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

☐ Study Valve Repair
☐ Aortic ☐ Mitral
Specify:_____
_____

☐ CABG

☐ Pacer Implantation

☐ Aneurysm Repair

☐ Non Study Valve
☐ Replacement ☐ Repair
Position: _____
Procedure: _____
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): _____/_____/_____

Investigator Names: Center: ☐☐	MCRI On-X Low Dose Anticoagulation Study CRF 6 Echocardiography Data (page 1 of 2)	Patient Initals: ☐☐☐ Study No.: ☐☐☐☐

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

Investigator Names: Center: ☐☐	MCRI On-X LOW DOSE ANTICOAGULATION STUDY CRF 6 Echocardiography Data (page 2 of 2)	Patient Initals: ☐☐☐ Study No.: ☐☐☐☐

Date of Echo (m/d/y) _____

7. RECORD ONLY DATA AS APPLICABLE TO VALVE EXAMINED:

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

_____ mmHg Mean gradient

_____ cm Velocity time integral

7b. TRANSMITRAL WAVEFORM (FOR MVR): _____ m/s Peak velocity

_____ mmHg Mean gradient

_____ cm Velocity time integral

_____ ms Pressure half-time

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

	Through	Paravalvular	Uncertain
None	☐	☐	☐
+1 Trivial/trace	☐	☐	☐
+2 Mild	☐	☐	☐
+3 Moderate	☐	☐	☐
+4 Severe	☐	☐	☐

9. LEFT VENTRICULAR FUNCTION:

☐ Normal (EF>50%)

☐ Mild impairment (EF40-50%)

☐ Moderate impairment (EF30-40%)

☐ Severe impairment (EF<30%)

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

11. OTHER ABNORMALITIES: Describe: _____

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

APPENDIX B

MCRI

INVESTIGATOR AGREEMENT FOR ON-X® PROSTHETIC HEART VALVE
Clinical Trial of the On-X® Valve Using Low Dose Anticoagulation

I wish to participate in the supplemental clinical investigation of the On-X Prosthetic Heart Valve using low dose anticoagulation. I understand that this is a commercially available prosthesis which is manufactured by MCRI and is planned for testing for optimum anticoagulation 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 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. 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.
3. All information which I hereafter obtain from MCRI or any other person acting on behalf of MCRI about or relating to this study of the prosthesis, and all information which I have or will obtain under or concerning this study is considered by MCRI to be proprietary and confidential to MCRI. 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 MCRI or prior public disclosure by MCRI. I will also assure that any and all co-investigators listed here and reporting to me will maintain confidentiality as described above.
4. I will notify MCRI, in writing, when approval for this investigational study is obtained from the Institutional Review Board (IRB) or Ethics Committee.
5. I have never participated in an investigational study which has been terminated for reasons of noncompliance.
6. Additional investigators 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

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 C

Clinical Trial of the On-X® Valve Using Low Dose Anticoagulation

Example Patient Informed Consent Form

Statement of Research

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

Please read the following explanation and ask your physician any and all questions that you have before agreeing to participate in this study which will involve the On-X Prosthetic Heart Valve.

Information about the Research

The On-X heart valve consists of an On-X pyrolytic carbon housing and leaflets with a titanium alloy ring around the housing. There is a sewing ring made of knitted polytetrafluoroethylene attached to the housing with two titanium rings and suture material. I understand these materials have a long history of use in cardiac prostheses.

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 or mitral valve, or previously implanted mechanical or tissue aortic or mitral valve.

The purpose of this study is to define the lowest level of required antithrombotic (anti-blood clot) therapy for the Prosthesis. It is a randomized trial of three different antithrombotic drug therapies. The therapies include three treatment groups for patients with: 1.) low risk of clotting having an aortic valve replacement, 2.) higher risk of clotting having an aortic valve replacement, and 3.) a mitral valve replacement. Your doctor can tell you to which group you belong. To belong to a group you may be required to have certain blood and urine tests done. These require the collection of about 3 tablespoons of blood and a urine sample. Each treatment group will have a control group that uses the presently recommended antithrombotic drug therapy of the American Heart Association using Coumadin® and aspirin. You will be randomly assigned to the treatment or the control group that goes with your group. The treatment drug therapy for the low risk aortic valve replacement group is a combination of two presently used drugs – aspirin and Plavix®. The treatment drug therapy for the high risk aortic valve replacement group and the mitral valve replacement is a reduced dose of Coumadin and aspirin.

The Prosthesis is a device with about 11 years of clinical experience which have indicated that the valve is safe and effective in standard use. The valve has governmental approval for sale throughout the world wherever such approval is required. Particularly the valve is approved for sale in the United States under a premarket approval application with FDA numbered P000037. This clinical study will involve approximately 1200 patients. All patients will follow the same procedures and follow-up schedule except that each patient will be placed into a particular anticoagulation drug therapy randomly. Once enrolled a patient will be followed in the study for up to 8 years, and the overall study is expected to take up to 11 years to complete. When the information has been collected, it will be submitted to the appropriate regulatory authorities for approval to modify the recommendations contained in the labeling regarding appropriate long-term drug therapy for the valve.

Patients who have valvular heart disease 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 any other commercially available prosthetic heart valve. 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 and six months after surgery, and 12 months following surgery. After the 12-month visit, you will see your doctor on a yearly basis for at least 1 and up to 8 years. At your 3 month visit you will be randomly assigned to one of two anticoagulation drug therapies depending upon the type of implant you receive and your general health apart from the valve. These two therapies are the standard anticoagulant therapy now used based on the recommendations of the American Heart Association or a therapy with a reduced dose of anticoagulation. Laboratory blood samples will be drawn and other diagnostic tests will be done according to the requirements of the protocol during the appropriate preoperative and follow-up visits. The results of these tests may result in your removal from the study if you are found to be more likely to clot than most people or if you are found to not respond to the drug therapy. You will be informed of this before your 3 month visit should it occur. The diagnostic tests will include echocardiograms (sound wave studies of the heart) at 1, 3 and 5 years following surgery. The drug therapy you will be placed on may require frequent laboratory blood tests. The understanding of the use of the medications you are assigned to is important to the success of this study. Autopsies are requested should death occur during the study period to confirm any potential complication related to the study.

Risks and Discomforts

The primary risk of this study if you are in a low dose treatment group is that the drug therapy you are given may not be as effective in controlling blood clots on or around your new valve as the normal therapy is with mechanical valves. Specifically, patients in the low dose treatment groups may have a higher risk of blood clots, called thrombi, on or around the new valve and a higher risk of blood clots breaking off the valve, called thromboemboli, traveling through the blood stream. These blood clots can possibly cause mini-strokes, major strokes, heart attacks, limb injuries or amputations or death.

Certain general risks are associated with any surgical procedure. General surgical risks include anesthesia complications, drug reactions, and infection. The primary risk associated with the Prosthesis is similar to that of other commercially available heart valves, that is, failure to restore function. Specifically, this might involve structural failure of the valve, blood leak around the valve, clotting on or around the valve, or infection. 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 or death.

The general risks of anticoagulant therapy include bleeding if anticoagulation is too strong and blood clotting if anticoagulation is too weak. These risks can be minimized by strict adherence to the timing and amounts of medicines prescribed by your doctor and by regular routine monitoring of your anticoagulation state. They can also be minimized when taking Coumadin by adhering to a diet low in vitamin K containing foods such as leafy green vegetables (spinach and the like), liver and cranberry juice. Additionally no prescription or over-the-counter medications should be taken without prior approval of your doctor.

Foreseeable risks and discomforts will be minimized by thorough preoperative evaluation and close intraoperative and postoperative monitoring of your condition, but unforeseeable risks may occur.

Benefits

It is generally believed that lowering the dose of anticoagulation will reduce the chance of suffering a bleeding event, but will increase the chance of suffering a blood clotting event. If a valve is less likely to have a clotting event, then reducing anticoagulation should not significantly increase the risk of blood clotting events. If assigned to the group using aspirin and Plavix, a further benefit will be not requiring monthly bleeding tests. Thus, the primary benefit of the study is restored function of the heart valve and restored general health with less chance of problems. Another benefit will be that your progress and health status will be carefully monitored. Those patients on Coumadin will be monitored by weekly home testing which is shown to significantly reduce adverse events for these patients. 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 mitral or aortic valve with a different commercially available mechanical or tissue heart valve; or repair 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.

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 nonbusiness 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 in this study at any time without fear of penalty or loss of medical care. Your surgeon may also withdraw you from the study for just cause without your prior consent, but will inform you if this action is taken.

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.

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 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 examinations, 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 the patient free of charge.

Signature

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.

_____ _____
Date Patient Signature
Reason, if patient 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

Labeling

Appendix E

IRB and Investigator Information

Institutional Information On-X Low Dose Anticoagulation Study

Institution	Investigator	Investigator's Address and Phone Number	IRB Chairman	IRB Address and Phone Number
Emory University, Atlanta, GA	John Puskas, MD	550 Peachtree St. NE, Ste 7700 Atlanta, GA 30365 (404) 686-2513	Dr James W. Keller	Emory University Institutional Review Board 1256 Briarcliff Road, NE Briarcliff Campus, Bldg A, 307-N Atlanta, Georgia 30306-2656 404-712-0720
Additional Centers to be Added				

Appendix F

MCRI On-X LOW DOSE ANTICOAGULATION 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.**

4.3 From the subaortic waveform (for prostheses in mitral or aortic positions): **peak velocity (v_1), mean pressure drop (p_1), velocity integral (VTI_1).**

4.4 From the transaortic waveform (prostheses in the aortic position only): p**eak velocity (v_2), mean pressure drop (p_2), velocity integral (VTI_2)**.

4.5 From the mitral waveform (prostheses in the mitral position only): **Pressure half-time (PHT), mean pressure drop, 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:**

$EOA = CSA \times VTI_1 / VTI_2$ [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:**

$MOA = CSA \times VTI_1 / DVI$ [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 pressured difference across the aortic valve:**

Mean $\Delta P = p_1 - p_2$ [5]

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.