TRIFECTA DURABILITY STUDY

Clinical Investigational Plan (CIP)
and Statistical Analysis Plan (SAP)

Project Name:	Trifecta Durability Study
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2 BACKGROUND

Valvular heart disease is responsible for nearly 93,000 valve related operations and 20,000 deaths each year in the United States. It is also a contributing factor for another 42,000 deaths each year. The majority of these cases involve disorders of the aortic valve (63%).[1] Specific aortic valvular disorders include: aortic stenosis, aortic regurgitation, or a combination of the two, with aortic stenosis being the leading indication for aortic valve replacement in adults.

The most common cause of aortic stenosis in adults is an idiopathic degenerative calcification process that produces an immobilization of the aortic valve cusps.[2] This disease progresses from the base of the cusps to the free edge, eventually causing a reduction in the effective valve area. Other causes include a congenital malformation (often a bicuspid valve) and rheumatic fever. Classic symptoms of aortic stenosis include angina, syncope, dyspnea, heart murmur, fatigue, and heart failure.

Common causes of aortic valve regurgitation include idiopathic aortic dilatation, congenital abnormalities (bicuspid valve), degenerative calcification, rheumatic fever, infective endocarditis, systemic hypertension, dissection of the ascending aorta, Marfan's syndrome, and many others that occur much less frequently.[2] Symptoms of aortic regurgitation include: angina, syncope, dyspnea, heart murmur, fatigue, and heart failure.

Patients with either aortic stenosis, regurgitation, or both may remain asymptomatic for many years however, after the onset of symptoms (angina, syncope, or dyspnea); the average survival is less than two to three years.[2] Aortic valve replacement (AVR) appears to be the only effective treatment for these patients.[2] For certain patients with severe aortic regurgitation who are not considered good surgical candidates, therapy with vasodilating agents may provide some benefit.[2]

Presently, there are two broad categories of aortic valve prostheses; mechanical and tissue (bioprosthesis). The ball and cage, tilting-disc, and bileaflet are the three basic types of mechanical valve prostheses available today. There is a wide variety of bioprostheses available including: autografts (a valve moved from one anatomical position to another within the same individual), homografts/allografts (human valves or tissue taken from cadavers), and heterografts/xenografts (valves or tissue taken from animals). There are currently several different heterografts available. Heterografts are primarily constructed from porcine aortic valves that have been preserved and sewn onto a frame (stented) or left intact (stentless). A stented bovine pericardial valve is another type of commonly accepted heterograft.[3, 4]

Each valve type, mechanical or tissue, has associated risks and benefits. Mechanical valves are associated with potential lifetime durability but require long-term anticoagulation therapy. Tissue valves are reported to have reduced device durability, but typically do not require long-term anticoagulation therapy and are therefore associated with lower incidence of thromboembolic and hemorrhagic events.[5, 6] Implanting physicians must not only consider the various valve characteristics when deciding which aortic prosthesis to implant, but also various patient factors including, but not limited to age, coexisting medical conditions, anticoagulation therapy tolerance, and cardiac physiology.[2, 3, 4]

3 OBJECTIVES

3.1 PRIMARY OBJECTIVE

3.1.1 The primary objective of this investigation is to evaluate the long-term durability of the Trifecta valve.

3.2 SECONDARY OBJECTIVES

3.2.1 The secondary objectives of this investigation are to evaluate valve-related complications in the long-term.

4 ENDPOINTS

4.1 PRIMARY ENDPOINT

4.1.1 Actuarial freedom from reoperation due to Structural Valve Deterioration[7] (SVD) at year 10 post implant for patients who have the Trifecta valve implanted.

4.2 SECONDARY ENDPOINTS

4.2.1 The secondary endpoints of this investigation are:

4.2.1.1 Actuarial survival rate;

4.2.1.2 Freedom from valve related death;

4.2.1.3 Freedom from structural valve deterioration.

5 PATIENT SELECTION CRITERIA

5.1 PATIENT ENROLLMENT

A patient who meets all the inclusion criteria and does not meet any of the exclusion criteria is eligible to participate in the investigation. A patient is enrolled in the investigation only when s/he has provided written informed consent. Once enrolled, a patient is expected to comply with the scheduled visits and required activities according to the protocol.

5.2 INCLUSION CRITERIA

5.2.1 Patients implanted for less than 9 months, or candidate for implantation with a St Jude Medical Trifecta valve, as per current guidelines;

5.2.2 Patient requires aortic valve replacement. (Note: patients undergoing concomitant procedures, e.g. coronary artery bypass grafting, supracoronary replacement of ascending aorta, mitral valve repair, tricuspid valve repair, atrial fibrillation ablation, patients that had previous aortic valve replacement or CABGs are eligible for this study).

5.2.3 Patient is legal age in host country.

5.2.4 Patients must be able and willing to provide written informed consent to participate in this investigation; and

5.2.5 Patients must be willing and able to comply with all follow-up requirements.

5.3 EXCLUSION CRITERIA

5.3.1 Patients with contraindication for cardiac surgery;

5.3.2 Patients who are pregnant.

5.3.2.1 Pregnancy will be assessed by patients informing the physicians.

5.3.3 Patient is unwilling to or has an inability that reduces his mobility in order to attend the required follow-up visits.

5.3.4 Patient has active endocarditis (patients with previous endocarditis must have two documented negative blood culture results prior to enrollment).

5.3.5 Patient has had an acute preoperative neurological event defined as patient has not returned to baseline 30 days prior to the planned valve implantation surgery.

5.3.6 Patient is undergoing renal dialysis.

5.3.7 Patient has a documented history of substance abuse within one year of enrollment or is currently a prison inmate.

5.3.8 Patient has a documented thrombus in left atrium or left ventricle.

5.3.9 Patient had in the past mitral or tricuspid valve replacement.

5.3.10 Patient needs mitral and/or tricuspid valve replacement.

5.3.11 Patient has an Ejection Fraction < 25%

5.3.12 Patient had the Trifecta™ valve implanted as part of this study, but then had the device explanted (a patient cannot be enrolled twice in this study).

5.3.13 Preoperative evaluation indicates other significant cardiovascular abnormalities such as aortic dissection or ventricular aneurysm.

5.3.14 Patient has a life expectancy less than two years.

6 INVESTIGATION DESIGN

6.1 TYPE

This investigation is a multicenter, prospective, observational study.

6.2 DURATION

6.2.1 The first enrollment is anticipated in 2010.

6.2.2 The enrollment period will be approximately 15 months.

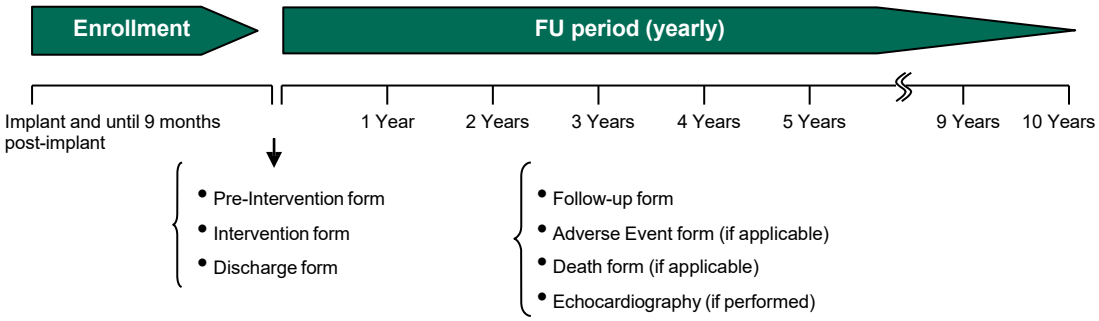
6.2.3 The patient will participate in this investigation for approximately 10 years from enrollment to the last follow-up.

6.2.4 The patient may withdraw from the investigation at any time, for any reason. In this case, the procedures for reporting should be followed as mentioned in the section 0 Early Conclusion to Patient Participation.

6.3 ENROLLMENT TARGET

6.3.1 The enrollment target for this investigation is 801 patients. For more information, refer to section 8.1 Sample Size Justification.

6.4 DESIGN



7 PRODUCT

The following market approved St. Jude Medical products are required to be used in the investigation:

7.1.1 The Trifecta valve:

The Trifecta valve is a tri-leaflet stented pericardial valve designed for supra-annular placement in the aortic position. The valve is fabricated using a polyester-covered titanium stent. The stent, excluding the sewing cuff, is then covered with porcine pericardial tissue. This covering minimizes mechanical wear by allowing only tissue-to-tissue contact during valve function. A silicone insert within the polyester sewing cuff is contoured to conform to the shape of the native annulus. The valve leaflets are fabricated from bovine pericardium. The porcine and bovine pericardium are preserved and crosslinked in glutaraldehyde. Glutaraldehyde, formaldehyde, and ethanol are used in the valve sterilization process. The Trifecta valve is processed using Linx™ anti-calcification technology. The Trifecta valve received CE mark in March 2010.

7.1.2 Trifecta Sizer Set TF2000:

The Trifecta™ Sizer Set Model TF2000 is a double-ended tool with a cylindrical annular sizing end and a valve replica end. The cylindrical annular sizing end of the sizer is used to determine the size of the annulus. The replica end of the sizer is used to visualize placement of the sewing cuff above the annulus and to confirm placement and fit of the valve in the supra annular space. Both the cylindrical sizing head and the valve replica head are connected to the sizer handle via a bendable section that allows for easier access to the aortic anatomy. The UT2000 Holder Handle interfaces with the Trifecta valve holder via a click-in mechanism. The holder handle is used to transport the valve from the jar and through the valve rinse procedure. In addition, the holder handle helps to facilitate valve suturing and delivery of the valve into the implant position.

8 STATISTICAL ANALYSIS PLAN

8.1 SAMPLE SIZE JUSTIFICATION

8.1.1 The sample size estimation is based on the primary endpoint of this study, freedom from reoperation due to SVD at year 10 post implant for patients who have the Trifecta valve implanted.

8.1.2 It is assumed that the expected freedom rate from reoperation due to SVD at year 10 post implant will be 96.5%±1.52%, in order to establish a one side 95% confidence interval for the freedom rate with the lower bound as 94%, the required number of patients at risk at year 10 post implant is at least 142 using non-parametric survival analysis with Peto's variance. Assuming the overall mortality rate will be 39.50% at year 5 and 63.4% at year 10, the minimum sample size is 641 patients.

8.1.3 With 20% drop out rate, in total at least 801 patients need to be recruited.

8.1.4 Taking into account the effect of learning curve of the surgeons, the first 3 patients implanted by each surgeon without any experience with the Trifecta valve are not counted as part of the sample size.

8.2 ENDPOINT ANALYSIS

8.2.1 Non-parametric survival analysis will be used to calculate the freedom rate(S) from reoperation due to SVD at year 10 post implant and the corresponding variance (Var_s) will be computed with Peto's formula for survival analysis. [i] The lower bound of the 95% confidence interval for S will be calculated using the formula $S\text{-}Z_{0.5} * (Var_s)^{1/2}$. If the lower bound of S is bigger than or equal to 94%, then the expected estimate is confirmed. The survival time will be calculated as the number of days from implant date to reoperation date due to SVD. A Kaplan-Meier curve with the cumulative survival rate will also be presented.

8.2.2 A Cox regression model will be used to further investigate the effects of the factors on the primary endpoint. These factors include baseline factors such as learning curve (1, 2, 3, >3), age, gender, NYHA Class etc..

8.3 ADDITIONAL DATA

8.3.1 For the time to event data, survival analysis will be used to estimate the survival rate and 95% confidence interval, and a Kaplan Meier curve will also be presented.

8.3.2 Continuous data will be summarized with mean, standard deviation, median and range. Frequency and percentage will be reported for all categorical data.

[i] Reference : Alan B cantor , SAS survival analysis techniques for medical research

9 PROTOCOL DESCRIPTION

9.1 PROTOCOL PROCEDURES - OVERVIEW

Table 1 – Protocol Procedure Overview

These activities are applicable to all patients.
(*) This is only when available

(**) This is **only to be performed when applicable.**

	When	Window	Activities
Pre-Intervention		Not Applicable	• Patient Eligibility • Patient Informed Consent • Patient Demographics & Physical Examination • Patient Cardiovascular History • Patient Current Cardiac Medications • Patient Medical History • Echo (*)
Intervention (+baseline)		Not Applicable	• Aortic Valve Replacement Information • Operative Information • Adverse Events(**) • Echo (*)
Pre-discharge		Not Applicable	• Patient Current Cardiac Medications • Adverse Events(**) • Echo (*)
Yearly follow-up	Yearly	<30 days >61 days	• Patient Current Cardiac Medications • Adverse Events (**) • Echo (*)

9.2 ADVERSE EVENTS

9.2.1 Definition of Adverse Event, Adverse Device Effect, Serious Adverse Event and Serious Adverse Device effect according to ISO 14155:

9.2.1.1 **Adverse Event (AE)** is defined as any untoward medical occurrence in a patient or clinical investigation patient.

9.2.1.1.1 This definition does not necessarily imply that there is a causal relationship between the adverse event and the device under investigation.

9.2.1.2 **Adverse Device Effect (ADE)** is defined as any untoward and unintended response to a medical device. This definition includes any event resulting from insufficiencies or inadequacies in the

instructions for use or the deployment of the device. It also includes any event that is a result of a user error.

9.2.1.2.1 **Valve-related adverse events**

Valve-related adverse events will be defined according to the definitions included in the current available guidelines: Akins CW, Miller CD, Marko I. Turina MI, Kouchoukos NT, Blackstone EH, Grunkemeier GL, Takkenberg JJM, David TE, Butchart EG,. Adams DH, David M. Shahian DM, Hagl S, Mayer JE , Lytle BW. Guidelines for reporting mortality and morbidity after cardiac valve interventions. EJCTS 33 528 (2008) 523—528.

9.2.1.3 **Serious Adverse Event (SAE)** is defined as an adverse event that:

9.2.1.3.1 Led to death;

9.2.1.3.2 Led to a serious deterioration in the health of a patient that:

- Resulted in a life threatening illness or injury;
- Resulted in a permanent impairment of a body structure or a body function;
- Required in-patient hospitalization or prolongation of existing hospitalization; and
- Resulted in medical or surgical intervention to prevent permanent impairment to a body structure or a body function.

9.2.1.3.3 Led to foetal distress, foetal death or a congenital abnormality or birth defect.

9.2.1.4 **Serious Adverse Device Effect (SADE)** is defined as an adverse device effect that has resulted in any of the consequences characteristic of a serious adverse event or that might have led to any of these consequences if suitable action had not been taken or intervention had not been made or if circumstances had been less opportune.

9.2.2 <u>List of Anticipated Adverse Events and Adverse Device Effects:</u>

The following represents a list of anticipated Adverse Events (AE) and Adverse Device Effects (ADE) experienced in either animal and/or clinical studies to date with aortic valve replacement operations, or reported in instructions for use and literature. Anticipated Adverse Events (AE) and Adverse Device Effects (ADE) include: Angina (chest pain), Cardiac arrhythmias, Bleeding events (including pre-operative bleeds), Death (valve and non-valve related), embolism, endocarditis, explant, hearth failure, hemolysis, haemolytic anemia, myocardial infarction, non-structural dysfunction, paravalvular leak, valve regurgitation, reoperation, stroke, structural deterioration, valve thrombosis, valvular pannus.

9.2.3 Procedure for Recording and Reporting Adverse Events

9.2.3.1 Safety surveillance and reporting will be done for all patients enrolled in the investigation.

9.2.3.2 Safety surveillance and reporting starts at the time when the patient is enrolled into the investigation (date of signature of the informed consent) until the last investigational visit has been performed, or the patient has died, or the patient concludes his participation into the study.

9.2.3.2.1 All **Serious Adverse Events** and all **Adverse Device Effects** are to be documented and reported to the sponsor **immediately**.

9.2.3.2.2 **Non-Serious Adverse Events** documentation and reporting are limited to cardiovascular and neurovascular events.

9.2.3.3 Should an AE occur, record AE information in the hospital records, document the information into the Adverse Event case report form (CRF) as soon as possible. By completing the CRF the sponsor will be notified.

9.2.3.3.1 Refer to appendices “Data Collection” and “Data Collection Method”.

9.2.3.3.2 Access the eCRF application.

9.2.3.3.3 Select the visit the AE is related to or indicate it as unscheduled visit.

9.2.3.3.4 Enter adverse event information into the **AE Notification** section of the CRF.

- Date the AE occurred;
- Date the center investigator or delegate became aware of the AE;
- Main complaints/symptoms of the AE;
- Initial diagnosis of the AE;
- Potential cause of the AE;
- Pre-existing medical conditions related to the AE;
- Seriousness of the AE;
- Device relationship to AE; and
- Status of the AE.

9.2.3.3.5 The CRF must be authorized by the principal investigator or delegated co-investigator.

9.2.3.3.6 Submit the CRF. When the CRF is submitted, an alert is generated notifying the sponsor.

9.2.3.3.7 As soon as the final details are available for the adverse event, the information should be reported on the AE Follow-Up section of the CRF.

9.2.3.3.8 Access the eCRF application.

9.2.3.3.9 Edit AE CRF, document information into the **AE Follow-Up** section of the case report form.

- Hospitalization details (if applicable);
- Diagnostic test information (if applicable);
- Treatment given (if applicable);
- Final medical diagnosis & cause;
- Patient condition;
- Final AE status;
- Seriousness of AE based on final medical diagnosis and cause;
- Relationship of AE to device based on final medical diagnosis & cause.

9.2.3.3.10 The CRF must be authorized by the principal investigator or delegated co-investigator.

9.2.3.3.11 Submit the CRF.

9.2.3.4 Additional information will be requested, if necessary, by the Sponsor for reporting of AEs to regulatory authorities.

9.2.3.5 The investigator must notify the EC or IRB, if appropriate, in accordance with national and local laws and regulations.

NOTE: If an adverse event is documented at the patient's last follow up visit (10 years), both the notification and follow-up information on the AE CRF are to be provided to the sponsor.

Pre-existing cardiac conditions that require planned hospitalization are not to be considered as AE.

9.3 Patient Death

9.3.1 Procedure for Recording and Reporting Patient Death

9.3.1.1 Safety surveillance and reporting will be done for all patients enrolled in the investigation.

9.3.1.2 Safety surveillance and reporting starts at the time when the patient is enrolled into the investigation (date of signature of the informed consent) until the last investigational visit has been performed.

9.3.1.2.1 All **Patient Deaths** are to be documented and reported to the sponsor **immediately**.

9.3.1.3 Should death occur, record death information in the hospital records, **immediately** document the information in the Death case report form (CRF). By completing the CRF the sponsor will be notified.

9.3.1.3.1 Refer to appendices “Data Collection” and “Data Collection Method”.

9.3.1.3.2 Access the eCRF application.

9.3.1.3.3 Select the visit the patient death is related to or indicate it as visit unscheduled visit.

9.3.1.3.4 Enter patient death information into the Patient Death CRF.

- Date the death occurred;
- Date the center investigator or delegate became aware of the death;
- Place where death occurred (e.g. hospital, nursing home, patient’s home);
- If death was witnessed;
- If autopsy was performed;
- If the Trifecta Valve was returned to SJM? If not, reason should be specified.
- Temporal cause of death
- Primary cause of death including if death was caused by valve-related complications (hemolysis, bleeding event, structural valve deterioration, endocarditis, non-structural dysfunction, valve reoperation, embolism, sudden unexplained, valve thrombosis)
- Details regarding death; and
- If details of serious adverse event associated to the death are known by the center/investigator/delegate.

9.3.1.3.5 The CRF must be authorized by the principal investigator or delegated co-investigator.

9.3.1.3.6 Submit the CRF. When the CRF is submitted, an alert is generated notifying the sponsor.

9.3.1.4 Patient death may be an outcome of a serious adverse event (SAE). If the death is related to a SAE, all the efforts to get SAE details should be made and the Adverse Event CRF must be completed.

9.3.1.5 Patient death is an early conclusion to the patient's participation in the investigation. Complete Termination CRF.

9.3.1.6 The investigator must notify the EC or IRB, if appropriate, in accordance with national and local laws and regulations.

9.4 EARLY CONCLUSION TO PATIENT PARTICIPATION

9.4.1 All reasonable efforts should be made to retain the patient in the clinical investigation until completion of the clinical investigation.

9.4.2 If a patient concludes their participation in the investigation, the patient's future medical care will not be influenced by this decision, whether it is voluntary or otherwise,

9.4.2.1 A patient/family member may request to withdraw from the investigation at any time; She/he would be able to do so without having to justify it and without affecting her/his relationship with the investigator.

9.4.2.2 An investigator may withdraw a patient from the investigation at any time if she/he thinks it is in the patient's best interest; or

9.4.2.3 An investigator may withdraw a patient, if the patient does not come for their scheduled visits and/or is not compliant with the regimen of the protocol. This patient will be considered "lost to follow-up"; A patient will be considered "lost to follow-up" when 3 attempts to contact the patient were unsuccessful: A minimum of 2 documented phone calls by a physician/delegate to the patient/emergency contact and a certified letter sent to the last known address.

9.4.2.4 The Investigation is temporarily stopped or terminated, either at the local, national or international level, at the request of Ethics Committees, Competent Authorities, Departments of Health or the investigational Sponsor.

9.4.2.5 A patient dies. Refer to section 9.3, "Patient Death";

9.4.3 Should a patient withdraw and conclude participation in the investigation, document the information in the Termination case report form (CRF) as soon as possible. By completing the CRF the sponsor will be notified.

9.4.3.1 Refer to appendices "Data Collection" and "Data Collection Method".

9.4.3.2 Access the eCRF application.

9.4.3.3 Select the visit the patient death is related to or indicate it as visit unscheduled visit.

9.4.3.4 Enter patient early conclusion information into the Termination CRF.

- Date the early conclusion occurred; and
- Reason for the early conclusion;

9.4.4 The CRF must be authorized by the principal investigator or delegated co-investigator.

9.4.5 Submit the CRF. When the CRF is submitted, an alert is generated notifying the sponsor.

9.5 DEVIATIONS

9.5.1 Investigators are required to adhere to the Clinical Investigational Plan, the signed Investigator's Agreement, applicable national or local laws and regulations, and any conditions required by the appropriate Ethics Committees or applicable regulatory authorities.

9.5.2 A **Deviation** is defined as a situation in which there is a non-compliance with the protocol.

9.5.3 Anticipated deviations:

9.5.3.1 Patient Informed Consent is not approved by Ethics Committee;

9.5.3.2 Patient Informed Consent is not signed and/or dated by the patient and/or investigator;

9.5.3.3 Study specific procedure was performed before the Patient Informed Consent was signed and dated by patient;

9.5.3.4 Investigational Required Visit not performed;

9.5.3.5 Investigational Required Visit performed outside the visit window;

9.5.4 Should a deviation occur, document the information in the Deviation case report form (CRF). By completing the CRF the sponsor will be notified.

NOTE: When a deviation occurs after enrollment for **patient consent,** record the information in the hospital record, **immediately** document the information in the Deviation and Termination case report form (CRF). By completing the CRF the sponsor will be notified.

- Refer to appendices "Data Collection" and "Data Collection Method".
- Access the eCRF application.
- Select the scheduled or unscheduled visit to which the deviation is related.
- Enter deviation information into the Termination CRF.
  - Date of deviation

- When the deviation occurred
- Type of deviation
- Medical justification

- The CRF must be authorized by the principal investigator or delegated co-investigator.
- Submit the CRF. When the CRF is submitted, an alert is generated notifying the sponsor.

When a deviation occurs after enrollment for **patient eligibility,** record the information in the hospital record, **immediately** document the information in the Deviation case report form (CRF). By completing the CRF the sponsor will be notified. All the efforts should be made to keep the patient in the study.

The investigator must notify the EC or IRB, if appropriate, in accordance with national and local laws and regulations.

9.6 ENROLLMENT

9.6.1 Enrollment activities are performed after patients are screened and may occur prior to or at the same time as the baseline visit.

9.6.2 The site should maintain a Patient Screening Log, accounting for the patients who are and are not eligible for the investigation. All patients that are considered for this investigation, should be mentioned on this Patient Screening Log.

9.6.3 A patient who meets the inclusion criteria and does not meet the exclusion criteria is eligible to participate in the investigation.

9.6.3.1 If a patient does not meet inclusion or meets exclusion criteria cannot participate in the investigation.

9.6.4 Inform the eligible patient about the investigation and provide the informed consent form to the patient.

9.6.4.1 The process of obtaining written consent from an eligible patient needs to comply with the Declaration of Helsinki, International Standards Organization (ISO) 14155-1 and applicable local laws and regulations.

9.6.5 Obtain the signature and date from the eligible patient on the ethics committee (EC) approved informed consent form.

9.6.5.1 If the eligible patient cannot sign and date the EC approved informed consent him/herself then refer to ISO 14155-1 regarding alternatives for obtaining signature on the informed consent.

9.6.5.2 If an eligible patient does not sign and date the informed consent, s/he cannot participate in the investigation. No further protocol activities are performed.

9.6.6 Obtain the signature and date from the principal investigator or delegate on the ethics committee (EC) approved informed consent form.

9.6.7 The patient is enrolled in the investigation when both the patient and investigator signed/dated the informed consent.

9.6.7.1 If there are deviations with regards to obtaining informed consent, notify the EC/IRB appropriately.

9.6.8 Provide one original signed and dated copy by patient and the principal investigator or delegate to the patient.

9.6.9 File the second original appropriately in the Investigator Study Binder (ISB).

9.6.10 Record enrollment information (name of the investigation, consent and inclusion/exclusion criteria) in the hospital records, complete the Enrollment Case Report Form. Every effort will be made to notify the sponsor within 5 working days of enrollment. The CRF must be authorized by the principal investigator or delegate.

9.6.10.1 Refer to “Appendix Data Collection” for access and information regarding patient data collected for this investigation.

9.7 BASELINE VISIT (INTERVENTION)

9.7.1 All Baseline activities are performed after the patient is enrolled in the investigation and no more than 30 days prior to undergoing cardiac surgery procedure.

9.7.2 The following information will be collected at the baseline visit either from hospital records or through patient interaction documented in the hospital records:

9.7.2.1 Patient Demographics & Physical Examination

- Collect the age;
- Collect the gender;
- Provide the most recent value (within the last month) of the patient height;
- Provide the most recent value (within the last month) of the patient weight;

9.7.2.2 Patient Cardiovascular History

- Provide the most recent value (within the last month) of the New York Heart Association (NYHA) classification;

9.7.2.3 Patient Anticoagulant/Antiplatelet Medication

- Identify the Anticoagulant/Antiplatelet medications the patient is taking currently;

9.7.2.4 Patient Medical History

- Indicate the pre-existing cardiac conditions and cardiac procedures; and
- Indicate the relevant non-cardiac medical conditions.

9.7.2.5 Baseline echo data (if available)

- Provide the most recent values (within the last month) of the specified echo variables;

9.7.2.6 Aortic Valve Replacement Information

- Indicate the details about valve being replaced (type, etiology, pathology, ect..)

9.7.2.7 Operative Information

- Indicate the details about valve replacement (suture technique, implanting surgeon and experience, details about Trifecta valve implanted and concomitant procedures).

9.7.2.8 Refer to "Appendix Data Collection" for access and information regarding patient data collected for this investigation.

9.7.3 Adverse Event (when applicable)

9.7.3.1 Check if any adverse event or adverse device effect occurred.

9.7.3.2 Report the adverse event according to specifications in section "Adverse Event".

9.8 PRE-DISCHARGE VISIT

9.8.1 The following information will be collected at the pre-discharge visit either from hospital records or through patient interaction (documented in the hospital records):

9.8.1.1 Patient Cardiac Medication

- Provide information on cardiac medication;

9.8.1.2 Echocardiography (if available)

- Provide pre-discharge echo data;

9.8.2 Record the pre-discharge information in the hospital records and complete the Follow Up Case Report Form (CRF).

9.8.3 Adverse Event (when applicable)

9.8.3.1 Check if any adverse events or adverse device effect occurred since the last visit and document this in the hospital records.

9.8.3.2 Report the adverse event according to specifications in section "Adverse Event" of the Case Report Form (CRF).

9.8.4 Patient Death (when applicable)

9.8.4.1 If the patient died before hospital discharge, report it immediately to the sponsor as indicated in section “Patient Death”.

9.8.5 Early Withdrawal (when applicable)

9.8.5.1 If the patient decides to withdraw from the investigation for whatever reason, report this immediately to the sponsor as indicated in section "Early conclusion to patient participation".

9.8.6 Refer to “Appendix Data Collection” for access and information regarding patient data collected for this investigation.

9.9 PROTOCOL REQUIRED FOLLOW-UP

9.9.1 Scheduled visits will occur yearly over 10 years after the implant date. The follow up will occur in the outpatient department of each participating institution or, if not possible, by telephone contact with the patient.

9.9.2 The Follow Up schedule is summarized in Table 1.

9.9.3 The following information will be collected at the follow up visit either from hospital records or through patient interaction (documented in the hospital records):

9.9.3.1 Provide the most recent value (within the last month) of the New York Heart Association (NYHA) classification;

9.9.3.2 Patient Cardiac Current Medication

- Provide information on cardiac medication therapy.;

9.9.3.3 Echocardiography (if available)

- Provide follow-up echo data (echo date must be in the follow-up window);

9.9.4 Record the follow up information in the hospital records and complete the Follow Up Case Report Form (CRF).

9.9.5 Adverse Event (when applicable)

9.9.5.1 Check with the patient if any adverse events or adverse device effect occurred since the last visit and document this in the hospital records.

9.9.5.2 Report the adverse event according to specifications in section “Adverse Event” of the Case Report Form (CRF).

9.9.6 Patient Death (when applicable)

9.9.6.1 If the patient died before the visit took place, report it immediately to the sponsor as indicated in section “Patient Death”.

9.9.7 Early Withdrawal (when applicable)

9.9.7.1 If the patient decides to withdraw from the investigation for whatever reason, report this immediately to the sponsor as indicated in section "Early conclusion to patient participation".

9.9.8 Refer to “Appendix Data Collection” for access and information regarding patient data collected for this investigation.

10 RISK DESCRIPTION AND MINIMIZATION

10.1 POTENTIAL BENEFITS

Potential benefits to the patients may include, but are not limited to, relief of valvular stenosis and/or incompetence and related symptoms. A patient may benefit from the improved longevity of the valve, due to the Linx™ treatment of the Trifecta valve (if the Linx™ treatment is proven effective). The patient will be monitored throughout the duration of the clinical study. Patients will be evaluated at pre-determined time points to assess their status. In addition, similar benefits may accrue to future subjects through experience gained in this clinical study.

10.2 POTENTIAL RISKS

It is expected that the study related procedures: clinical assessment and the determination of the NYHA classification entail no additional risks to the patient other than those commonly associated with the follow-up of patients who have had a prosthetic heart valve implanted.

11 ETHICAL BASIS

This investigation will be performed in accordance with the World Medical Association Declaration of Helsinki (appendix C), ISO 14155 and all local legal and regulatory requirements.

Prior to the start of the investigation, the clinical investigational plan will be submitted together with its associated documents (patient information sheets, patient informed consent forms in the local language) to the relevant Ethics Committee (EC) / Institutional Review Board (IRB) for review.

EC/IRB approval document should clearly identify

- the date of the meeting,
- constitution of the committee and voting members present at the meeting
- the approved version of the clinical investigational plan CIP
- the approved version of the patient information and informed consent.

Approval from the EC/ IRB is necessary prior to the start of the investigation. The original approval is to be filed in the Investigator Study Binder and a copy of the approval is provided to St. Jude Medical prior to the first investigational assessment.

Any amendments to the protocol should be submitted to the relevant EC/IRB.

EC/IRB will be informed about SAEs and UADEs in accordance with local and national requirements.

APPENDIX A: ABBREVIATIONS

Abbreviation	Description
ACC	American College of Cardiology
ADE	Adverse Device Effect
AE	Adverse Event
AF	Atrial Fibrillation
AHA	American Heart Association
AVR	Aortic Valve Replacement
CA	Competent Authority
CABG	Coronary Artery Bypass Grafting
CIP	Clinical Investigation Plan
CPL	Clinical Projects Leader
CRA	Clinical Research Associate
CV	Cardiovascular
CRF	Case Report Form
EC	Ethics Committee
eCRF	Electronic Case Report Form
FU	Follow Up
INR	International Normalized Ratio
IFU	Instruction for Use
IRB	Institutional Review Board
ISB	Investigator Study Binder
PIC	Patient Informed Consent
SAE	Serious Adverse Event
SMF	Site Master File
SOP	Standard Operating Procedures
SVD	Structural Valve Deterioration
SJM	St. Jude Medical

APPENDIX B: REFERENCES

1. American Heart Association. *Heart Disease and Stroke Statistics – 2005 Update*. Dallas, Texas.: American Heart Association 2005.
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3. Werner JA, Crawford MH. Choosing a Prosthetic Heart Valve. *Cardiol Clin.* 1998;16:491-504.
4. Fann JI, Burdon TA. Are the Indications for tissue valves different in 2001 and how do we communicate these changes to our cardiology colleagues? *Curr Opin Cardiol*. 2001;16:126-35.
5. Cartier PC, Metras J, Dumesnil JG, Pibarot P, Lemieux M. Midterm Follow-up of Unstented Biological Valves. *Seminars in Thoracic and Cardiovascular Surgery* 1999;11:22-7.
6. Fradet G, Bleese N, Busse E, Jamieson E, Raudkivi P, Goldstein J, Metras J. The Mosaic Valve Clinical Performance at Seven Years: Results from a Multicenter Prospective Clinical Trial. *J Heart Valve Dis* 2004;13:239-47.
7. iAkins CW, Miller CD, Marko I. Turina MI, Kouchoukos NT, Blackstone EH, Grunkemeier GL, Takkenberg JJM, David TE, Butchart EG,. Adams DH, David M. Shahian DM, Hagl S, Mayer JE , Lytle BW. Guidelines for reporting mortality and morbidity after cardiac valve interventions. EJCTS 33 528 (2008) 523—528
8. Alan B Cantor , *SAS survival analysis techniques for medical research*, page 17-25.
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APPENDIX C: DECLARATION OF HELSINKI

WORLD MEDICAL ASSOCIATION DECLARATION OF HELSINKI
Ethical Principles for Medical Research Involving Human Subjects

Adopted by the 18th WMA General Assembly, Helsinki, Finland, June 1964, and amended by the:
29th WMA General Assembly, Tokyo, Japan, October 1975
35th WMA General Assembly, Venice, Italy, October 1983
41st WMA General Assembly, Hong Kong, September 1989
48th WMA General Assembly, Somerset West, Republic of South Africa, October 1996
52nd WMA General Assembly, Edinburgh, Scotland, October 2000
53rd WMA General Assembly, Washington 2002 (Note of Clarification on paragraph 29 added)
55th WMA General Assembly, Tokyo 2004 (Note of Clarification on Paragraph 30 added)
59th WMA General Assembly, Seoul, October 2008

A. INTRODUCTION

1. The World Medical Association (WMA) has developed the Declaration of Helsinki as a statement of ethical principles for medical research involving human subjects**,** including research on identifiable human material and data.

   The Declaration is intended to be read as a whole and each of its constituent paragraphs should not be applied without consideration of all other relevant paragraphs.

2. Although the Declaration is addressed primarily to physicians, the WMA encourages other participants in medical research involving human subjects to adopt these principles.

3. It is the duty of the physician to promote and safeguard the health of patients, including those who are involved in medical research. The physician's knowledge and conscience are dedicated to the fulfilment of this duty.

4. The Declaration of Geneva of the WMA binds the physician with the words, “The health of my patient will be my first consideration,” and the International Code of Medical Ethics declares that, “A physician shall act in the patient's best interest when providing medical care.”

5. Medical progress is based on research that ultimately must include studies involving human subjects. Populations that are underrepresented in medical research should be provided appropriate access to participation in research.

6. In medical research involving human subjects, the well-being of the individual research subject must take precedence over all other interests.

7. The primary purpose of medical research involving human subjects is to understand the causes, development and effects of diseases and improve preventive, diagnostic and therapeutic interventions (methods, procedures and treatments). Even the best current interventions must be evaluated continually through research for their safety, effectiveness, efficiency, accessibility and quality.

8. In medical practice and in medical research, most interventions involve risks and burdens.
9. Medical research is subject to ethical standards that promote respect for all human subjects and protect their health and rights. Some research populations are particularly vulnerable and need special protection. These include those who cannot give or refuse consent for themselves and those who may be vulnerable to coercion or undue influence.

10. Physicians should consider the ethical, legal and regulatory norms and standards for research involving human subjects in their own countries as well as applicable international norms and standards. No national or international ethical, legal or regulatory requirement should reduce or eliminate any of the protections for research subjects set forth in this Declaration.

B. PRINCIPLES FOR ALL MEDICAL RESEARCH

11. It is the duty of physicians who participate in medical research to protect the life, health, dignity, integrity, right to self-determination, privacy, and confidentiality of personal information of research subjects.

12. Medical research involving human subjects must conform to generally accepted scientific principles, be based on a thorough knowledge of the scientific literature, other relevant sources of information, and adequate laboratory and, as appropriate, animal experimentation. The welfare of animals used for research must be respected.

13. Appropriate caution must be exercised in the conduct of medical research that may harm the environment.

14. The design and performance of each research study involving human subjects must be clearly described in a research protocol. The protocol should contain a statement of the ethical considerations involved and should indicate how the principles in this Declaration have been addressed. The protocol should include information regarding funding, sponsors, institutional affiliations, other potential conflicts of interest, incentives for subjects and provisions for treating and/or compensating subjects who are harmed as a consequence of participation in the research study. The protocol should describe arrangements for post-study access by study subjects to interventions identified as beneficial in the study or access to other appropriate care or benefits.

15. The research protocol must be submitted for consideration, comment, guidance and approval to a research ethics committee before the study begins. This committee must be independent of the researcher, the sponsor and any other undue influence. It must take into consideration the laws and regulations of the country or countries in which the research is to be performed as well as applicable international norms and standards but these must not be allowed to reduce or eliminate any of the protections for research subjects set forth in this Declaration. The committee must have the right to monitor ongoing studies. The researcher must provide monitoring information to the committee, especially information about any serious adverse events. No change to the protocol may be made without consideration and approval by the committee.

16. Medical research involving human subjects must be conducted only by individuals with the appropriate scientific training and qualifications. Research on patients or

healthy volunteers requires the supervision of a competent and appropriately qualified physician or other health care professional. The responsibility for the protection of research subjects must always rest with the physician or other health care professional and never the research subjects, even though they have given consent.

17. Medical research involving a disadvantaged or vulnerable population or community is only justified if the research is responsive to the health needs and priorities of this population or community and if there is a reasonable likelihood that this population or community stands to benefit from the results of the research.

18. Every medical research study involving human subjects must be preceded by careful assessment of predictable risks and burdens to the individuals and communities involved in the research in comparison with foreseeable benefits to them and to other individuals or communities affected by the condition under investigation.

19. Every clinical trial must be registered in a publicly accessible database before recruitment of the first subject.

20. Physicians may not participate in a research study involving human subjects unless they are confident that the risks involved have been adequately assessed and can be satisfactorily managed. Physicians must immediately stop a study when the risks are found to outweigh the potential benefits or when there is conclusive proof of positive and beneficial results.

21. Medical research involving human subjects may only be conducted if the importance of the objective outweighs the inherent risks and burdens to the research subjects.

22. Participation by competent individuals as subjects in medical research must be voluntary. Although it may be appropriate to consult family members or community leaders, no competent individual may be enrolled in a research study unless he or she freely agrees.

23. Every precaution must be taken to protect the privacy of research subjects and the confidentiality of their personal information and to minimize the impact of the study on their physical, mental and social integrity.

24. In medical research involving competent human subjects, each potential subject must be adequately informed of the aims, methods, sources of funding, any possible conflicts of interest, institutional affiliations of the researcher, the anticipated benefits and potential risks of the study and the discomfort it may entail, and any other relevant aspects of the study. The potential subject must be informed of the right to refuse to participate in the study or to withdraw consent to participate at any time without reprisal. Special attention should be given to the specific information needs of individual potential subjects as well as to the methods used to deliver the information. After ensuring that the potential subject has understood the information, the physician or another appropriately qualified individual must then seek the potential subject's freely-given informed consent, preferably in writing. If the consent cannot be expressed in writing, the non-written consent must be formally documented and witnessed.

25. For medical research using identifiable human material or data, physicians must normally seek consent for the collection, analysis, storage and/or reuse. There may be situations where consent would be impossible or impractical to obtain for such research or would pose a threat to the validity of the research. In such situations the research may be done only after consideration and approval of a research ethics committee.

26. When seeking informed consent for participation in a research study the physician should be particularly cautious if the potential subject is in a dependent relationship with the physician or may consent under duress. In such situations the informed consent should be sought by an appropriately qualified individual who is completely independent of this relationship.

27. For a potential research subject who is incompetent, the physician must seek informed consent from the legally authorized representative. These individuals must not be included in a research study that has no likelihood of benefit for them unless it is intended to promote the health of the population represented by the potential subject, the research cannot instead be performed with competent persons, and the research entails only minimal risk and minimal burden.

28. When a potential research subject who is deemed incompetent is able to give assent to decisions about participation in research, the physician must seek that assent in addition to the consent of the legally authorized representative. The potential subject's dissent should be respected.

29. Research involving subjects who are physically or mentally incapable of giving consent, for example, unconscious patients, may be done only if the physical or mental condition that prevents giving informed consent is a necessary characteristic of the research population. In such circumstances the physician should seek informed consent from the legally authorized representative. If no such representative is available and if the research cannot be delayed, the study may proceed without informed consent provided that the specific reasons for involving subjects with a condition that renders them unable to give informed consent have been stated in the research protocol and the study has been approved by a research ethics committee. Consent to remain in the research should be obtained as soon as possible from the subject or a legally authorized representative.

30. Authors, editors and publishers all have ethical obligations with regard to the publication of the results of research. Authors have a duty to make publicly available the results of their research on human subjects and are accountable for the completeness and accuracy of their reports. They should adhere to accepted guidelines for ethical reporting. Negative and inconclusive as well as positive results should be published or otherwise made publicly available. Sources of funding, institutional affiliations and conflicts of interest should be declared in the publication. Reports of research not in accordance with the principles of this Declaration should not be accepted for publication.

C. ADDITIONAL PRINCIPLES FOR MEDICAL RESEARCH COMBINED WITH MEDICAL CARE

31. The physician may combine medical research with medical care only to the extent that the research is justified by its potential preventive, diagnostic or therapeutic value and if the physician has good reason to believe that participation in the research study will not adversely affect the health of the patients who serve as research subjects.

32. The benefits, risks, burdens and effectiveness of a new intervention must be tested against those of the best current proven intervention, except in the following circumstances:
    - The use of placebo, or no treatment, is acceptable in studies where no current proven intervention exists; or
    - Where for compelling and scientifically sound methodological reasons the use of placebo is necessary to determine the efficacy or safety of an intervention and the patients who receive placebo or no treatment will not be subject to any risk of serious or irreversible harm. Extreme care must be taken to avoid abuse of this option.

33. At the conclusion of the study, patients entered into the study are entitled to be informed about the outcome of the study and to share any benefits that result from it, for example, access to interventions identified as beneficial in the study or to other appropriate care or benefits.

34. The physician must fully inform the patient which aspects of the care are related to the research. The refusal of a patient to participate in a study or the patient's decision to withdraw from the study must never interfere with the patient-physician relationship.

35. In the treatment of a patient, where proven interventions do not exist or have been ineffective, the physician, after seeking expert advice, with informed consent from the patient or a legally authorized representative, may use an unproven intervention if in the physician's judgement it offers hope of saving life, re-establishing health or alleviating suffering. Where possible, this intervention should be made the object of research, designed to evaluate its safety and efficacy. In all cases, new information should be recorded and, where appropriate, made publicly available.