Abbott	Clinical Investigational Plan and Statistical Analysis Plan

NCT Number: NCT01593917
Trifecta™ Long Term Follow-Up Study
Long Term Follow-Up Study of the St. Jude Medical Trifecta™ Valve
Study Document No: SJM-CIP-100063, SJM Protocol: 1104
Version A
Date: 09 January 2012

Sponsor: St. Jude Medical, Inc
177 County Road B. East
St Paul, MN 55117

Table of Contents

PROTOCOL SUMMARY

Study Title: Long Term Follow Up Study of the St. Jude Medical Trifecta™ Valve

Study Device: Trifecta™ Valve

Study Purpose: To collect long term follow up study data of the Trifecta™ valve in subjects who had the Trifecta™ valve implanted during the IDE study.

Study Objectives:

Primary Objective:

1. The primary objective is to collect long-term study data including long term valve-related events of the Trifecta™ valve.

Study Endpoints:

Primary Endpoint:

1. Freedom from reoperation due to Structural Valve Deterioration (SVD) at year 10 post implant.

Secondary Endpoint:

1. Freedom from all-cause mortality;
2. Freedom from valve related mortality;
3. Freedom from SVD

Study Design: This is a multi-center, prospective, non-randomized, post marketing study to collect long term follow up study data. It will be conducted in the United States and Canada. Subjects enrolled in this clinical study received the Trifecta™ valve during the investigational study that was conducted to obtain FDA approval.

In parallel to this study, a post-approval study (PAS) mandated by FDA is being conducted at 6 of the IDE sites in which follow-up data through 5 years post-implant is being collected. At the completion of the PAS study these sites and their participating subjects will be invited to participate in this long-term follow-up study.

Subjects meeting the eligibility criteria and who have signed the Subject Informed Consent will undergo an NYHA functional classification assessment, a general clinical assessment and a transthoracic-echocardiogram (TTE)

based on their original Trifecta™ implant date at the following time points: 3 year, 5 year, 7 year and 10 year. The alternate years a phone follow-up will be completed.

Study Population: Subjects previously implanted with a Trifecta™ prosthetic valve at the selected sites during the IDE clinical investigational study and who meet all eligibility criteria will be invited to participate.

Sponsor: St. Jude Medical
177 County Road B. East
St Paul, MN 55117

1.0 Introduction

1.1 Valvular Disease 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 the contributing factor for another 42,000 deaths each year. The majority of these cases involve disorders of the aortic valve (63%).[i] 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.[ii] 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.[iii] Symptoms of aortic regurgitation include angina, syncope, dyspnea, heart murmur, fatigue, and heart failure.

Subjects 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.[ii] Aortic valve replacement (AVR) appears to be the only effective treatment for these subjects.[ii] For certain subjects with severe aortic regurgitation who are not considered good surgical candidates, therapy with vasodilating agents may provide some benefit. [ii]

Presently, there are two broad categories of aortic valve prostheses; mechanical and tissue (bioprosthesis). The tilting-disc, and bileaflet are the two 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.[iii,iv]

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.[v,vi] Implanting physicians must not only consider the various valve characteristics when deciding which aortic prosthesis to implant, but also various subject factors including, but not limited to, age, coexisting medical conditions, anticoagulation therapy tolerance, and cardiac physiology.[ii,iii,iv] As a result, physicians frequently encounter a subject where the choice of valve type is unclear.

1.2 Trifecta™ Valve

Trifecta™ valve sizes 19mm through 29mm were evaluated in the Trifecta™ IDE clinical study.

The Trifecta™ valve was approved in the following geographies.

- U.S. FDA approval April 20th, 2011
- Health Canada approval October 18th, 2010

2.0 Study Design Overview

This is a multi-center, prospective, non-randomized, post marketing study to collect long term follow up study data. It will be conducted in the United States and Canada. Subjects enrolled in this clinical study received the Trifecta™ valve during the IDE study that was conducted to obtain FDA approval.

All previously available study data for all subjects from participating sites will be included in the data set for this study. This will include data collected during the IDE study as well as from the FDA-mandated post-approval study, when available.

Subjects meeting the eligibility criteria and who have signed the Subject Informed Consent will undergo an NYHA functional classification assessment, a general clinical assessment and a transthoracic-echocardiogram (TTE) based on their Trifecta™ implant date at the

following time points: 3 year, 5 year, 7 year and 10 year. The alternate years a phone follow-up will be completed.

3.0 Study Objectives and Endpoints

3.1 Study Objective

The primary objective is to collect long-term study data including long term valve-related events of the Trifecta™ valve.

3.2 Study Endpoints

3.2.1 Primary Endpoint

Freedom from reoperation due to Structural Valve Deterioration (SVD) at year 10 post implant.

3.2.2 Secondary Endpoint:

1. Freedom from all-cause mortality;
2. Freedom from valve related mortality;
3. Freedom from SVD

4.0 Subject Population

4.1 Inclusion Criteria

1. Patient currently has a Trifecta™ valve that was implanted at one of the U.S. or Canadian investigational sites during the Trifecta™ IDE study.
2. Patient met eligibility criteria prior to enrollment in the Trifecta™ IDE study.
3. Patient agrees to complete all required follow-up visits.
4. Patient provided written informed consent prior to any study related procedure, as approved by the governing Institutional Review Board (IRB) or the Ethics Committee (EC) of the investigational site.

4.2 Exclusion Criteria

1. Patient is currently participating or planning to participate in any other study unless approved by SJM.

4.3 Additional study data

Data from the Trifecta™ IDE and PAS studies for all participating subjects will be included in the data sets for this study. See Analysis Population section of the Statistical Analysis Plan in Appendix B.

4.4 Sample Size and Study Duration

The long term follow-up study will enroll subjects who were previously implanted with the Trifecta™ valve in the IDE study and meet section 4.1 criteria and will be followed for ten (10) years from their Trifecta™ implant procedure or until a final event, such as valve explant, death, or change in status (e.g. lost to follow-up or withdrawal from study).

4.5 Method of Enrollment

Subjects are considered enrolled at the time the informed consent is signed.

5.0 Confidentiality and Subject Informed Consent and Research Authorization

This study will be performed in accordance with applicable confidentiality, privacy and security, and data protection laws

The Investigator, or an individual designated by the Investigator, must obtain written study-specific informed consent and research authorization (using the most recent IRB/REB approved document) from an eligible subject prior to commencing any study-related procedures.

The process of obtaining informed consent must be consistent with the FDA published regulations, the Declaration of Helsinki and the reviewing IRB/EC. The subject or legal guardian must be given the opportunity to ask questions of, and receive satisfactory answers from, the investigator or study personnel prior to signing the consent document.

Subjects will be asked to provide consent so that data can be gathered. After the subject signs the informed consent document, the original is to be filed in the subject's medical record, a copy filed in the subject's study binder, and a copy given to the subject.

6.0 Study Procedures

6.1 Summary of Study Procedures

Subjects will begin follow up visits according to the anniversary date of their Trifecta™ valve implant. However, prior to this visit, the patient must sign the informed consent.

Follow-up assessments will include the following (Refer to Table 7, Schedule of Assessments):

- Transthoracic-echocardiogram (TTE)
- NYHA functional classification assessment to be completed by a Study Investigator
- General clinical assessment
- Serious Adverse Event (SAE) Assessment

Table 7: Schedule of Assessments

	Screening	Year 2,4,6,8, and 9* (± 60 days)	Year 3,5,7 and 10* (± 60 days)	Early Termination
Informed Consent	X			
Echocardiogram			X	X
Clinical Assessment*			X	X
NYHA			X	X
Phone Assessment*		X		
Serious Adverse Events	X	X	X	X

*Subjects will continue the assessment schedule from the IDE study.

7.0 Echocardiography Core Laboratory Procedures

Echocardiography examinations will be conducted at the 3, 5, 7 and 10 year assessments. Each site is responsible for performing the echocardiogram according to the Echocardiography Manual of Operations. Echocardiography examinations will be forwarded to the Echocardiography Core Laboratory for interpretation.

The responsibility of the Echocardiography Core Laboratory is to complete the echocardiography data collection forms and submit these to the Sponsor.

The Echocardiography Core Laboratory will provide the study required interpretation and documentation of each follow-up echocardiogram submitted. SJM will use only the measurements from the Echocardiography Core Laboratory for analysis. If the Core Laboratory determines the echocardiogram is unreadable, the subject may be asked to return for another echocardiogram.

7.1 Phone Assessment

Phone follow up will be conducted at the 2, 4, 6, 8, and 9 year assessment schedule. This will consist of routine questions asking if any serious adverse events have occurred since the last assessment.

7.2 Study Termination

Each subject will be followed through 10 years post implant or until time of death, explant, lost to follow up, withdrawal or study termination.

7.3 Subject Withdrawal

Participation in this study is voluntary. Subjects are free to withdraw from the study at any time without reason, however, subjects should be encouraged to complete the ten years of follow up. .

7.4 Lost to Follow-Up Procedures

Every effort should be made to obtain follow-up data. Potential methods of subject tracking may include:

- Attempting to contact the subject by multiple phone calls and letters documented at the site.
- Mailing a registered letter to the subject's last known address requesting that the subject contact the site.
- Contacting individuals identified by the subject as alternative contacts.

Subjects who cannot be located after at least three documented contact attempts will be reported as "lost to follow-up" by the study site, who must complete a Study Subject Status CRF and provide it to Sponsor. Subjects who are deemed lost to follow up may re-enroll in the study by signing the current IRB/EC approved informed consent.

8.0 Data Collection and Management

To ensure data quality and completeness, all required data will be recorded on standardized specific CRFs, as provided by SJM.

The site will maintain the CRFs and documentation in the respective subject binders.

The Investigator or his/her designee at each site is responsible for recording all data onto the CRFs. The data on each CRF must be legibly written in indelible ink only. If changes are required prior to submission to SJM, a single line must be drawn through the incorrect information, the correct information written in, and the changes initialed and dated. The obscuring of any incorrect data (use of white-out, correction tape, or scribbling out) is strictly prohibited.

If an error is discovered after submission of the CRF to SJM, notify SJM. SJM will generate a data clarification form (DCF) or query and send to the site for resolution.

9.0 Serious Adverse Events (SAE)

Only serious adverse events are being collected for this study.

A serious adverse event is any event on health or safety that is

- Fatal or life threatening
- Results in persistent or significant disability
- Requires intervention to prevent permanent impairment/damage
- Results in hospitalization or prolongation of hospitalization (> 24 hours)

All SAEs including those specified in Edmunds Criteria[vii] (1996) that occur throughout the conduct of the study will be reported on the Serious Adverse Event case report form. The Edmunds Criteria events include:

- Structural Deterioration
- Nonstructural Dysfunction
- Embolism (Valve Related)
- Valve Thrombosis
- Major Bleeding Event
- Endocarditis
- Death (all cause mortality)

SJM will request that additional information such as operative notes, discharge summaries, histopathology reports, and a physician's summary of the event, be provided to SJM as supporting documentation for any reported SAE.

In the event of a subject death, an autopsy should be performed whenever possible and the Trifecta™ valve explanted and returned to SJM for evaluation. If available, death summaries and autopsy reports should be provided to SJM.

All SAEs, regardless of perceived causal relationship, should be communicated by study personnel to SJM within 48 hours of first learning of the event.

It is the responsibility of the Principal Investigator to notify his/her IRB/EC of any SAEs, as required. SAEs will be reviewed by SJM personnel. All complaints/ Medical Device Report (MDR) will be reported to the appropriate regulatory body per geography requirements through the SJM Product Surveillance Department.

Study specific Adverse Event definitions are located in Appendix C.

10.0 Clinical Events Committee (CEC)

An independent Clinical Events Committee (CEC) will be established prior to study enrollment. The CEC will be comprised of two members from the original Trifecta™ IDE study Data Monitoring Committee which will provide continuity to the adjudication process. These members are independent from the Sponsor, and the participating investigators in this long term follow up study. The CEC consists of a cardiac surgeon and a cardiologist. The cardiac surgeon will be serving as the chairperson.

A CEC Charter will be developed and agreed upon by the Sponsor and both CEC members prior to the review of data. The Charter will describe the functions of the CEC.

The CEC will meet at a minimum, on a bi-annual basis. However, the CEC may convene more often if deemed necessary by the committee and/or the Sponsor.

11.0 Data Analysis

11.1 Primary Endpoint

Freedom from reoperation due to Structural Valve Deterioration (SVD) at year 10 post-implant.

11.2 Secondary Endpoints

1. Freedom from all-cause mortality;
2. Freedom from valve related mortality;
3. Freedom from SVD.

Additionally, NYHA, specific hemodynamic parameters (e.g. for calculating mean gradient, EOA) and confounding factors, including but not limited to demographic data, anticoagulation/antiplatelet therapy, beta blocker and calcium channel blocker use, and coexisting medical conditions will be collected, to the extent possible, to aid and support the interpretation of the analysis.

11.3 Additional Analysis

Summary information will be provided in graphical and/or tabular format. For continuous variables, summary statistics (N, mean, standard deviation, and percentiles) will be provided. For categorical or ordinal variables, the number of subjects having each attribute and the percentage of total subjects used will be presented.

The following analyses will be performed:

1. Survival (Kaplan-Meier) analyses for all primary and secondary end point events occurring in the post-operative period.
2. Number and linearized rates of subjects experiencing primary and secondary end point late events (>30 days post-implant).
3. A summary of specific hemodynamic (mean gradient, effective orifice area) data
4. NYHA functional classification assessment over time

11.4 Analysis of Scientific Soundness

The scientific soundness of the long term follow up study is established by the following characteristics:

- Principal Investigators and appropriate research staff will be trained on the study protocol and methodologies.
- The purpose of the study is defined.
- Standard definitions are provided for study endpoints.
- Uniform study procedures and echocardiographic methods will be used to ensure consistent measurement of study endpoints.
- The long term follow up study will be conducted in a prospective manner allowing use of current diagnostic methodologies and treatment practices.

- The supporting statistical analysis methods are appropriate for the type of study endpoints and objectives.
- An Echocardiography Core Laboratory will be used.
- The conduct of the study will be monitored on an ongoing basis. Actions to secure and restore compliance will be implemented as appropriate.

12.0 Risk Analysis

12.1 Potential Benefits

Potential benefits to the subjects participating in the study may include study-related assessments including annual transthoracic echocardiograms (TTE) and clinical assessments. Future subjects participating in valve studies may benefit from the experience gained in this long term follow up study.

12.2 Potential Risks

It is expected that the procedures: (TTE, a clinical assessment and the determination of the NYHA functional classification) involve no additional known risks to the subject other than those commonly associated with the follow-up of subjects who have had a prosthetic heart valve implanted.

13.0 Monitoring Procedures

13.1 Study Monitors

All sites will be monitored by Sponsor or Sponsor's designee to ensure the long term follow up study is being conducted in accordance with the protocol, investigator agreement, applicable regulations, and SJM policies and procedures. Only monitors qualified by training and experience who will be trained on the study protocol will be allowed to monitor. The monitor's qualifications and training on the protocol will be documented.

13.2 Monitoring Plan

Prior to initiating site monitoring activities, a study specific Monitoring Plan will be created and revised by the Sponsor as needed over the course of the study.

13.3 Compliance

It is the responsibility of the Sponsor to promptly secure compliance from any site that is not complying with the requirements of this study protocol. If compliance is unable to be secured, SJM may terminate the Investigator's participation in the study.

14.0 Protocol Modifications

14.1 Amendments to the Protocol

If a protocol amendment becomes necessary during the conduct of the study, SJM will submit the amendment to the site and to the respective IRB/EC, as necessary.

14.2 Deviations from the Protocol

Investigators are required to adhere to this protocol, the signed Study Agreement, applicable national or local laws and regulations, and any conditions required by the IRB or REB or appropriate applicable regulatory authorities.

A deviation is used to describe situations in which this protocol was not followed. All deviations must be reported to the Sponsor on the Protocol Deviation Case Report Form. All deviations must be reported to the IRB or EC per their requirements.

15.0 Records & Reports

15.1 Study Sponsor

The Sponsor is responsible for the study design, conduct, analysis, and reporting of the results from this study. The Sponsor is also accountable for monitoring and performing those actions necessary to protect the rights of subjects and the scientific credibility of the manner in which this long term follow up study is conducted. SJM reserves the right to obtain data clarification and/or additional medical documentation on subjects enrolled in this study at any time.

15.2 Study Investigators

The study Investigator is responsible for ensuring that the long term follow up study is conducted according to the Study Agreement and all amendments thereto, Protocol, any conditions of approval imposed by applicable regulatory authorities and/or the reviewing IRB/REBs and all applicable laws and regulations.

15.2.1 Record Retention

Subject study records, correspondence files, all supporting study documentation, and reports as described above must remain on file at the site for a minimum of two years after the termination of this study or per local laws. All Study Investigators must contact SJM prior to destroying or

archiving off-site any records and reports pertaining to this study to ensure that they no longer need to be retained on-site.

16.0 Regulatory Compliance

The Principal Investigator and all research staff participating in this investigation are expected to adhere to the study agreement, the study protocol, the Declaration of Helsinki, 21 CFR parts 50, 54, and 56, applicable Canadian privacy, security and other Canadian laws applicable to the conducting of this study, applicable U.S. Federal and State privacy and security laws.

16.1 Institutional Review Board (IRB)/ Ethics Committee (EC) Approval

A duly constituted IRB/EC representing the prospective study site must review and approve the subject informed consent and research authorization document, the study protocol, the prospective investigator's participation in the study, and any other study related information to be provided to the subjects prior to subject enrollment. Additionally, the Investigator must be aware of and adhere to all IRB/EC requirements such as, but not limited to: the submission of progress reports, serious adverse events, and protocol deviations.

Appendix A: Statistical Analysis Plan

Summary

The long term follow up data of the Trifecta™ valve will be collected for summary and analysis.

In this long term follow up study, subjects who had the Trifecta™ valve implanted as part of the IDE study and enroll (refer to section 4.1) in this study will be followed for a minimum of:

- Ten years post-implant or
- Until time of death, explant, lost to follow-up, withdrawal or study termination.

Additionally, all previously available study data (from Trifecta™ IDE and Trifecta™ post approval study (PAS)) for all subjects (who met eligibility criteria prior to enrollment in the Trifecta™ IDE study) from these participating sites will be included in the analysis datasets for this long term study. This includes prior study data for subjects from these participating study sites who died, were explanted, or were lost to follow-up prior to this long term study as well as prior study data for subjects from these participating study sites who do not consent to participation in this long term study.

The summary data of study primary and secondary endpoints will be provided based on CEC adjudication.

In addition, NYHA functional classification and key specific hemodynamic data will also be provided.

Study endpoints

Primary endpoint

1. Freedom from reoperation due to structural valve deterioration (SVD) at 10 years post implant.

Secondary endpoints

1. Freedom from all cause mortality;
2. Freedom from valve related mortality;
3. Freedom from SVD

Sample size

Approximately 13 sites (among these, 6 sites originally from PAS) who participated in the Trifecta™ valve IDE study with approximately 650 active subjects at the end of the IDE study will be approached for participation in this study.

Analysis Population

Attempts will be made to approach all previous Trifecta™ IDE subjects at the sites participating in the long term follow up study (who were actively being followed and who met eligibility criteria prior to enrollment in the Trifecta™ IDE study) for participation in this study.

In addition to the data collected during this long term follow up study, the study analysis datasets will include all previously available study data (from Trifecta™ IDE and Trifecta™ PAS) for all subjects (who met eligibility criteria prior to enrollment in the Trifecta™ IDE study) from sites participating in the long term follow up study and the PAS.

Data Analysis and Reporting

Data summary and analysis will be performed based on all available data. Statistical analysis software SAS version 9.2 (or newer if available) will be used for the analysis, except when otherwise specified.

Valve Event Analysis

Survival (Kaplan-Meier) Analysis for time-associated mortality, valve-related mortality, SVD, and reoperation due to SVD will be based on the time to the first occurrence of the adverse event for each subject. Kaplan-Meier analysis will be performed to evaluate the freedom from adverse events data over time. Adverse events occurring in the postoperative period will be included in this analysis. The time to event will be determined from the date of implant to the first occurrence of the event (for subjects experiencing the event) or to the last date of contact (for subjects not experiencing the event).

Late Serious Adverse Event (Linearized) Rate will be reported for serious adverse events when appropriate, as defined by the number of late events per 100 late patient-years at risk:

$$\text{Linearized Rate (\%/late patient - year)} = \frac{number\ of\ late\ events}{total\ late\ patient-years} * 100\%$$

Late events are those that occur 31 or more days post-implant. The late patient-years for each subject are calculated from 31 days following implant to the last date of contact or adverse event as appropriate.

Data Presentation

Summary information will be provided in graphical and/or tabular format. For continuous variables, summary statistics (N, mean, standard deviation, and percentiles) will be provided. For categorical or ordinal variables, the number of subjects having each attribute and the percentage of total subjects used will be presented.

The following data will be presented when necessary:

1. Age at implant
2. Gender
3. Valve size
4. Medical history

The following analyses will be performed:

1. Survival (Kaplan-Meier) analyses for all primary and secondary end point events occurring in the post-operative period.
2. Number and linearized rates of subjects experiencing primary and secondary end point late events (>30 days post-implant).
3. A summary of specific hemodynamic (mean gradient, effective orifice area) data
4. NYHA functional classification assessment over time

Ad hoc analyses may be performed as appropriate.

Appendix B: Definitions

A. EDMUNDS CRITERIA AND SERIOUS ADVERSE EVENTS[vii,viii ix,x]

Major Bleeding Event

Any episode of major internal or external bleeding that causes death, hospitalization, operation, pericardiocentesis, or permanent injury (e.g., vision loss) or requires transfusion. A bleeding event is reportable whether or not the subject is taking anticoagulation or antiplatelet drugs, since bleeding events can occur in subjects who are not receiving anticoagulants.

Embolic stroke complicated by bleeding is classified as a neurological event under "embolism" and is not included as a separate bleeding event.

Death

Valve-related Mortality: Death due to any of the following events involving the study valve: structural valvular deterioration, nonstructural dysfunction, valve thrombosis, embolism, bleeding event, endocarditis, or reoperation. Sudden, unexplained deaths of subjects with an operated valve are included as valve related mortality.

Sudden, unexpected, and unexplained deaths are sudden when they occur within one hour of an event of abrupt onset; unexpected if they occur in a previously well subject; and unexplained if no cause can be determined.

Other cardiac Mortality: Death resulting from cardiac causes, excluding valve-related mortality. Examples include congestive heart failure, acute myocardial infarction, and documented fatal arrhythmias.

Other cause Mortality: Death due to any cause, excluding valve-related mortality or other cardiac mortality.

Embolism

Embolism is any embolic event that occurs in the absence of infection after the immediate perioperative period (when anesthesia-induced unconsciousness is completely reversed). Only arterial emboli will be captured. Pulmonary emboli, cardiac mural thromboemboli and atherosclerotic particle emboli are not to be reported. Subsets of embolic events are:

Neurologic Event:

Any new, temporary, or permanent focal or global neurological deficit. Psychomotor deficits determined by specialized testing are not considered neurologic events related to operated valves. Types of neurologic events are:

- Transient Ischemic Attack (TIA): Fully reversible neurologic deficit that lasts less than or equal to 24 hours, and if an imaging study is performed, shows no evidence of infarction.
- Reversible Ischemic Neurologic Deficit (RIND): Fully reversible neurologic deficit that lasts more than 24 hours and less than or equal to three weeks.
- Stroke or permanent neurologic event: A neurologic deficit that lasts more than three weeks, causes death or lasts less than or equal to three weeks with a brain imaging study showing an infarction.

Systemic Embolic Event:

An operative, autopsy or clinically documented embolus that produced symptoms from complete or partial obstruction of a peripheral (non-cerebral) artery. Systemic events should be classified as:

- Minor: symptoms resolve completely without medical or surgical intervention
- Major: permanent injury or medical/surgical intervention required
- Fatal: death results as a consequence of the embolism or from related adverse events (less than or equal to 30 days or during the same course of hospitalization)

Endocarditis

Valvular endocarditis is any infection involving an operated valve. The diagnosis of operated valvular endocarditis is based on customary clinical criteria including an appropriate combination of positive blood cultures, clinical signs and/or histologic confirmation of endocarditis at reoperation or autopsy. Morbidity associated with active infection, such as valve thrombosis, thrombotic embolus, bleeding event, or paravalvular leak, is included under this category and is not included in other areas of morbidity.

Nonstructural Dysfunction

Nonstructural dysfunction is any abnormality resulting in stenosis or regurgitation at the operated valve that is not intrinsic to the valve itself. Nonstructural dysfunction refers to nonstructural problems that result in dysfunction of a study valve *exclusive of thrombosis or infection* diagnosed by reoperation, autopsy, or clinical investigation.

Examples of nonstructural dysfunction include: entrapment by pannus, tissue, or suture; paravalvular leak, inappropriate sizing or positioning, residual leak or obstruction from valve implantation or repair, and clinically significant hemolytic anemia.

Sudden or progressive dysfunction or deterioration of the study valve may be structural, nonstructural, or both as determined by reoperation, autopsy, or clinical investigation.

Reoperation

Reoperation is any operation that repairs, alters or replaces the study valve. The reasons for reoperation are to be reported and may include reasons other than valve-related morbidity, such as recall, excessive noise, or incidental or prophylactic removal.

Thrombolytic or catheter-aided therapy of valve-related morbidity is not considered reoperation; however, the morbid event that prompted the intervention should be reported.

Structural Deterioration

Structural valve deterioration is any change in function of a study valve resulting in an intrinsic abnormality of the valve that causes stenosis or regurgitation.

Structural valvular deterioration includes study valve dysfunction or deterioration *exclusive of infection or thrombosis* as determined by reoperation, autopsy, or clinical investigation. The term structural deterioration refers to changes intrinsic to the valve, such as wear, stent fracture, calcification, leaflet tear, stent creep, and suture line disruption of components (e.g., leaflets) of an operated valve.

Valve Thrombosis

Valve thrombosis is any thrombus, *in the absence of infection*, attached to or near the study valve that occludes part of the blood flow path or that interferes with function of the valve. Valve thrombosis may be documented by operation, autopsy, or clinical investigation. Valve thrombosis is categorized as follows:

- Obstructive valve thrombosis: The accumulation of thrombus on a replacement valve with (potentially) catastrophic hemodynamic or embolic consequences.
- Non-obstructive valve thrombosis: An incidental finding without (potentially) catastrophic hemodynamic consequences (e.g., thrombus on the outflow aspect of the bioprosthesis, etc.)

Serious Adverse Event
A serious adverse event is any adverse event on health or safety, that is fatal or life threatening, results in persistent or significant disability, requires intervention to prevent permanent impairment/damage, or an event that results in hospitalization or prolongation of hospitalization (> 24 hours).

B. OTHER STUDY RELATED DEFINITIONS

New York Heart Association (NYHA) Functional Classification:

Class I: No limitations of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, or dyspnea.

Class II: Slight limitation of physical activity. They are comfortable at rest. Ordinary physical activity results in fatigue, palpitation, or dyspnea.

Class III: Marked limitation of physical activity. Comfortable at rest, but ordinary physical activity causes fatigue, palpitation, or dyspnea.

Class IV: Unable to carry out any physical activity without discomfort. Symptoms of cardiac insufficiency at rest. If any physical activity is undertaken, discomfort is increased.

Appendix C: References

[i]American Heart Association. *Heart Disease and Stroke Statistics – 2005 Update*. Dallas, Texas: American Heart Association 2005.

[ii]Bonow RO, Carabello B, de Leon AC Jr, et al. ACC/AHA Guidelines for the Management of Patients with Valvular Heart Disease. *J Am Coll Cardiol* 1998;32:1486-588.

[iii]Werner JA, Crawford MH. Choosing a Prosthetic Heart Valve. *Cardiol Clin.* 1998;16:491-504.

[iv]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

[v]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.

[vi]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.

[vii]Edmunds LH, Clark RE, Cohn LH, Grunkmeier GL, Miller DC, Weisel RD. Guidelines for reporting morbidity and mortality after cardiac valvular operations. J Thorac Cardiovasc Surg 1996;112:708-11.

[viii]Bodnar E, Butchart EG, Bamford J, Besselaar AMPH, Grunkmeier GL, et al. Proposal for reporting thrombosis, embolism, and bleeding after heart valve replacement. *J Heart Valve Dis* 1994;3:120-3.

[ix]US Food and Drug Administration, Division of Cardiovascular, Respiratory, and Neurological Devices, October 14, 1994. Replacement Heart Valve Guidance Document.

[x]International Standard ISO – 5840:2005