Clinical Investigation Plan

NCT Number: NCT03016169
Trifecta GT PMCF
Trifecta™ GT Post Market Clinical Follow-up
Study Document No: SJM-CIP-10120
Version B
Date: 15 May 2018

Sponsored by:

Abbott
5050 Nathan Ln N
Plymouth, MN 55442
USA

[redacted]

Clinical Investigation Plan

SJM-CIP-10120
Trifecta GT PMCF
Trifecta™ GT Post Market Clinical Follow-up

Version Number	B
Date	15 MAY 2018
Steering Committee	[redacted]
Planned Number of Sites and Region(s)	Approximately 35 (EU, US, CA)
Clinical Investigation Type	Prospective, multi-center, single arm, open-label, multi -center, clinical investigation.
Abbott Medical Expert	[redacted]
Sponsor	Abbott 5050 Nathan Ln N Plymouth, MN 55442
Electronic Data Capture Software	[redacted]
Core Laboratories	[redacted]
CIP Author of Current Version	[redacted]

Clinical Investigation Plan

SITE PRINCIPAL INVESTIGATOR SIGNATURE PAGE

I have read and agree to adhere to the clinical investigation plan and all regulatory requirements applicable in conducting this clinical study.

Site Principal Investigator

Printed name:
Signature:
Date:

Clinical Investigation Plan

STEERING COMMITTEE CHAIR

SIGNATURE PAGE

I have read and agree to adhere to the clinical investigation plan and all regulatory requirements applicable in conducting this clinical study.

Steering Committee Chair

Printed name:
Signature:
Date:

Clinical Investigation Plan

Table of Contents

Clinical Investigation Plan

Clinical Investigation Plan

Clinical Investigation Plan

1 Introduction

This document is a clinical investigation plan (CIP) for the Trifecta GT post-market clinical follow-up (PMCF) clinical study. This clinical study is intended to evaluate 5 year performance of the Trifecta GT valve in patients indicated for aortic valve replacement to satisfy a CE mark approval requirement in Europe. This clinical study is sponsored by St. Jude Medical (SJM).

This clinical study will be conducted in accordance with this CIP. All parties involved in the conduct of the clinical study will be qualified by education, training, or experience to perform their tasks and this training will be documented appropriately.

2 Background and Justification for Clinical Study

SJM's Trifecta family of aortic heart valves is used in patients with valvular heart disease. Valvular heart disease is characterized by abnormal heart valve function with interruption of normal blood flow through the heart. This may result in symptoms such as fatigue, weakness, shortness of breath, chest pain and/or heart palpitations. There are two types of heart valve disease: narrowed heart valve and leaky heart valve. A narrowed heart valve (also known as valvular stenosis) is characterized by a narrowed valve opening, requiring the heart to work hard to pump blood. A leaky heart valve (also known as valvular regurgitation) is characterized by a valve that does not close tightly. If the valve cannot fully close, blood can leak backwards across the valve causing the heart to work harder, resulting in less blood flow to the body. Some patients may have a mixture of both types of heart valve disease involving one or more of the valves.

Valvular heart disease can be congenital or may be acquired as a result of various diseases or infections, including rheumatic fever and endocarditis. Other causes of valvular heart disease may include, but are not limited to, atherosclerosis, cardiomyopathy, hypertension, aortic aneurysms, and connective tissue diseases.

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.

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 2 to 3 years.[2] Aortic valve replacement (AVR) appears to be the most effective treatment for these patients.[2]

For patients that need an aortic valve replacement, the Trifecta Glide Technology (GT) aortic valve is one option. [redacted]

The Trifecta valve received approval in Europe on 4 March 2010, in Canada on 18 October 2010 and in the United States on 20 April 2011. The Trifecta GT valve was approved in Europe on 1 February 2016, in Canada on 8 July 2016 and in the United States on 24 April 2016.

[redacted]

3 Device Overview

3.1 Identification and Description of the Devices Used in this Study

3.1.1 Identification

Table 1: Identification of Proposed Devices

Device name	Model/Type	Manufacturer	Region/ Country*	Investigational or Market Released
TFGT-19A	19mm valve	St. Jude Medical	United States, European Union (and EEA), Canada.	Market Released
TFGT-21A	21mm valve	St. Jude Medical		Market Released
TFGT-23A	23mm valve	St. Jude Medical		Market Released
TFGT-25A	25mm valve	St. Jude Medical		Market Released
TFGT-27A	27mm valve	St. Jude Medical		Market Released
TFGT-29A	29mm valve	St. Jude Medical		Market Released

The Trifecta series sizer set model TF2000-2 is a multicomponent kit that facilitates the size selection of the Trifecta valve and Trifecta valve with Glide Technology. The sizer set contains two rigid handles and six flexible sizers.

3.1.2 Device Description and Intended Purpose

The Trifecta valve with Glide Technology is a tri-leaflet stented pericardial valve designed for supra-annular placement in the aortic position.

[redacted]

[redacted]

The valve is intended as a replacement for a diseased, damaged, or malfunctioning aortic heart valve. The valve may also be used as a replacement for a previously implanted aortic prosthetic heart valve.

Please refer to the IFU for additional information regarding the device used in this clinical investigation.

3.1.3 Device Handling and Storage

Sponsor requires all study products be stored, according to the labeling and Instructions for Use.

3.2 Devices Accountability

Since this is a post market study, there are no special requirements for device accountability beyond those required for commercial distribution.

Clinical Investigation Plan

4 Clinical Study Design

4.1 Clinical Study Design

This study is a multi-center, prospective 5 year study of approximately 350 subjects intended to be implanted with a SJM Trifecta GT valve. It will be conducted in approximately 35 sites worldwide.

[redacted]

To ensure an adequate number of subjects at each site, no individual site may enroll more than 10% of the maximum sample size (n=35 subjects) without prior approval from the sponsor.

4.2 Objective

The objective of this study is to evaluate the safety and performance of the Trifecta™ GT valve through 5 year follow-up in a prospective, multi-center, real-world setting. This study is intended to satisfy post-market clinical follow-up requirements of CE Mark in Europe. This study is sponsored by St. Jude Medical.

4.3 Endpoints

There is one primary endpoint and five descriptive endpoints in this clinical study.

4.3.1 Primary Endpoint

- Freedom from surgical valve replacement or transcatheter valve-in-valve implantation at 5 years post implant.

4.3.2 Descriptive Endpoints

- Freedom from all-cause mortality at 5 years post implant
- Freedom from valve related mortality at 5 years post implant
- Freedom from Structural Valve Deterioration (SVD) at 5 years post implant
- Freedom from surgical valve replacement or transcatheter valve Implantation due to SVD at 5 years post implant
- Valve hemodynamic performance (e.g. left ventricular ejection fraction, mean and peak gradients, aortic insufficiency and effective orifice area via any available/performed echocardiograms) at pre-discharge, 6 months, 3 years and 5 years post implant.

4.4 Study Population

The intended population for this clinical study is subjects who are indicated for surgical aortic valve replacement per current guidelines and intended to be implanted with a St. Jude Medical Trifecta GT valve with or without the following concomitant procedures:

- coronary artery bypass grafting (CABG)
- supracoronary replacement of ascending aorta
- aortic annulus or root enlargement
- atrial fibrillation ablation
- mitral valve repair
- tricuspid valve repair

Subjects who have had a previous aortic valve replacement or coronary artery bypass graft surgery are eligible for this study.

4.4.1 Inclusion Criteria

1. Subject is a candidate for surgical aortic valve replacement per current guidelines and is intended to be implanted with a St. Jude Medical Trifecta GT valve.
2. Subject is of legal age in the country where the subject is enrolled.
3. Subject must be willing and able to provide written informed consent to participate in this study.

[redacted]

4. Subject must be willing and able to comply with all follow-up requirements.

4.4.2 Exclusion Criteria

1. Subject undergoes a concomitant procedure of mitral or tricuspid valve replacement at the time of the Trifecta GT valve implantation surgery.
2. Subject has contraindication for cardiac surgery.
3. Subject is pregnant. Pregnancy will be assessed by the subject informing the physicians.
4. Subject has active endocarditis (subjects who have previously experienced endocarditis must have two documented negative blood culture results while off antibiotic therapy prior to the valve implantation surgery).
5. Subject has had a stroke or transient ischemic attack within 6 months prior to the planned valve implantation surgery.
6. Subject is undergoing renal dialysis.
7. Subject has a history of active drug addiction, active alcohol abuse, or psychiatric hospital admission for psychosis within the prior 2 years.
8. Subject has a documented thrombus in the left atrium or left ventricle at the time of the valve implantation surgery.
9. Subject has a left ventricular ejection fraction < 30%.
10. Subject previously enrolled in the Trifecta GT PMCF study and withdrawn (a subject cannot be enrolled twice in this study).
11. Preoperative evaluation indicates other significant cardiovascular abnormalities such as aortic dissection or ventricular aneurysm.
12. Subject has a life expectancy less than 2 years.

5 Procedures

The clinical study will not commence at a site until SJM receives written approval from the IRB/EC and relevant regulatory authorities and all required documents have been collected from the site. Approval from the Sponsor must be received prior to initiating study procedures.

The following sections provide a detailed description of procedures required by this CIP.

5.1 Informed Consent Process

The Principal Investigator or his/her authorized designee will conduct the Informed Consent Process, as required by applicable regulations and the center's IRB/EC. This process will include a verbal discussion with the subject on all aspects of the clinical study that are relevant to the subject's decision to participate, such as details of clinical study procedures, anticipated benefits, and potential risks of clinical study participation. During the discussion, the Principal Investigator or his/her authorized designee will avoid any improper influence on the subject and will respect subject's legal rights. The subject shall be provided with the informed consent form written in a language that is understandable to the subject and has been approved by the center's IRB/EC. The subject shall have adequate time to review, ask questions and consider participation.

If the subject agrees to participate, the Informed Consent form must be signed and dated by the subject and by the person obtaining the consent. The signed original will be filed in the subject's hospital or research charts, and a copy will be provided to the subject.

The Principal Investigator or his/her authorized designee will document the informed consent process in the subject's hospital and/or research charts. The date of signature will be entered on an applicable Case Report Form (CRF).

Failure to obtain informed consent from a subject prior to clinical study participation should be reported to Sponsor within 5 working days and to the reviewing center's IRB/EC according to the IRB's/ EC's reporting requirements.

If, during the clinical study, new information becomes available that can significantly affect a subject's future health and medical care, the Principal Investigator or his/her authorized designee will provide this information to the subject. If relevant, the subject will be asked to confirm their continuing informed consent in writing.

5.2 Screening

All subjects presenting at the study site can be screened by designated members of the study team previously trained on the CIP and delegated to do so.

Subjects who do not meet the inclusion/exclusion criteria will not be eligible to participate in this study.

5.3 Point of Enrollment

A subject is considered enrolled in the clinical study when the subject has provided written informed consent, has been confirmed to meet all of the inclusion criteria and none of the exclusion criteria, and implantation of the Trifecta GT valve has been attempted.

The Principal Investigator or delegated study personnel will record enrollment information (name of the clinical study, date of consent, inclusion/exclusion information and implant information) in the hospital records and complete and submit applicable CRFs in a timely manner.

Notification of enrollment to the Sponsor is considered to have occurred when the Sponsor has received the applicable CRFs.

All subjects enrolled in the clinical study (including those withdrawn from the clinical study or lost to follow-up) will be accounted for and documented, by assigning an identification code linked to their names, alternative identification and/or contact information. This is documented on the Enrollment Log.

This log will be kept up to date throughout the clinical study by the Principal Investigator or his/her authorized designee. To ensure subject privacy and confidentiality of data, this log must be maintained throughout the clinical study at the clinical site.

5.4 Scheduled Procedures

The PI is responsible for ensuring all clinical study data is collected as required per CIP scheduled procedures.

5.4.1 Baseline

The following activities are performed at baseline:

- Screening of potential subjects to determine subject eligibility for the study
- Record baseline information (date of consent and inclusion/exclusion information) in the hospital records and complete and submit the Inclusion/Exclusion and Baseline Forms to SJM in a timely manner (recommended within 5 days)
- Demographics
- Physical examination
- Cardiovascular and other relevant medical history
- Cardiac medications
- Indication for implant (aortic regurgitation or aortic stenosis)
- NYHA class
- STS score and EuroSCORE II
- Serum Creatinine
- Echo (if available)

5.4.2 Intervention

Subjects will undergo a Trifecta GT valve implantation surgery. If the implant procedure is attempted but the Trifecta GT valve is not implanted, the subject will be withdrawn from the study after a 30-day adverse

event collection period. If the implant procedure results in successful implantation of the Trifecta GT valve, the subject will have follow-up visits pre-discharge, 6 months, and annually through 5 years. Upon completion of the 5 year follow-up visit, the subject will be considered to have completed the follow-up requirements of this clinical study. The Principal Investigator should arrange for appropriate care of subjects following study completion.

The following information will be collected at the end of the surgical procedure to implant the Trifecta GT valve:

- Echo (if available)
- Aortic valve replacement information
- Operative information
    - Suture technique
    - Implanting physician
    - Details of valve implantation surgery and concomitant procedures

5.4.3 Pre-Discharge

The following information will be collected at discharge or 7 days post intervention whichever is sooner:

- Cardiac medications
- Echo
- Adverse events (if applicable)
- Death (if applicable)

5.4.4 Scheduled Follow-ups (6 Months and Annually Through 5 Years)

Scheduled study follow-ups should occur at the participating institution. If an office visit is not possible, follow-up may occur via a telephone call with the subject for years 1, 2 and 4. The following information will be collected at each follow-up visit.

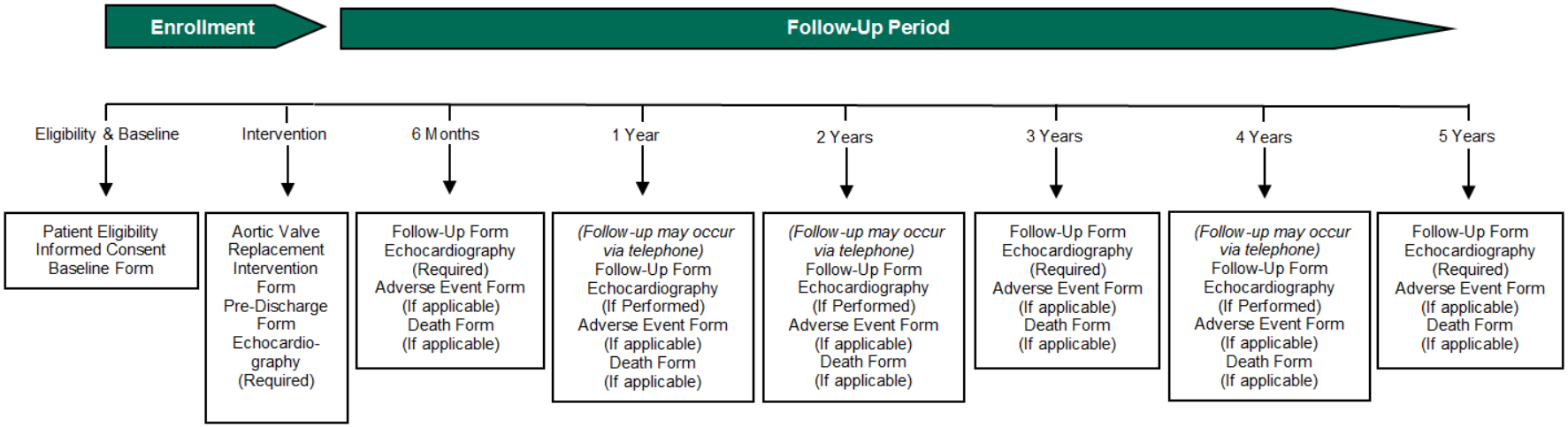
- NYHA class (not required for telephone visits)
- Cardiac medications
- Echo (required at 6 months, 3 years and 5 years including delivery to core laboratory)
- Adverse events (if applicable)
- Death (if applicable)

Clinical Investigation Plan

5.5 Study Flow Chart

The Study Flow Chart (Figure 1) and Table 2 below summarize subject flow and visit requirements for this clinical study.

Figure 1: Study Flow Chart



Clinical Investigation Plan

Table 2: List of Tests and Procedures

Visit Study Activity	Baseline	Intervention (Implant within 30 days of consent)	Pre-discharge (Discharge or 7 days post-implant, whichever is sooner)	6 Month (+/- 30 days)	1 Year Follow-Up (+/- 60 days)	2 Year Follow-Up (+/- 60 days)	3 Year Follow-Up (+/- 60 days)	4 Year Follow-Up (+/- 60 days)	5 Year Follow-Up (+/- 60 days)
Patient Eligibility	X								
Informed Consent Process	X								
Demographics	X								
Physical Examination	X								
Cardiovascular History	X								
Current Cardiac Medications	X								
Medical History	X								
NYHA	X			X	(X)	(X)	X	(X)	X
STS and EuroSCORE II	X								
Serum Creatinine	X								
Echo	(X)	(X)	X	X	(X)	(X)	X	(X)	X
Aortic Valve Replacement Information		X							
Operation Information		X							
Adverse Event		(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)
Cardiac Medication Assessment			X	X	X	X	X	X	X

(X) If applicable

Clinical Investigation Plan

5.6 Description of Activities Performed by Sponsor Representatives

Trained Sponsor personnel may provide technical expertise and technical guidance on the use of the Trifecta GT device. This may include training and case coverage.

While Sponsor representatives may perform these activities, the Principal Investigator remains responsible for ensuring all clinical study data are collected as required per CIP.

5.7 Subject Study Completion

Subject participation in the clinical study will conclude upon completion of the 5 year visit. Upon completion of subject participation in the clinical study, the subject will return to standard of care.

5.8 Subject Withdrawal or Discontinuation

Subjects must be informed about their right to withdraw from the clinical study at any time and for any reason without sanction, penalty or loss of benefits to which the subject is otherwise entitled. Withdrawal from the clinical study will not jeopardize their future medical care or relationship with the investigator. Subjects will be requested to specify the reason for the request to withdraw, however a response is not required. The investigator must make all reasonable efforts to retain the subject in the clinical study until completion of the clinical study.

Reasons for subject's withdrawal include, but are not limited to:

- Subject refuses to continue participating in the study
- Subject is deceased (cause must be documented)
- Subject has a failed Trifecta GT valve implantation attempt (30 day AE collection period required)
- Subject has Trifecta GT valve explanted
- Subject is lost to follow-up: A subject will be considered 'Lost to Follow-up' after two missed visit(s) and a minimum of two unsuccessful phone calls from study site personnel to the subject or contact to schedule the next follow-up visit. These two phone calls must be documented in the subject's hospital records. If the subject is deemed lost to follow-up, a letter identifying the subject's date of withdrawal from the study should be sent to the subject's last known address or to the subject's general practitioner (GP) and a copy of the letter must be maintained in the subject's hospital records.

If a subject withdraws from the clinical study, the site will record the subject's reason for withdrawal, on a Withdrawal Form. When subject withdrawal from the clinical study is due to an adverse event, the subject will be followed by the site until resolution of that adverse event or determination that the subject's condition is stable. The status of the subject's condition should be documented at the time of withdrawal.

In case of subject withdrawal, the site should make attempts to schedule the subject for a final study visit. At this final study visit, the subject will undergo the following assessments:

- Adverse event collection (if applicable)

5.9 Echocardiographic Core Laboratory

Echocardiographic examinations at Pre-Discharge, 6 months, 3 years and 5 years will be forwarded to an echocardiographic core laboratory for interpretation. However, it is the responsibility of each site to perform the local interpretation of the echocardiogram for clinical assessment.

The echocardiographic core laboratory will provide interpretation and documentation of each echocardiogram submitted to the Sponsor. Data obtained from the core laboratory readings will be used for study purposes only and not for clinical treatment of the subject.

Service details are outlined in the Service Agreement.

5.10 Study Committees

5.10.1 Steering Committee (SC)

A Steering Committee will advise the Sponsor on key aspects related to the development, execution, analysis and reporting, and overall conduct of the clinical study. A Steering Committee charter will define membership of the committee and outline the purpose, roles, responsibilities, and general rules of operation for the Steering Committee. This charter is maintained by the Sponsor and sets forth the procedures for the implementation of the Steering Committee.

5.10.2 Clinical Events Committee (CEC)

An independent CEC will be established for the study to provide review and adjudication of pre-defined clinical events (e.g. Edmunds Criteria[5] events). The primary function, responsibilities and membership of the CEC will be described in detail in a CEC charter.

6 Statistical Considerations

6.1 Endpoints

6.1.1 Primary Endpoint

The primary endpoint is freedom from surgical valve replacement or transcatheter valve-in-valve implantation at 5 years post implant.

6.1.1.1 Analysis Methodology

Kaplan-Meier (KM) estimate and 95% confidence interval will be reported for the freedom from surgical valve replacement or transcatheter valve-in-valve implantation at 5 years post implant. [redacted].

6.1.1.2 Analysis Population

[redacted].

6.1.2 Descriptive Endpoints

Freedom from all-cause mortality at 5 years post implant

Kaplan-Meier (KM) estimate and 95% confidence interval will be reported for the freedom from all-cause mortality at 5 years post implant. [redacted]

Freedom from valve related mortality at 5 years post implant

Kaplan-Meier (KM) estimate and 95% confidence interval will be reported for the freedom from valve related mortality at 5 years post implant. [redacted]

Freedom from structural valve deterioration (SVD) at 5 years post implant
Kaplan-Meier (KM) estimate and 95% confidence interval will be reported for the freedom from SVD at 5 years post implant. [redacted]

Freedom from reoperation due to structural valve deterioration (SVD) at 5 years post implant
Kaplan-Meier (KM) estimate and 95% confidence interval will be reported for the freedom from reoperation due to SVD at 5 years post implant. [redacted]

Valve hemodynamic performance at pre-discharge, 6 months, 3 years and 5 years post implant
Left ventricular ejection fraction, mean gradient, peak gradient and effective orifice area (EOA), as assessed by the echocardiographic core laboratory, will be summarized using descriptive statistics including mean, standard deviation, median, and range. Aortic insufficiency will be summarized by frequency and percentage. [redacted]

6.2 Sample Size

The sample size of 350 is based on [redacted]

6.3 Timing of Analysis

The analyses for final report will be conducted on datasets locked after all enrolled subjects have had the 5-year study visit (excepting deaths, withdrawals and loss-to-follow-up before 5 years) or crossed the 5-year visit window without a visit (missed visit).

6.4 Success Criteria

The study has one primary endpoint without formal hypothesis. The primary endpoint result will be compared with data reported in the literature.

6.5 Interim Analysis

No interim analyses are planned for this study.

6.6 Statistical Criteria for Termination

There are no pre-specified criteria for terminating the clinical study on statistical grounds.

6.7 Deviations from Statistical Plan

There is no plan to deviate from this analysis plan. If such a deviation occurs it will be described in the clinical study report.

7 Risks and Benefits

Risks associated with the Trifecta GT valve have been estimated in accordance with ISO 14971: Risk Management for Medical Device, prior to conducting a clinical study. The risk analysis includes or refers

to an objective review of published and available unpublished medical and scientific data. The risk management review of surveillance and monitoring activities finds that the Trifecta family of valves, accessories, and components/materials are safe for their intended use and that all identified residual risks associated with their use are outweighed by the benefits.

7.1 Risks Associated with the Devices Used in this Study

7.1.1 Anticipated Adverse Device Effects

The following is a list of anticipated adverse device effects:

- angina
- cardiac arrhythmias
- endocarditis
- heart failure
- hemolysis
- hemolytic anemia
- hemorrhage
- leak, transvalvular or paravalvular
- myocardial infarction
- nonstructural dysfunction (entrapment by pannus or suture, inappropriate sizing or positioning or other)
- prosthesis regurgitation
- stroke
- structural deterioration (calcification, leaflet tear or other)
- thromboembolism
- valve thrombosis

7.1.2 Risks Associated with Clinical Study Assessments

The follow up procedures required for the clinical study are considered within the scope of the standard of care for subjects undergoing aortic valve replacement, such that there is no added risk for participation in the study.

7.2 Risk Control Measures

Every possible effort will be taken to minimize the risks, including:

- Careful selection of experienced Investigators for the clinical study
- Adequate monitoring for each clinical study site
- Conducting the clinical study in accordance with the CIP, all applicable laws and regulations and any conditions of approval imposed by the appropriate IRB/EC or applicable regulatory authorities where the clinical study is performed
- Preparation of the Trifecta GT valve device and performance of the implantation procedure in accordance with the device IFUs
- Training of Investigators both on the CIP and Trifecta GT implantation procedure.

7.3 Possible interactions with concomitant treatments

The Trifecta GT valve has magnetic resonance conditions and any use of MRI in implanted subjects should be done according to the current Instructions for Use (IFU).

7.4 Anticipated Benefits

Potential benefits to the subjects may include, but are not limited to:

- relief of valvular pathology (aortic stenosis, and/or aortic regurgitation)
- improved hemodynamic performance

- avoidance of long term anticoagulation therapy

In addition to these benefits, additional benefits may occur to future patients through experience gained in this clinical study.

7.5 Risk-to-Benefit Rationale

Patients who have a malfunctioning native or prosthetic aortic valve require intervention. Without intervention, patients whom have a malfunctioning aortic valve also will have a poor long-term prognosis with mortality rates that can exceed 50% by 5 years[3]. Trifecta heart valves have been in commercial use since 2010 and provide a lifesaving technology for patients with few associated risks. These valves have an excellent safety profile. [redacted] As such, the benefits outweigh the risks associated with the use of the device and its components/materials.

8 Requirements for Investigator Records and Reports

8.1 Deviations from CIP

A deviation is defined as an instance(s) of failure to follow, intentionally or unintentionally, the requirements of the CIP. The investigator should not deviate from the CIP.

In some cases, failure to comply with the CIP may be considered failure to protect the rights, safety and well-being of subjects; such non-compliance exposes subjects to unreasonable risks. Examples: failure to adhere to the inclusion/exclusion criteria, failure to perform safety assessments intended to detect adverse events. Investigators should seek to minimize such risks by adhering to the CIP.

The PI must maintain accurate, complete, and current records, including documents showing the date of and reason for each deviation from the CIP. Relevant information for each deviation will be documented as soon as possible on the applicable CRF. The site will submit the CRF to the Sponsor.

The PI is required to adhere to local regulatory requirements for reporting deviations to IRB/EC.

Under emergency circumstances, deviations from the CIP to protect the rights, safety and well-being of subjects may proceed without prior approval of the Sponsor and the IRB/EC. Such deviations shall be documented and reported to the Sponsor and the IRB/EC as soon as possible.

8.2 Safety Reporting

Safety surveillance and the safety reporting by the investigator starts as soon as the subject is enrolled in this clinical study. Refer to Section 5.3 for the definition of subject enrollment.

The safety surveillance and the safety reporting will continue until the last study visit has been performed, the subject is deceased, the subject/investigator concludes his participation into the clinical study or the subject withdrawal from the clinical study.

The PI will report the event to the IRB/EC per their reporting requirements. The following are reportable events per this CIP (see Appendix B for definitions):

- Adverse Device Effects (regardless of seriousness)
- Serious Adverse Events (regardless of severity) including those specified in Edmunds Criteria[5] which include:
  - Structural valve deterioration

Clinical Investigation Plan

- Nonstructural dysfunction
- Embolism (valve related)
- Valve thrombosis
- Major bleeding event
- Endocarditis
- Death

The above events will be reported to the Sponsor. The Sponsor will ensure that all events are reported to the relevant authorities as per regulations. The sites should notify the Sponsor of reportable adverse events by creating and saving the applicable CRF within the electronic data capture (EDC) system.

The investigator should report all SAEs to the Sponsor as soon as possible but no later than outlined below.

Clinical Site	Reporting timelines
All Sites	SAEs must be reported to the Sponsor no later than 3 calendar days from the day the study personnel became aware of the event or as per the investigative site's local requirements, if the requirement is more stringent than those outlined.

The date the study staff became aware the event met the criteria of an SAE must be recorded in the source document. The Investigator will further report the SAE to the local IRB/EC according to the institution's IRB/EC reporting requirements.

Adverse events will be monitored until they are adequately resolved or the subject has ended his/her participation in the trial, whichever comes first. The status of the subject's condition should be documented at each visit.

Records relating to the subject's subsequent medical course must be maintained and submitted (as applicable) to the Sponsor until the event has subsided or, in case of permanent impairment, until the event stabilizes and the overall clinical outcome has been ascertained. Adverse events will be monitored until they are adequately resolved. The status of the subject's condition should be documented at each visit.

The following information should be collected for each event:

- Date AE occurred
- Date the site, PI, became aware of the event
- Main symptoms of the event
- Treatment
- Seriousness
- Relationship to device
- Resolution status

Additional information may be requested, when required, by the Sponsor in order to support the reporting of AEs to regulatory authorities.

The PI must notify the IRB/EC, if appropriate, in accordance with national and local laws and regulations, of the AEs reported to the Sponsor.

8.2.1 Subject Death

All subject deaths are to be documented on the Death Form and reported to the Sponsor as soon as possible after becoming aware of the event.

The subject Death Form should always be accompanied with the relevant Adverse Event Form and relevant source documentation. In the event of a subject death, an autopsy should be performed whenever possible and the Trifecta GT valve explanted and returned to SJM for evaluation. If available, death summaries and autopsy reports should be provided to SJM.

8.2.2 Complaints

During the study, the investigator will be responsible for reporting all complaints. A complaint is defined as any written, electronic or oral communication that alleges deficiencies related to the identity, quality, durability, reliability, safety, effectiveness or performance of a device after it is released for distribution.

If the complaint involves an adverse event (AE), the investigator must complete an Adverse Event CRF, including the information on the complaint and submit to SJM as soon as possible.

If the complaint does not involve an AE, the investigator must notify the SJM Post Market Surveillance Department by submitting the information on the device via email to [redacted] as soon as possible after becoming aware of the complaint. This information will not be collected on a CRF for the study.

For study sites in the United States:
Should a subject death be caused by the SJM device or the device contributed to the death, the investigator should complete a Form 3500A (MedWatch) and submit to SJM and the FDA within 10 days after becoming aware of the event.

8.3 Source records

Source documents will be created and maintained by the site throughout the clinical study. The data reported on the CRFs will be derived from, and be consistent with, these source documents, and any discrepancies will be explained in writing.

8.4 Records Retention

The Sponsor and the Principal Investigators will maintain the clinical study documents as required. Measures will be taken to prevent accidental or premature destruction of these documents. The Principal Investigator or the Sponsor may transfer custody of records to another person/party and document the transfer at the study site or the Sponsor's facility, as appropriate.

These documents must be retained by the study site for a period of 2 years after the conclusion of the clinical study and made available for monitoring or auditing by the Sponsor's representative or representatives of the applicable regulatory agencies.

All original source documents must be stored for the maximum time required by the regulations at the hospital, research institute, or practice in question. If original source documents can no longer be maintained at the site, the investigator will notify the Sponsor.

9 Clinical Data Handling

The Sponsor will be responsible for the data handling. The Sponsor and/or its affiliates will be responsible for compiling and submitting all required reports to governmental agencies. Data will be analyzed by the

Sponsor and may be transferred to the Sponsor's locations worldwide and/or any other worldwide regulatory authority in support of a market-approval application.

The PI or institution will provide direct access to source data during and after the clinical study for monitoring, audits, IRB/EC review and regulatory authority inspections. As required, the PI or institution will obtain permission for direct access to source documents from the subject, hospital administration and national regulatory authorities before starting the clinical study.

9.1 Protection of Personally Identifiable Information

SJM respects and protects personally identifiable information collected or maintained for this clinical study. The privacy of each subject and confidentiality of his/her information will be preserved in reports and when publishing any data. Confidentiality of data will be observed by all parties involved at all times throughout the clinical study. All data will be secured against unauthorized access.

9.2 Data Management Plan

A Data Management Plan (DMP) will describe procedures used for data review, database cleaning, and issuing and resolving data queries. If appropriate, the DMP may be updated throughout the clinical study duration. All revisions will be tracked and document controlled.

Subject data will be captured in a validated electronic data capture (EDC) system hosted by the Sponsor.

Only authorized site personnel will be permitted to enter the CRF data through the EDC system deployed by SJM. An electronic audit trail will be used to track any subsequent changes of the entered data.

9.3 Document and Data Control

9.3.1 Traceability of Documents and Data

The investigator will ensure accuracy, completeness legibility and timeliness of the data reported to the Sponsor on the CRFs and in all required reports.

9.3.2 Recording Data

The CRF will be reviewed by the authorized site personnel. An appropriate comment will be provided to explain changes to data reported on the CRF.

10 Monitoring

It is the responsibility of the Sponsor to ensure the clinical study is conducted, recorded and reported according to the approved CIP, subsequent amendment(s), applicable regulations and guidance documents.

Monitoring will be conducted according to SJM's Clinical Monitoring work instruction. Prior to beginning the clinical study, the Sponsor will contact the investigator or designee to discuss the clinical study and data requirements. A designated monitor will periodically review the subject records and associated source documents. The investigator shall make subject and clinical study records available to the clinical monitor for monitoring.

Clinical Investigation Plan

11 Compliance Statement

11.1 Statement of Compliance

This clinical study will be conducted in compliance with the most current regional and local laws and regulations. Principles of Good Clinical Practice will be followed as based on the most current version of the World Medical Association (WMA) Declaration of Helsinki.

The investigator will sign a Clinical Trial Agreement and agrees to be compliant with it. The investigator will not start enrolling subjects or requesting informed consent from any subject prior to obtaining IRB/EC approval and relevant Regulatory Authority approval, if applicable, and authorization from the Sponsor in writing for the clinical study. If additional requirements are imposed by the IRB/EC or relevant Regulatory Authority, those requirements will be followed. If any action is taken by an IRB/EC or a relevant Regulatory Authority with respect to the clinical study, that information will be forwarded to the Sponsor.

As the Sponsor, SJM has taken up general liability insurance in accordance with the requirements of the applicable local laws. An appropriate SJM country representative will be utilized to understand the requirements for the type of insurance that will be provided for subjects, and such information will be incorporated into the site informed consent, as applicable. If required, additional subject coverage or a clinical study specific insurance will be provided by the Sponsor.

11.2 Quality Assurance Audits and Regulatory Inspections

The investigator and/or delegate should contact the Sponsor immediately upon notification of a regulatory authority inspection at the site. A monitor or designee will assist the investigator and/or delegate in preparing for the audit. The Sponsor may perform quality assurance audits, as required.

The Principal Investigator or institution will provide direct access to source data during and after the clinical study for monitoring, audits, IRB/EC review and regulatory authority inspections, as required. The Principal Investigator or institution will obtain permission for direct access to source documents from the subject, hospital administration and national regulatory authorities before starting the clinical study.

11.3 Repeated and Serious Non-Compliance

In the event of repeated non-compliance or a one-time serious non-compliance, as determined by the Sponsor, a monitor or designee will attempt to secure compliance by one or more of the following actions:

- Visiting the investigator,
- Contacting the investigator by telephone,
- Contacting the investigator in writing,
- Retraining of the investigator.

If an investigator is found to be repeatedly non-compliant with the signed agreement, the CIP or any other conditions of the clinical study, the Sponsor will either secure compliance or, at its sole discretion, terminate the investigator's participation in the clinical study. In case of termination, the Sponsor will inform the responsible regulatory authority, as required, and ensure that the IRB/EC is notified, either by the Principal Investigator or by the Sponsor.

12 Suspension or Premature Termination of the Clinical Study

The Sponsor reserves the right to terminate the clinical study at any stage, with appropriate written notice to the investigators, IRB/ECs and relevant Regulatory authorities, if required.

Clinical Investigation Plan

A Principal Investigator, IRB/EC or regulatory authority may suspend or prematurely terminate participation in a clinical study at the study sites for which they are responsible. The investigators will follow the requirements specified in the Clinical Trial Agreement.

If suspicion of an unacceptable risk to subjects arises during the clinical study or when so instructed by the IRB/EC or regulatory authority, the Sponsor may suspend the clinical study while the risk is assessed. The Sponsor will terminate the clinical study if an unacceptable risk is confirmed. If the Sponsor completes an analysis of the reasons for the suspension, implements the necessary corrective actions, and decides to lift the temporary suspension, the Sponsor will inform the Principal Investigators, IRB/EC, or regulatory authority, where appropriate, of the rationale, providing them with the relevant data supporting this decision. Approval from the IRB/EC or regulatory authority, where appropriate, will be obtained before the clinical study resumes. If subjects have been informed of the suspension, the Principal Investigator or authorized designee will inform them of the reasons for resumption.

If the Sponsor suspends or prematurely terminates the clinical study at an individual study site in the interest of safety, the Sponsor will inform all other Principal Investigators.

If suspension or premature termination occurs, the Sponsor will remain responsible for providing resources to fulfill the obligations from the CIP and existing agreements for following up the subjects enrolled in the clinical study, and the Principal Investigator or authorized designee will promptly inform the enrolled subjects at his/her study site, if appropriate.

13 Clinical Study Conclusion

The study will be concluded when:

- All sites are closed AND
- The Final Report generated by SJM has been provided to sites or SJM has provided formal documentation of study closure.

14 Publication Policy

Publications or presentations of clinical study methods or results will adhere to SJM's publication policy, which is based on Good Publication Practices and International Committee of Medical Journal Editors (ICMJE) guidelines. A copy of the policy will be provided upon request of the investigator.

Publication planning and authorship determinations will be overseen by the Steering Committee, and investigators will be notified via email about the dissemination of study data and opportunities for involvement as authors on publications/presentations.

15 Reporting Results on ClincalTrials.gov Website

This study will be posted on ClinicalTrials.gov and results will be posted on ClinicalTrials.gov as required.

Clinical Investigation Plan

Appendix A: CIP Revisions

[redacted]

Clinical Investigation Plan

Appendix B: Definitions

Non-study Specific Definitions

Adverse Event (AE)
Any untoward medical occurrence, unintended disease or injury, or untoward clinical signs (including abnormal laboratory findings) in subjects, users or other persons, whether or not related to the medical device under study.

This definition includes events related to the medical device or the comparator.
This definition includes events related to the procedures involved.

Serious Adverse Event (SAE)
An adverse event that led to:

- Death
- A serious deterioration in the health of the subject, that either resulted in:
    - A life-threatening illness or injury OR
    - A permanent impairment to a body structure or a body function OR
    - An in-patient or prolonged hospitalization OR
    - A medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body OR
- A malignant tumor
- Fetal distress, fetal death or a congenital abnormality or birth defect

A planned hospitalization for a pre-existing condition, or a procedure required by the CIP is not considered a serious adverse event.

Adverse Device Effect (ADE)
An adverse event related to the use of an investigational medical device.

This definition includes adverse events resulting from insufficient or inadequate instructions for use, deployment, implantation, installation, or operation, or any malfunction of the investigational medical device.

This definition includes any event resulting from the use error or from intentional misuse of the investigational medical device.

Serious Adverse Device Effect (SADE)
Adverse device effect that has resulted in any of the consequences characteristic of a serious adverse event.

Study Specific Definitions

EDMUNDS CRITERIA[5]

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.

Clinical Investigation Plan

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. A transcatheter aortic valve valve-in-valve replacement procedure is considered a reoperation.

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.)

Clinical Investigation Plan

Appendix C: Bibliography

1. American Heart Association. Heart Disease and Stroke Statistics – 2005 Update. Dallas, Texas.: American Heart Association 2005.
2. 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.
3. Reginelli, Joel P. Griffin, Brian, Cleveland Clinic Journal of Medicine Volume 71, Number 6, June 2004
4. St. Jude Medical Trifecta Valve Clinical Compendium, Six-Year Data. Data on file.
5. Edmunds L.H., et al. Guidelines for reporting morbidity and mortality after cardiac valvular operations. J Thorac Cardiovasc Surg1988; 96:351-353.

Clinical Investigation Plan

Appendix D: Case Report Form

[redacted]

Clinical Investigation Plan

Appendix E: Informed Consent Form

[redacted].