Clinical Investigation Plan NCT 03139721

Clinical Investigation Plan/Study Title	Medtronic **Ha**ncock II® and **M**osaic **M**itral and Aortic Valves: A Study to **O**bserve the Effects of the Stent Material **C**hange to PEE**K** **P**ost **A**pproval **S**tudy (HAMMOCK PAS)
Clinical Investigation Plan Identifier	MDT16002SUR001
Study Product Name	Mosaic™ and Hancock II™ porcine bioprosthesis valves containing Polyetheretherketone (PEEK) material
Sponsor/Local Sponsor	Medtronic, plc Coronary Structural Heart Clinical 8200 Coral Sea Street N.E. MVS66 Mounds View, MN 55112 USA Medtronic Bakken Research Centre BV (Europe) Coronary and Structural Heart Endepolsdomein 5 6229 GW Maastricht The Netherlands
Document Version	3.0 / 13 November 2017
Document Reference Number	1024882DOC

Confidentiality Statement

1. Version History

Version	Summary of Changes	Author(s)/Title
1.0	• Not Applicable, New Document	Shari Benoit, Sr. Clinical Research Specialist
2.0	• Administrative updates for version numbering and dates • Administrative changes for wording and moving paragraph to provide clarity. • Update Section 3 glossary for additional items • Updated study design elements based on recommendations from global regulatory agency for the following: • Study type to PMCF from PMR. • Investigation purpose of study • Updated eligibility criteria to not allow redo AVR or MVR subjects • Added clarifying language regarding vulnerable subjects • Update the number of sites allowed per geography • Updated the primary and secondary objectives, endpoints and analysis to provide clarity on data collection and reporting Sections 6 and 14. • Updated Table 4 to provide more information on data requirements. • Updated Section 10.3.2 to include EuroSCORE requirements. • Administrative consistencies with data collection in Section 10.3.6 and 10.3.7 • Updated tables in section 10.5 to reflect clarity with trial definitions. • Section 11 Risks-Benefit section updated for ISO 5840-2 regulatory guideline • Administrative changes to Section13 for clarity Clinical Events Committee. • Administrative changes to Section12.2 for clarity in AE reporting.	Shari Benoit, Sr. Clinical Research Specialist
3.0	• Administrative updates for version numbering and dates • Administrative grammatical updates	Julie Rapp, Sr. Clinical Research Specialist

	• Update to discharge window for consistency in sections 4, 10.3, 10.10, and 14.3 • Removed maximum number of enrolled subjects and/or updated maximum number of implanted subjects to sections 7 and 14.4.3 • Update to baseline assessments in section 10.3.1 • Update to reporting of adverse events in section 12	

2. Investigator Statement

Study product Name	Mosaic™ and Hancock II™ porcine bioprosthesis valves containing Polyetheretherketone (PEEK) material
Sponsor	Medtronic Coronary Structural Heart
Clinical Investigation Plan Identifier	MDT16002SUR001
Version Number/Date	3.0 / 13 November 2017

I have read the protocol, including all appendices, and I agree that it contains all necessary details for me and my staff to conduct this study as described. I will conduct this study as outlined herein and will make a reasonable effort to complete the study within the time designated.

I agree to comply with ISO 14155:2011, except where noted in the clinical investigation plan, and the International Conference on Harmonization Guidelines on Good Clinical Practice under which the study is being conducted. I agree to ensure that the confidential information contained in this document will not be used for any purpose other than the evaluation and conduct of the clinical investigation without the prior written consent of Medtronic.

I will provide all study personnel under my supervision copies of the protocol and access to all information provided by Medtronic. I will discuss this material with them to ensure that they are fully informed about the products and the study.

Investigator's Signature:	
Investigator's Name:	
Institution:	
Date:	

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3. Glossary

Term	Definition
AE	Adverse Event
ADE	Adverse Device Effect
ASE	American Society of Echocardiology
AOA	Alpha-amino Oleic Acid
AHP	Acetal Homopolymer
aPTT	Activated Partial Thromboplastin Time
AR	Aortic Regurgitation
AS	Aortic Stenosis
AVR	Aortic Valve Replacement
CA	Competent Authority
CE – Mark	Conformité Européenne (European Conformity)
CEC	Clinical Events Committee
CI	Confidence Interval
CFR	U.S. Code of Federal Regulations
CIP	Clinical Investigation Plan
DD	Device Deficiency
DSMB	Data Safety Monitoring Board
DTL	Delegated Task List
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
EOA	Effective Orifice Area
EOAI	Effective Orifice Area Index
EU	European Union

Term	Definition
EuroSCORE	European System for Cardiac Operative Risk Evaluation
FDA	U.S. Food and Drug Administration
HIPAA	Health Insurance Portability and Accountability Act
IB	Investigator Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonization
ID	Inner Diameter
IDE	Investigational Device Exemption
IFU	Instructions for use
INR	International Normalized Ratio
IRB	Institutional Review Board
ISO	International Organization for Standardization
LDH	Lactate Dehydrogenase
MEC	Medical Ethics Committee
MI	Myocardial Infarction
mL	Milliliters
mm	Millimeters
MVR	Mitral Valve Replacement
NYHA	New York Heart Association
OD	Outer Diameter
OPC	Objective Performance Criteria
PE	Product Experience
PEEK	Polyether ether ketone
PI	Principal Investigator
PI/ICF	Patient Information/ Informed Consent Form
PPM	Patient Prosthesis Mismatch

Term	Definition
PT	Prothrombin time
PVL	Paravalvular leak
SOP	Standard Operating Procedures
STS	Society of Thoracic Surgeons

4. Synopsis

Title	Medtronic **Ha**ncock II® and **M**osaic **M**itral and Aortic Valves: A Study to **O**bserve the Effects of the Stent Material **C**hange to PEE**K** **P**ost **A**pproval **S**tudy (**HAMMOCK PAS**)
Clinical Study Type	Phase IV (US), Interventional Post Market Clinical Follow-up (PMCF) study (EU)
Product Name	Mosaic™ porcine bioprostheses, (Model 305 aortic position, Model 310, mitral position, and Ultra Model 305) and Hancock II™ (Model T505 aortic position and Model T510 mitral position).
Sponsor	Medtronic, plc Coronary Structural Heart 8200 Coral Sea Street N.E. MVS66 Mounds View, MN 55112 USA
Local Sponsor	Medtronic Bakken Research Center BV (Europe) Coronary, Structural Heart Endepolsdomein 5 6229 GW Maastricht The Netherlands
Investigation Purpose	This study is being conducted to satisfy the post-CE approval requirement of assessing whether the change in the stent material to PEEK does not adversely affect patient safety or clinical performance of the Hancock II or Mosaic valves when used according to intended use per Medtronic labeling in a patient population undergoing surgical aortic or mitral valve replacement.
Product Status	The Mosaic and Hancock II porcine bioprosthetic heart valves available for the aortic and mitral positions are approved for use in the US and Europe. They have full approval from the FDA and approval for CE mark with the condition of conducting this clinical study.
Primary Objective(s)	The primary objective of the study is to characterize the freedom from valve related deaths, re-intervention of or explants related to the Mosaic and Hancock II valves with PEEK stent material in a patient population undergoing aortic or mitral valve replacement of native aortic or mitral valve at 1year post implant. All subjects will be followed and evaluated up to 3 years.
Secondary Objective(s)	To characterize the clinical performance of Mosaic and Hancock II valves containing PEEK stent material at 1 year. All subjects will be followed and evaluated up to 3 years.
Study Design	Subjects requiring aortic or mitral valve replacement of the native valve

	and intended to be implanted with a Mosaic or Hancock II device are eligible for enrollment. Data for these subjects will be collected preoperatively, intra-operatively, at discharge or ≤ 30 days post-implant (whichever comes first), 1 year (primary endpoint), 2 years, and up to 3 years post-operatively.
Sample Size	A minimum of 100 subjects will be enrolled and implanted in the study at up to 15 sites worldwide with approximately up to 7 sites in the United States and up to 8 sites in Europe.
Eligibility Criteria	Inclusion: Subjects must meet all of the following criteria to be included in the study. 1. Subject who requires aortic or mitral valve replacement of his/her native valve with a Mosaic or Hancock II bioprosthesis with PEEK Material. 2. Subject is geographically stable and willing to return to the implanting site for all follow-up visits. 3. Subject is of legal age to provide informed consent in the country where they enroll in the study. 4. Subject has been adequately informed of risks and requirements of the study and is willing and able to provide informed consent for participation in the clinical study. Exclusion: Subjects who meet any of the following criteria will not qualify for participation in the study. 1. Subject requires concomitant replacement of the aortic and mitral valves. 2. Subject requires a replacement of a previously implanted failed prosthetic aortic or mitral valve. 3. Subject requires a Bentall procedure for replacement of aortic valve. 4. Subject presents with active endocarditis, active myocarditis, or other active systemic infection. 5. Subject has a non-cardiac major or progressive disease, with a life expectancy of less than 1 year. These conditions include, but are not limited to: • Child-Pugh Class C liver disease • Terminal cancer • End-stage lung disease. 6. Subject has chronic renal failure, defined as dialysis therapy or GFR<30 mL/min/1.73 m2. 7. Subject has hyperparathyroidism. 8. Subject is participating in another investigational device or drug study or observational competitive study.

	9. Subject is pregnant, lactating, or planning to become pregnant during the study period. 10. Subject has systolic EF<20% as assessed by echocardiography. 11. Subject has Grade IV Diastolic Dysfunction. 12. Subject requires emergency surgery. 13. Subject is less than legal age of consent, legally incompetent, or otherwise vulnerable such that subject cannot provide informed consent.
Study Procedures and Assessments	Data will be collected for subjects meeting the eligibility criteria preoperatively, at discharge or ≤ 30 days post-implant (whichever comes first), 1 year (primary endpoint), 2 years, and 3 years post-operatively.
Safety Assessments	Data will be collected on all Serious Adverse Events, all device and procedure related Adverse Events and all Device Deficiencies. All valve related deaths and potential primary safety endpoint events will be assessed by an independent clinical events committee review. Adverse events and device deficiencies need to be reported on eCRFs per the reporting requirements for this study and on specific country requirements per local law.
Statistics	In order to characterize the freedom from valve related deaths, re-intervention of, or explants related to the Mosaic or Hancock II valve containing PEEK stent material at 1 year the following statistical method will be used: A sample size of 89 at 1-year will provide a one-sided 95% confidence interval width of 5%, when the sample event free proportion assumed to be 97% at 1 year post implant. Considering the attrition rate of 10% per year, a minimum of 100 subjects will be enrolled and treated. A survival analysis, using Kaplan-Meier method will estimate the 1-year event free probability (valve related deaths, re-intervention of, or explant related to the Mosaic and Hancock II valves with PEEK stent material) using a 1-sided lower 95% CI to evaluate. All subjects will be followed and evaluated up to 3 years.
Endpoints	A survival analysis, using Kaplan-Meier method will estimate the 1-year event free (valve related deaths, re-intervention of, or explant related to the Mosaic and Hancock II valves with PEEK stent material) probability using a 1-sided lower 95% CI to evaluate. All subjects will be followed and evaluated annually up to 3 years. The secondary endpoints are designed to assess the performance of the Mosaic and Hancock II valves with PEEK material, using common clinical measures of hemodynamic performance via echocardiography that are consistent with evaluations and NYHA Functional Classification at 1 year post implant. Clinical performance will be evaluated based upon clinically acceptable

	hemodynamic performance.

5. Introduction

5.1. Background

The Mosaic and Hancock II bioprostheses received CE Mark in 1995, and FDA approval in 2000 and 1999 respectively. The Mosaic and Hancock II have been in the market worldwide for over 20 years. The devices have a safe history of use as indicated by the published clinical data and by the low complaint and adverse event rates collected through product surveillance. The durability of both valves is well documented[1,2,3,4] in peer-reviewed publications with safety and clinical performance demonstrated when implanted in either the aortic or mitral position.

The current stent material used for the bare stent in the Mosaic and Hancock II bioprostheses, acetal homopolymer (AHP), has been discontinued by the supplier. Medtronic completed a formal material selection process to evaluate replacement materials and selected PolyEther Ether Ketone (PEEK) as the optimal replacement material for the stent. As part of the pre-clinical qualification for the substitution of acetal homopolymer (AHP) with PEEK material in Mosaic and Hancock II valve stents, Medtronic completed a thorough analysis to identify potential risks associated with the material change. Design verification testing demonstrated equivalent functional performance and non-inferior structural performance and durability of the PEEK stented valves versus the prior stented valve with AHP stent material.

5.2. Purpose

The purpose of the study is to assess whether the change in the stent material to PEEK adversely affects patient safety or performance of the Hancock II or Mosaic valves when used according to intended use per Medtronic labeling. Medtronic will provide the Notified Body with supplemental post market clinical follow-up data on the clinical safety and performance of the Mosaic and Hancock II devices with PEEK material at 1 year post implant for the primary endpoint with a pre-determined and agreed upon study follow-up duration of 3 years post treatment.

This study will characterize the freedom from valve-related death, re-intervention of, or explant related to the Mosaic/Mosaic Ultra (hereafter referred to collectively as Mosaic) or Hancock II/Hancock II Ultra (hereafter referred to collectively as Hancock II) valves containing PEEK stent material as well as functional performance of the device with the new PEEK stent material. The Mosaic and Hancock II valves containing PEEK are currently approved by FDA and received CE Mark in Europe.

The scope of the study includes both Mosaic and Hancock II valves, in either the aortic or mitral position. Mosaic and Hancock II valves have identical stent configuration and material composition. Any residual risk introduced with the PEEK material would be equally likely in either valve. Furthermore, bench data supports the equivalence of both Mosaic and Hancock II valves when manufactured with PEEK material to the valves when manufactured with AHP, regardless of valve position or size.

6. Objectives and Endpoints

6.1. Objectives

6.1.1. Primary Objective(s)

The primary objective of the study is to characterize the freedom from valve related deaths, re-intervention of, or explants related to the Mosaic and Hancock II valves with PEEK stent material in a patient population undergoing aortic or mitral valve replacement of his/her native aortic or mitral valve, at 1 year post implant. All subjects will be followed and evaluated annually up to 3 years.

6.1.2. Secondary Objective(s)

The secondary objective is to characterize the clinical performance of Mosaic and Hancock II valves containing PEEK stent material at 1 year post implant. All subjects will be followed and evaluated annually up to 3 years.

6.2. Endpoints

The primary and secondary endpoints for this study are designed to evaluate the clinical safety and performance of the Mosaic and Hancock II valves with PEEK stent material in the patient population being treated. The primary endpoints of valve related death, re-intervention of, or explant of the study device, are terminal outcomes for a valve bioprosthesis, thus are justified in characterizing the safety of the valve. Likewise, the secondary endpoints are designed to assess the performance of the device using common clinical measures of hemodynamic performance via echocardiography that are consistent with evaluations described in the EN ISO5840:2015.

6.2.1. Primary Endpoint(s)

The primary endpoints are the following event related to the Mosaic and Hancock II valves with PEEK stent material:

- valve related death
- re-intervention on the study device
- explant of the study device

6.2.2. Secondary Endpoint(s)

The secondary endpoints are defined by the following:

- Clinically acceptable hemodynamic performance which will be evaluated through the following hemodynamic measurements at discharge or ≤30 days post-implant (whichever comes first), 1 year and annually up to 3 years:
    - effective orifice area (EOA)
    - effective orifice area index (EOAI)
    - peak pressure gradient
    - mean pressure gradient
    - performance index
    - cardiac output

  - cardiac index
  - valve regurgitation

- NYHA Functional Classification (at 1 year and annually thereafter through 3 years)

7. Study Design

This is a prospective, interventional, non-randomized, worldwide, multi-center study, with each site following a single common protocol. The design of the study adheres to the principles of International Conference on Harmonization Guidelines on Good Clinical Practice (GCP), Declaration of Helsinki and ISO 14155:2011.

Regarding Adverse Event collection the study is deviating from ISO 14155:2011 as Adverse Events collection is limited to all Serious Adverse Events, all device and procedure related Adverse Events and all Device Deficiencies.

The study will be conducted at up to 15 sites worldwide with approximately up to 7 sites in the US and up to 8 sites in Europe with up to 110 total subjects implanted and a minimum of 100 study subjects implanted. Enrolled subjects who do not receive the study device and exit the study may be replaced in the study as long as the replacement does not exceed the 22 subject implants at the site or the 110 total subject maximum. Subjects eligible for aortic or mitral valve replacement and compliant with the enrollment criteria will be considered by the Investigator for inclusion in the study.

Enrollment parameters are included in the study to avoid introduction of bias to the study results due to disproportionate enrollment. Per site there is no minimum implant requirement; however, a maximum of 22 implanted subjects per site (or 20% of the total implanted population) will be allowed.

Sponsor shall avoid improper influence on, or inducement of, the subject, monitor, any investigator(s) or other parties participating in, or contributing to, the clinical study.

Selection of subjects, treatment of subjects and evaluation of study data are potential sources of bias. Methods incorporated in the study design to minimize potential bias include (but are not limited to):

- For sites that are participating in other Aortic or Mitral valve studies which may have similar enrollment criteria as the HAMMOCK PAS study, a written process for avoiding selection bias is strongly recommended
- Demographics and medical history will be collected at baseline in order to later assess possible characteristics that may influence endpoints
- Data collection requirements and study procedures will be standardized across all geographies
- All geographies will follow the same version of the CIP and eCRFs
- No more than 20% of expected implants may come from a single site
- All study Investigators will be required to meet the requirements of 21 CFR Part 54, Financial Disclosure by Clinical Investigators
- All study site and Medtronic personnel will be trained using standardized training materials
- Study sites should follow their institutional procedures for maintenance of echocardiography and laboratory equipment used for assessing the study variables.
- Regular monitoring visits will be conducted to verify adherence to the CIP and source data

- An independent Clinical Events Committee (CEC) will be utilized to regularly review and adjudicate reported endpoint related adverse events

7.1. Duration

Enrollment is estimated to take approximately 15 months to complete, and subjects will consent to be followed annually up to 3 years post procedure. A minimum of 89 subjects is required to be followed to 1 year to satisfy the primary endpoint requirements: freedom from valve related death, re-intervention of, or explant related to the Mosaic and Hancock II valves with PEEK stent material. Total expected duration of the study is approximately 5 years. The study will be considered complete when the last active implanted subject completes the 3 year required follow-up.

7.2. Rationale

The purpose of this study is to support continuation of CE Mark and for regulatory approvals in geographies requiring supplemental clinical data to confirm the safety and clinical performance of the Mosaic and Hancock II valves following the stent material change to PEEK and is therefore justified for clinical evaluation.

8. Product Description

8.1. General

The Hancock II™ and Mosaic™ are porcine bioprosthetic valves that are designed for both the aortic position and mitral positions. The Medtronic Mosaic and Hancock II valves are sterile, single-patient use, invasive and implantable valves for the treatment of cardiac valvular disease when the replacement of the pathologic or prosthetic aortic or mitral heart valve is the treatment of choice. The function of the valve is to ensure unidirectional flow of blood through the heart.

The Mosaic porcine bioprostheses are designed for both the aortic position (Model 305) and the mitral position (Model 310). The sewing ring diameter on the Mosaic Ultra Small Root System (Model 305) aortic bioprosthesis has been reduced to facilitate implantation in patients with small aortic roots. The aortic valve stent and sewing ring are scalloped, whereas the mitral valve stent and sewing ring are flat. The stents are covered with polyester fabric. The mitral valve sewing ring contains polyester felt. The aortic valve sewing ring is scalloped to enable implantation either within the annulus or in the supra-annular position. The aortic sewing ring is mounted flush with the inflow edge of the stent. If the supra-annular position is preferred, the entire valve can be seated supra-annularly allowing the use of a larger aortic valve in the patient with a small aortic annulus.

The Mosaic porcine bioprostheses, (Model 305 aortic, Model 310 mitral, and Ultra Model 305 aortic), consist of porcine aortic valves that have been cross-linked and preserved in buffered 0.2% glutaraldehyde and then fitted and secured to cloth covered flexible stents. The crosslinking of the porcine aortic root tissue is accomplished using Physiologic Fixation™, a process in which hydrostatic pressure is applied to the root while maintaining a zero pressure differential across the valve leaflets. Mosaic is also treated with the AOA® process, which uses alpha-amino oleic acid (AOA), a naturally occurring long-chain fatty acid that has been shown to mitigate calcification in animal studies and to reduce structural valve degeneration (SVD) in patients (Flameng et al., 2013)[5]. The Mosaic valve with PEEK material (Figure 1 - Figure 3) consists of polyester covered stent frame, which is machined from

extruded PEEK rods. Each stent post tip contains a small Haynes alloy ring to facilitate radiographic visualization of the stent post tips.

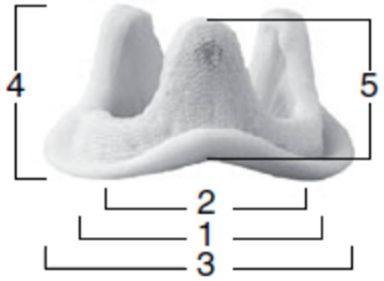

Figure 1. Mosaic Aortic Valve, Model 305

Figure 1 shows the Mosaic aortic valve, model 305, displays valve size measurement (1), orifice diameter (2), suture ring diameter (3), valve height (4) and aortic protrusion (5).

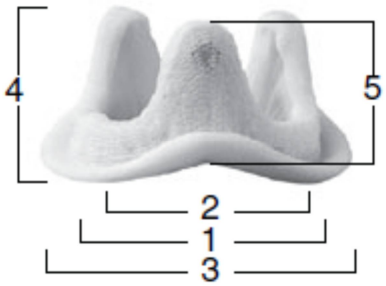

Figure 2. Mosaic Ultra Small Root System 305

Figure 2 shows the Mosaic Ultra Small Root System with valve size measurement (1), orifice diameter (2), suture ring diameter (3), valve height (4) and aortic protrusion (5).

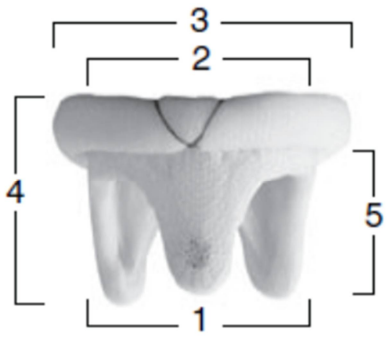

Figure 3. Mosaic Mitral Valve, Model 310

Figure 3 depicts the Mosaic mitral valve, model 310 with valve size measurement (1), orifice diameter (2), suture ring diameter (3), valve height (4) and ventricular protrusion (5).

A sewing ring, fabricated from polyester cloth, is integrated into the inflow base of the stent cover to allow for suturing and seating of the valve in the appropriate position. The sewing ring diameter on the Mosaic Ultra configuration has been reduced to facilitate implantation in patients with small aortic roots. Mosaic valves are available in the sewing ring diameters and sizes shown in Table 1 and Figure 1, Figure 2 and Figure 3.

Table 1. Mosaic models, available sizes and diameters

Model	(1) Valve Size (Stent OD[1]) (±0.5 mm)	(2) Orifice Diameter (Stent ID) (±0.5 mm)	(3) Suture Ring Diameter (±1 mm)	(4) Valve Height (±0.5 mm)	(5) Aortic and Ventricular Protrusion (±0.5 mm)
Aortic Valve (305)	19	17.5	25	13.5	11.0
	21	18.5	27	15.0	12.0
	23	20.5	30	16.0	13.5
	25	22.5	33	17.5	15.0
	27	24.0	36	18.5	15.5
	29	26.0	39	20.0	16.0
Aortic Ultra (305)	19	17.5	24	13.5	11.0
	21	18.5	26	15.0	12.0
	23	20.5	28	16.0	13.5
	25	22.5	30	17.5	15.0
	27	24.0	32	18.5	15.5
	29	26.0	34	20.0	16.0
Mitral Valve (310)	25	22.5	33	18.0	13.5
	27	24.0	35	19.0	14.0
	29	26.0	38	20.5	15.5
	31	28.0	41	22.0	17.0
	33	30.0	43	23.0	17.5

[1]Stent OD: equivalent to annulus diameter.

Disposable Cinch® Advanced Implant System (Cinch II for aortic valves and Cinch for mitral valves) holders are sutured to both aortic and mitral valves. These holders incorporate a ratchet mechanism, which, after screwing the valve holder onto the handle, is actuated by further handle rotation. This then causes the stent posts to be drawn inward, easing valve implantation. In the case of the mitral valve, the suture attaching the valve holder also prevents looping of the surgeon's sutures during implantation.

The disposable holders are designed to fit the reusable Valve Handles (Model 7639). Each valve handle is also used with the Mosaic valve obturators (Model 7310) for measuring the mitral annulus. Proper valve size selection is an important part of heart valve replacement. The size of the Mosaic to be implanted is determined by the surgeon with the aid of Mosaic Cinch aortic sizers (Model 7308C), Mosaic Ultra aortic sizer (Model 7308U) for the aortic valve or Obturators (Model 7310) for the mitral valve.

Mosaic Obturator Models 7310 (mitral) are manufactured using transparent polysulfone. These obturators are intended to aid the surgeon in selecting the optimum size for Mosaic mitral valve and are intended for use only with this valve. The Medtronic Valve Handle Model 7639 is composed of surgical stainless steel and can be screwed on the obturator for sizing or the Cinch holder for valve cinching/ratcheting for implantation. A thinned section of the handle allows for repeated bending to facilitate implantation of the valve. The handle is offered in two lengths (234 mm and 368 mm).

Mosaic Ultra Supra-X (supra-annular) sizer model 7308U and Mosaic Cinch sizer model 7308C are manufactured using transparent polysulfone and stainless steel to enable direct observation of the bioprosthetic valve profile within the patient's native valve annulus. Each sizer has two ends connected by malleable stainless steel wires through a central blue polysulfone handle. These are intended to aid the surgeon in selecting the optimum size Mosaic Ultra aortic or Mosaic aortic valve.

Hancock II porcine bioprostheses are designed for both the aortic position (Model T505) and mitral position (Model T510). The sewing ring diameter on the Hancock II Ultra aortic bioprosthesis has been reduced to facilitate implantation in patients with small aortic roots. The aortic valve stent and sewing ring are scalloped, whereas the mitral valve stent and sewing ring are flat. The stents are covered with polyester fabric. The mitral valve sewing ring contains polyester felt. The aortic valve sewing ring is scalloped to enable implantation either within the annulus or in the supra-annular position. The aortic sewing ring is mounted flush with the inflow edge of the stent. If the supra-annular position is preferred, the entire valve can be seated supra-annularly allowing the use of a larger aortic valve in the patient with a small aortic annulus.

The Hancock II porcine bioprostheses (Model T505 aortic, Model T510 mitral and Ultra aortic Model T505) consist of porcine aortic valves, preserved in 0.2% glutaraldehyde with a pressurized aortic root fixation process, and fitted and secured to cloth-covered flexible stents. Hancock II valves are treated with a surfactant, sodium dodecyl sulfate (SDS), referred to as the *T6* process, which purpose is to mitigate calcification. The Hancock II valve with PEEK material (Figure 4 – Figure 6) consists of a polyester covered stent frame which is machined from extruded PEEK rods. Both the aortic and mitral valves contain an annular band made from Haynes alloy to facilitate radiographic visualization of the valve annulus. Each stent post tip also contains a small Haynes alloy ring to facilitate radiographic visualization of the stent post tips.

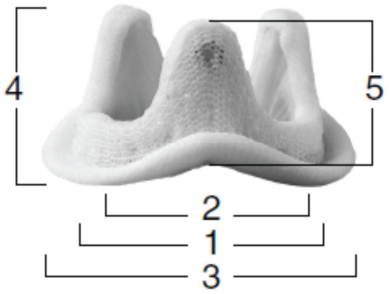

Figure 4. Hancock II Model T505

Figure 4 illustrates Hancock II, model T505 showing valve size measurement (1), orifice diameter (2), suture ring diameter (3), valve height (4) and aortic protrusion (5).

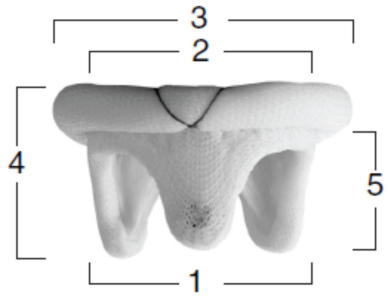

Figure 5. Hancock II Model T510

Figure 5 illustrates Hancock II, Model T510 showing valve size measurement (1), Orifice Diameter (2), Suture Ring Diameter (3), Valve Height (4) and Ventricular Protrusion (5).

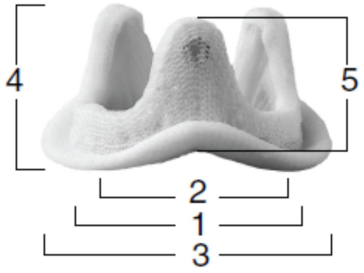

Figure 6. Hancock II Ultra Small Root System (Model T505)

Figure 6 illustrates Hancock II Ultra showing valve size measurement (1), orifice diameter (2), suture ring diameter (3), valve height (4) and aortic protrusion (5).

A sewing ring, fabricated from polyester cloth, is integrated into the inflow base of the stent cover to allow for suturing and seating of the valve in the appropriate position. The sewing ring diameter on the Hancock II Ultra configuration has been reduced to facilitate implantation in patients with small aortic roots. Hancock II valves are available in the sewing ring diameters and sizes shown in Table 2 and, Figure 4, Figure 5 and Figure 6.

Table 2. Hancock II models, available sizes and diameters.

Model	(1) Valve Size (Stent OD[1]) (±0.5 mm)	(2) Orifice Diameter (Stent ID) (±0.5 mm)	(3) Suture Ring Diameter (±1 mm)	(4) Valve Height (±0.5 mm)	(5) Aortic or Ventricular Protrusion (±0.5 mm)
Aortic Valve T505	21	18.5	27	15.0	12.0
	23	20.5	30	16.0	13.5
	25	22.5	33	17.5	15.0
	27	24.0	36	18.5	15.5
	29	26.0	39	20.0	16.0

Model	(1) Valve Size (Stent OD[1]) (±0.5 mm)	(2) Orifice Diameter (Stent ID) (±0.5 mm)	(3) Suture Ring Diameter (±1 mm)	(4) Valve Height (±0.5 mm)	(5) Aortic or Ventricular Protrusion (±0.5 mm)
Aortic Ultra Valve T505	21 23 25 27 29	18.5 20.5 22.5 24.0 26.0	26 28 30 32 34	15.0 16.0 17.5 18.5 20.0	12.0 13.5 15.0 15.5 16.0
Mitral Valve T510	25 27 29 31 33	22.5 24.0 26.0 28.0 30.0	33 35 38 41 43	18.0 19.0 20.5 22.0 23.0	13.5 14.0 15.5 17.0 17.5

[1]Stent OD: equivalent to annulus diameter.

Disposable Cinch ® Advanced Implant System (Cinch II for aortic valves and Cinch for mitral valves) holders are sutured to both aortic and mitral valves. These holders incorporate a ratchet mechanism, which, after screwing the valve holder onto the handle, is actuated by further handle rotation. This then causes the stent posts to be drawn inward, easing valve implantation. In the case of the mitral valve, the suture attaching the valve holder also prevents looping of the surgeon's sutures during implantation.

The disposable holders are designed to fit the reusable Valve Handles (Model 7639). Each valve handle is also used with the Hancock II valve obturators (Models 7505 (aortic) and 7510 (mitral)) for measuring the aortic or mitral annulus, respectively. Proper valve size selection is an important part of heart valve replacement. The size of the Hancock II to be implanted is determined by the surgeon with the aid of Hancock II aortic obturators (Model 7505) for the aortic valve, Hancock II Ultra Supra-X aortic sizer (Model 7505UX) for the Ultra aortic valve or Obturators (Model 7510).

Hancock II Obturator Models 7505 (aortic) and 7510 (mitral) are manufactured using transparent polysulfone. These obturators are intended to aid the surgeon in selecting the optimum size for Hancock II and are intended for use only with this valve. The Medtronic Valve Handle Model 7639 is composed of surgical stainless steel and can be screwed onto the obturator for sizing or the Cinch holder for cinching/ratcheting for implantation. A thinned section of the handle allows for repeated bending to facilitate implantation of the valve. The handle is offered in two lengths (234 mm and 368 mm).

Hancock II Ultra Supra-X aortic sizer Model 7505UX are manufactured using transparent polysulfone and stainless steel to enable direct observation of the bioprosthetic valve profile within the patient's native valve annulus. Each sizer has two ends connected by a malleable, stainless steel wire through a central blue polysulfone handle. These are intended to aid the surgeon in selecting the optimum size for Hancock II Ultra.

The Mosaic and Hancock II valves with PEEK material are FDA approved for use in the United States and CE Marked in Europe and are used within approved intended use. Use of the valve and accessories is not limited to the clinical investigation. Complete Instructions for Use are provided under separate cover. Device classification of the Mosaic and Hancock II valves and their accessories are listed in Table 3.

Table 3. Device Classification

Device	Model	USA (FDA)	Europe (MDD)
Mosaic™ Bioprosthesis			
Mosaic aortic bioprosthetic valves	305	Class III	Class III
Mosaic mitral bioprosthetic valves	310	Class III	Class III
Mosaic Ultra bioprosthetic valves	305	Class III	Class III
Mosaic aortic valve sizers	7308C	Class I	Class I
Mosaic Ultra aortic valve sizer	7308U	Class I	Class I
Mosaic mitral valve obturators	7310	Class I	Class I
Mosaic/Hancock II valve handles	7639	Class I	Class I
Hancock II™ Bioprosthesis			
Hancock II aortic bioprosthetic valves	T505	Class III	Class III
Hancock II mitral bioprosthetic valves	T510	Class III	Class III
Hancock II Ultra bioprosthetic valves	T505	Class III	Class III
Hancock II Mosaic Ultra Supra-X sizer	7505UX	Class I	Class I
Hancock II aortic valve obturators	7505	Class I	Class I
Hancock II mitral valve obturators	7510	Class I	Class I
Mosaic/Hancock II valve handles	7639	Class I	Class I

8.2. Manufacturer

All products listed in table 3 are manufactured by:

Medtronic, plc
710 Medtronic Parkway
Minneapolis, MN 55432, USA

8.3. Packaging

Labeling and package for all products used in this study will follow the local regulatory requirements, if applicable. In geographies where the market released products are commercially available, original device labeling will be used unless local regulations require otherwise.

8.4. Intended Population

Subjects requiring aortic valve replacement (AVR) or mitral valve replacement (MVR) of their native valve for any reason may be considered for this study if they meet all of the inclusion and none of the exclusion criteria.

8.5. Product Training Requirements

It is required that the clinical Investigators have prior experience with the implant of Mosaic or Hancock II devices prior to the clinical site's first subject enrollment. Site selection will be based on the clinical Investigator's prior implant experience with Medtronic Mosaic or Hancock II bioprosthetic devices. Medtronic will provide training of the investigative team on the trial requirements and technical overview of the device(s).

8.6. Equipment

Medtronic will not provide any study-specific equipment to the sites. Equipment used for assessing study variables (e g. echocardiographic systems) should be maintained/calibrated per the site's standard procedures.

8.7. Product Receipt and Tracking

The HAMMOCK PAS is conducted with product approved for the use in humans by the FDA and CE Mark approval. A normal hospital procurement procedure for this product at the individual study sites is required. Tracking for the devices used for this study, lot/serial numbers is recorded at the time of the procedure on the case report form and in turn, tracked in the study database.

8.8. Product Storage

There are no special requirements for the storage area for study product and normal hospital inventory procedures should be followed.

8.9. Product Return

In the event of a device malfunction of the Mosaic or Hancock II valve prior to, during or after implant (due to reintervention or autopsy), the device should be returned to Medtronic. Sites should contact their Medtronic clinical study representative to obtain further instruction on device return procedures. All explanted devices will be analyzed by an independent pathology lab. Additional information regarding the pathology lab is provided in Section 18.7 (Other Institutions).

8.10. Product Accountability

The Mosaic and Hancock II valve bioprosthesis have CE mark and FDA approval. Devices used for this study will come from available commercial stock at the implanting site. No device accountability log is required to be maintained for this study; however, device information for each subject is collected on the implant eCRF.

9. Selection of Subjects

9.1. Study Population

Subjects requiring aortic or mitral valve replacement (AVR/MVR) of their native valve for any reason may be considered for this study if they meet all of the inclusion and none of the exclusion criteria.

9.2. Subject Enrollment

Subjects may be recruited through the Investigator's practice and referring physicians. Potential subjects may be identified through site database query (chart review) or as new or existing patients attend clinic visits.

The point of enrollment for this study is when the IRB/EB approved subject informed consent document has been signed and dated by all required parties.

9.3. Inclusion Criteria

Subjects must meet all of the following criteria to be included in the study.

1. Subjects who require aortic or mitral valve replacement of their native with a Mosaic or Hancock II bioprosthesis with PEEK Material.
2. Subject is geographically stable and willing to return to the implanting site for all follow-up visits.
3. Subject is of legal age to provide informed consent in the country where they enroll in the study.
4. Subject has been adequately informed of risks and requirements of the study and is willing and able to provide informed consent for participation in the clinical study.

9.4. Exclusion Criteria

Subjects who meet any of the following criteria will not qualify for participation in the study.

1. Subject requires concomitant replacement of the aortic and mitral valves.
2. Subject requires a replacement of a previously implanted prosthetic aortic or mitral valve.
3. Subject requires a Bentall procedure for replacement of aortic valve or aortic root.
4. Subject presents with active endocarditis, active myocarditis, or other active systemic infection.
5. Subject has a non-cardiac major or progressive disease, with a life expectancy of less than 1 year. These conditions include, but are not limited to:
    - Child-Pugh Class C liver disease
    - Terminal cancer
    - End-stage lung disease
6. Subject has chronic renal failure, defined as dialysis therapy or GFR<30 mL/min/1.73 m2.
7. Subject has hyperparathyroidism.
8. Subject is participating in another investigational device or drug study or observational competitive study.
9. Subject is pregnant, lactating, or planning to become pregnant during the study period.
10. Subject has systolic EF<20% as assessed by echocardiography.
11. Subject has Grade IV Diastolic Dysfunction.
12. Subject requires emergency surgery.
13. Subject is less than legal age of consent, legally incompetent, or otherwise vulnerable such that they cannot provide informed consent.

10. Study Procedures

10.1. Schedule of Events

A schedule of assessments for enrolled subjects is provided below in Table 4. Prior to beginning any study related testing, subjects must be screened, consented and enrolled as described in the following sections of this investigational plan.

10.2. Subject Screening

Subjects identified with malfunctioning aortic and /or mitral valves requiring replacement will be screened by the site's investigative team for possible inclusion in the study. All sites will be required to maintain a record of subjects screened for the study, including reason for screen failure if applicable.

Subjects who meet all inclusion and no exclusion criteria will be asked to participate in the study. If the subject agrees to participate, prior to any study-specific tests or procedures, a personally signed and dated informed consent will be obtained, as detailed in Section 10.5 of this document. The point at which the informed consent is executed by all parties will be considered the point of enrollment, and the subject is from then on considered a study subject. Sites will maintain a subject enrollment and identification log.

Failure to obtain a handwritten signed and hand-dated informed consent prior to any study-specific procedures constitutes a protocol deviation, which is reportable to the IRB/EB (all henceforth referred to as an" Ethics Board"), and other regulatory authorities as applicable. However, if any required baseline exams (e.g. Transthoracic Echocardiography (TTE), labs, 12-lead ECG) have been performed as standard of care for diagnostic purposes prior to consenting the subject, they can be used as the baseline/qualifying exams and will not be considered a protocol deviation, provided they meet the following criteria:

- The Principal Investigator (PI) determines that the exams contain the protocol-required data and are adequate for evaluation
- The exams were completed within 45 days (TTE within 180 days) prior to scheduled implant procedure

10.3. Study Assessments

Table 4 indicates the parameters expected to be routinely evaluated by physicians participating in the study.

Table 4. Schedule of assessments

Data Collection Requirement	**Assessment Intervals**					
	Baseline	Implant	Discharge	1 Year	Annually years 2-3	Exit
Window from implant	-45 days/ -180 days for TTE	Date of Mosaic and Hancock II valves with PEEK material Implant	≤ 30 days	-+30 days	± 60 days	Date of Exit
Demographics	X					
Physical Examination	X					

Data Collection Requirement	Assessment Intervals					
	Baseline	Implant	Discharge	1 Year	Annually years 2-3	Exit
Window from implant	-45 days/ -180 days for TTE	Date of Mosaic and Hancock II valves with PEEK material Implant	≤ 30 days	-+30 days	± 60 days	Date of Exit
Pregnancy Test	X*					
Medical History	X					
NYHA Classification	X			X	X	
12-Lead ECG	X		X	X	X	
Blood Labs (Lab Assessment eCRF)				X	X	
Transthoracic Echocardiogram (TTE) (Site Echo eCFR)	X		X	X	X	
Transesophageal Echocardiogram (TEE) (Implant eCRF)		X				
Adverse Event (Adverse Event eCRF)/ Device Deficiency (Device Deficiency eCRF)	X**	X	X	X	X	X
Relevant Medications	X	-	X	X	X	
STS Risk Score	X					
EuroScore II	X					
Operative Information (Implant eCRF)		X				
Protocol Deviations (Deviation eCRF)		X	X	X	X	X
Study Exit (Exit eCRF)						X

* Pregnancy test is required for female subjects who are not exempt, see Section 10.3.1.

** Investigators are required to evaluate and document in the medical record all AEs and Device Deficiencies observed in study subjects from the time they are enrolled until they are no longer participating in the trial, see Section 12.1.2.

10.3.1. Baseline Assessments

A careful medical history (comorbidities) and physical examination should be taken prior to the implant procedure. Attention should be taken to document any chronic illnesses and pre-existing cardiac arrhythmias.

For any cardiac interventions, the date of the most recent intervention should be collected.

Use of the following medications will be collected at baseline; see Section 10.3.7 for additional information about specific data collection for medications:

- Anticoagulants
- Aspirin
- Other Antiplatelet agents

Data to be collected at baseline:

- Gender
- Age at time of enrollment (in years and months – with exceptions specific to geography)
- Race/Ethnicity to be collected except where prohibited by local law/regulation
- Co-existing cardiovascular conditions (including, but not limited to congestive heart failure, cardiomyopathy, peripheral vascular disease, coronary artery disease, previous myocardial infarction (MI), atrial enlargement, cardiac arrhythmias)
- Previous cardiovascular operations (including, but not limited to implanted cardiac device (pacemaker, defibrillator, CRT device), coronary artery bypass, coronary artery angioplasty, percutaneous valvuloplasty, operative valvuloplasty, previous aortic heart valve replacement, annuloplasty, previous ablation procedure for cardiac arrhythmias)
- Co-existing chronic and transient medical conditions (including, but not limited to liver, kidney, lung disease, substance abuse (alcohol/drug), diabetes (Type I or Type II), hypertension, endocarditis)
- 12-Lead ECG to collect cardiac rhythm (sinus rhythm, atrial fibrillation, atrial flutter, heart block, etc.)
- Transthoracic echocardiography (TTE) (within 180 days of implant)
- NYHA Classification
- Physical exam / Vital Signs
- STS risk score
- EuroSCORE II
- Medications

For female subjects of child-bearing potential, a pregnancy test will be done at baseline to confirm that the subject is not pregnant. Subjects exempt from this requirement are those who have been surgically sterilized, who are infertile, or who have been post-menopausal for at least 12 months (no menses).

10.3.2. Risk Scores

The EuroSCORE II and Society of Thoracic Surgeons (STS) Risk Scores should be calculated at baseline for each subject using the online calculator:

- EuroSCORE: http://euroscore.org/calc.html
- STS Risk Score: http://riskcalc.sts.org/stswebriskcalc/#/

The online calculators provide additional guidance and definitions for each of the parameters used to calculate the scores. For the EuroSCORE II, the definitions for each of the parameters can be found as notes under the online calculator. The variable definitions for the STS risk score model can be accessed by clicking on the field names in the online calculator.

The EuroSCORE II and STS Risk Scores should be printed from the online calculator and filed as source documentation for study subjects.

The STS procedures in the STS Risk Calculator may be unsupported. Please default to the most similar support procedures to be used for the particular subject being evaluated.

10.3.3. NYHA Functional Classification

The New York Heart Association (NYHA) Functional Classification is a system for defining cardiac disease and related functional limitations into four broad categorizations as defined in Table 5.

Table 5. New York Heart Association (NYHA) Classification

Class I	Subject with cardiac disease but without resulting limitations of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnea, or anginal pain.
Class II	Subjects with cardiac disease resulting in slight limitation of physical activity. They are comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnea, or anginal pain.
Class III	Subjects with cardiac disease resulting in marked limitation of physical activity. They are comfortable at rest. Less than ordinary physical activity causes fatigue, palpitation, dyspnea, or anginal pain.
Class IV	Subjects with cardiac disease resulting in inability to carry on any physical activity without discomfort. Symptoms of cardiac insufficiency or of the anginal syndrome may be present even at rest. If any physical activity is undertaken, discomfort is increased.

NYHA classification will be assessed at baseline and 1 through 3 year follow-up visits with the results recorded on the appropriate eCRF.

10.3.4. 12-Lead ECG

A standard 12-Lead ECG will be taken at baseline, discharge or ≤ 30 days (whichever comes first), and all 1 through 3 year scheduled follow-up visits to assess cardiac rhythm, noting any cardiac arrhythmias and indications for pacing. The site will record ECG data on the appropriate eCRF.

The Investigator or Sub-Investigator should review and sign/date each 12-lead ECG recording conducted as part of the study requirements, verify or correct any automated diagnosis generated by the ECG machine, and note the clinical significance of any diagnosis/finding of the ECG.

10.3.5. Echocardiography

Transthoracic Echocardiography (TTE) is required at baseline, discharge or ≤ 30 days (whichever comes first), and all 1 through 3 year scheduled follow-up visits to assess valve hemodynamics. The site will record TTE data on the appropriate eCRF.

A peri-procedural Transesophageal Echocardiogram (TEE) is required before the subject leaves the operating room/theater to assess the valve implant and evaluate/characterize any paravalvular leakage. The site will record the TEE data on the appropriate eCRF.

All TTE baseline and follow-up echocardiograms will be sent to an independent Echo Core Lab for central assessment; the Echo Core Lab will record the central assessment on the appropriate eCRF.

Details of the echocardiography methods and the procedure for sending TTEs are included in an Echocardiographic Procedures Manual provided under separate cover. Additional information regarding the Echo Core Lab can be found in Section 18.7 (Other Institutions).

10.3.6. Hematology/Chemistry

This section describes the laboratory parameters required at 1 through 3 year scheduled follow-up visits. Hematology should be reported on the appropriate eCRF.

10.3.6.1. Hematology/Clinical Chemistry

- Plasma Free Hemoglobin*
- Reticulocytes Count
- Haptoglobin
- Serum lactate dehydrogenase (LDH)

*Plasma free hemoglobin (PFH) will be the primary lab result used to diagnose hemolysis; however, if PFH results are inconclusive or not available, serum lactate dehydrogenase, haptoglobin and reticulocyte count may be used together to diagnose hemolysis, and may do so without reporting a protocol deviation. If neither PFH nor the combination of serum lactate dehydrogenase, haptoglobin and reticulocyte count are completed, the site must report a protocol deviation.

10.3.7. Medications

Use and indication of the following medications will be collected at baseline, discharge and all 1 through 3 year scheduled follow-up visits. Medication should be recorded on the appropriate eCRF as applicable for the type of anticoagulant:

- Anticoagulants
- Aspirin
- Other Antiplatelet agents

The physician will determine the appropriate anticoagulation therapy for each subject. Except where contraindicated, Medtronic recommends anticoagulation therapy during the initial healing stages after implantation in accordance with normal practices for bioprosthetic valves. Long-term anticoagulant and/or antiplatelet therapy should be considered for subjects with a dilated left atrium, a history of thromboembolic events, or a cardiac rhythm of atrial fibrillation or atrial flutter.

Subjects should be weaned off of anticoagulants per the Investigator's standard clinical practice.

10.3.8. Implant Procedures

The implant technique for the Mosaic and Hancock II valves with PEEK material are expected to be to the same as that of the previous AHP stented version of the valves. The implantation procedure is performed according to the standard procedures of the implanting physicians. Procedural aspects specific to the Mosaic and Hancock II valves with PEEK material should be performed according to the Instructions for Use. Detailed information is provided in the "Instructions for Use" included in each valve package.

10.3.8.1. Index Procedure

The Index Procedure is defined as the procedure where the Mosaic or Hancock II valves with PEEK material is implanted or attempted in the study subject.

The following implant data will be collected and recorded for the implant procedure.

- Procedure details including condition of explanted valve and any additional procedures or interventions (as applicable)

- Serial number, valve size and disposition of implanted valve or opened valve packages
- Documentation of device failure or malfunction (as applicable)
- Peri-operative Transesophageal Echocardiography (TEE)
- Adverse events/device deficiency

10.3.8.2. Attempted Procedure

If the Mosaic or Hancock II valve with PEEK material is attempted but not implanted, the subject will be exited from the study. SADE data following implant of study device should be collected on the AE eCRF, and study exit data on the appropriate study exit eCRF, for further detail on reporting see Table 6.

10.3.8.3. Valve Reintervention

Any intervention post-index procedure, which is required to repair, remove, alter, or replace a previously implanted Mosaic or Hancock II valves with PEEK material is considered a valve reintervention. All Mosaic or Hancock II valves with PEEK material reinterventions are considered prosthesis-related. The details and reasons for a reintervention should be collected on the appropriate eCRFs.

If a subject's study valve is explanted, the subject will be exited. SADE, explant, re-intervention and study exit data should be collected on the on the appropriate eCRF.

10.3.9. Discharge (≤ 30 days Post-Implant)

The discharge visit window is defined as post-index procedure through 30 days whichever comes first. The visit will occur at the time of subject's discharge from the hospital, but no later than 30 days post-procedure (whichever comes first). The following evaluations will be completed and data recorded on the appropriate eCRF:

- 12-lead ECG
- Transthoracic Echocardiography (TTE)
- Relevant medications
- Adverse events/device deficiency

If the required testing is not completed as part of the subject's hospital discharge visit, it may be performed any time during the discharge visit window through 30 days post-index procedure without a protocol deviation.

10.3.10. 1 Year (365 ± 30 days) Post-Procedure Follow-up Assessment

Subjects will be seen at 1 year (± 30 days) post-procedure. The following evaluations will be completed and data recorded on the appropriate eCRFs:

- NYHA classification
- 12 lead ECG
- Hematology/chemistry data
- Transthoracic Echocardiography (TTE)
- Relevant medications
- Adverse events/device deficiency

10.3.11. Annual Year 2 (730 ± 60 days) Post-Procedure Follow-up Assessment

Subjects will be seen at 2 years (730 ± 60 days) post-procedure. The following evaluations will be completed and data collected on the appropriate eCRFs:

- NYHA classification
- 12 lead ECG
- Hematology/chemistry data
- Transthoracic Echocardiography (TTE)
- Relevant medications
- Adverse events/device deficiency

10.3.12. Annual Year 3 (1095 ± 60 days) Post-Procedure Follow-up Assessment

Subjects will be seen at 3 years (1095 ± 60 days) post-procedure. The following evaluations will be completed and data collected on the appropriate eCRFs:

- NYHA classification
- 12 lead ECG
- Hematology/chemistry data
- Transthoracic Echocardiography (TTE)
- Relevant medications
- Adverse events/device deficiency

10.4. Subject Accountability

10.4.1. Missed Follow-up Visits

Every effort should be made to ensure subjects return to the clinic for all protocol required follow-up visits. If the subject is unable to return for an in-person clinic visit, the Investigator (or designee) must document the reason the subject was unable to complete the visit and, if applicable, follow the requirements for deviation reporting as outlined in Section 10.9. The Investigator should also make every effort to contact the subject within the visit window, to collect the subject's vital status (recorded on the appropriate eCRFs) as well as information related to potential adverse events (recorded on the AE eCRF).

10.4.2. Unscheduled Follow-up Visits

If a subject returns to the institution between the protocol-required follow-up visits for a study valve-related complication, the visit will be treated as an unscheduled visit, and the assessments completed at this visit will be done at the discretion of the Investigator. The reason for the unscheduled visit as well as any assessment data will be recorded on the appropriate eCRFs and AE data on the AE eCRF.

10.4.3. Emergency Use

To allow for adequate time for the subject to provide informed consent, emergency cases are not allowed under this protocol.

10.5. Subject Consent

Geography-specific templates of the Patient Information and Informed Consent Form (PI /ICF) are provided under separate cover. These templates may be modified to suit the requirements of the individual site. For US sites, this must include Health Insurance Portability and Accountability Act (HIPAA) Authorization language. This language may be incorporated into the consent form or if required by the IRB, included as a separate document.

Medtronic, the Competent Authorities (CA), and site Ethics Board shall approve all informed consent documents prior to implementation in the study. Medtronic, Ethics Board, and CAs, where applicable, must pre-approve all language changes to the PI/ICF throughout the course of the study prior to implementation. The original Ethics Board-approved PI/ICF must be retained at the investigational site, and a copy sent to Medtronic prior treatment with study device. Any updated PI/ICF must be sent to Medtronic upon approval of the materials by the Ethics Board.

Medtronic will provide any important new information that impacts the health, safety or welfare of study subjects, for inclusion in PI/ICF updates as it becomes available. Sites should follow any Medtronic, CA or Ethics Board requirements for disseminating new information and re-consenting subjects during the course of the study.

The Investigator or authorized designee must administer the approved PI/ICF to each prospective study subject without coercion or undue improper influence on, or inducement of, the subject to participate. During the consent discussion the Investigator (or designee) must fully inform the subject of all aspects of the study relevant to the subject's decision to participate, using native non-technical language that is understandable to the subject. The subject must be informed about their right to withdraw from the study at any time and for any reason without sanction, penalty, or loss of benefits to which the subject is otherwise entitled, and also informed that withdrawal from the study will not jeopardize their future medical care. The subject must also be informed that participation in the study does not waive or appear to waive the subject's legal rights. The subject must have ample time and opportunity to read, inquire about details of the study and understand the informed consent form; and to decide whether or not to participate in the clinical study. All questions about the study should be answered to the satisfaction of the subject. All items discussed in the PI/ICF must be explained.

Informed consent will be obtained in writing from the subject. The date of consent and process by which the consent was obtained (including documentation of special circumstances, if applicable; see Section 10.5.1) will be documented in the subject's medical record prior to any study-specific procedures. Subject informed consent must be obtained in accordance with the national and local laws, regulations and guidelines of each site. The institutional standard procedure consent form does not replace the study PI/ICF.

The subject's signature and date of consent serve to document that they understand the written and verbal information that the Investigator (or designee) provides, and their agreement to participate. The Investigator or authorized delegate who conducted the informed consent process must provide their handwritten signature and date the consent was completed on the PI/ICF. The PI or qualified designee will document the informed consent process, including the date of consent and name of person conducting the consent process in the subject's medical record. The original signed consent form will be retained in the subject's study records. A copy of the signed informed consent will be provided to the subject and a copy of the signed consent will be placed in the subject's medical record.

10.5.1. Special Circumstances for Informed Consent Process and Signature

If a subject cannot read or write, an impartial witness must be present during the entire informed consent discussion. The written informed consent form and any other information shall be read aloud and explained to the subject and witness. The witness signs and personally dates the informed consent form attesting that the information was accurately explained and that informed consent was freely given. The subject will sign and date if possible. Notation should also be in the subjects' medical record that a witness signed the consent attesting that the information was accurately explained and that informed consent was freely given in the case where the subject is unable to sign consent.

10.6. Assessment of Clinical Performance

An Interim report on the study will be conducted at the completion of all subject's 1 year follow-up visit. Secondary endpoints used to evaluate the clinical performance will be conducted through a review of valve hemodynamics and NYHA functional classification.

10.7. Assessment of Safety

An Interim report on the study will be conducted at the completion of all subject's 1 year follow-up visit. The primary endpoint will be used to measure the safety of the study device. Primary endpoint adverse events of valve related death, and reintervention of, or explant related to the Mosaic and Hancock II valves with PEEK stent material will be regularly reviewed by an independent CEC. All device and therapy related adverse events will be collected throughout the study.

10.8. Recording Data

eCRFs are recommended to be entered into the RDC system within 10 days of the completion of the all follow-up visits, or sooner as requested by the sponsor.

Data entered must be traceable to source documents. Source documentation is defined as the first time data appear, and may include original documents, data and records (e.g., hospital records, clinical and office charts, procedure reports, laboratory notes, memoranda, subjects' diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate copies, microfiches, photographic negatives, microfilm or magnetic media, x-rays, subject files, and records kept at the pharmacy, at the laboratories and at medico-technical departments involved in the clinical study).

The eCRFs (or paper copies) may not serve as source documents. Source documentation for data elements not routinely captured in medical records (e.g. echocardiography variables) may vary from site to site; the site may use source document worksheets if identified as source documents.

10.9. Deviation Handling

A study deviation is an event where the Investigator or investigative site personnel did not conduct the clinical study according to the Clinical Investigation Plan or Clinical Trial Agreements. The Investigator may not deviate from the CIP, unless the deviation is necessary in an emergency situation to protect the rights, safety and wellbeing of the subject. Deviations may include, but are not limited to the following:

- Failure to obtain informed consent prior to participation
- Incorrect version of the informed consent form used
- Failure to obtain EC/IRB approval before the start of enrolling subjects in the study

- Implanted subject did not meet inclusion criteria or met the exclusion criteria
- Required testing and/or measurements not done or incorrectly done
- Subject did not attend follow-up visit
- Follow-up visit was completed outside window
- Adverse events/UADE or device deficiencies not reported in the required timeframe by country regulation or as specified in the CIP
- Source data permanently lost
- Enrollment of subjects during lapse of EC/IRB approval

Reporting of all other study deviations should comply with Ethics Board policies and/or local laws and must be reported to Medtronic as soon as possible upon the center becoming aware of the deviation. Deviations will be entered into the study database to allow a comprehensive review on a regular basis for identifying trends that warrant additional preventative or corrective actions to mitigate further occurrence. Study deviations must be reported to Medtronic, regardless of whether medically justifiable, pre-approved by the study management, or taken to protect the subject in an emergency. In the case that the deviation involves a failure to obtain a subject's informed consent or is made to protect the life or physical well-being of a subject in an emergency, the deviation must be reported to the EC/IRB as well as study management as soon as possible after the occurrence of the event. Reporting of all other study deviations should comply with EC/IRB policies and/or local laws.

Medtronic is responsible for analyzing deviations, assessing their significance, and identifying any additional corrective and/or preventive actions which may include amending the CIP, conducting additional training, terminating the investigation, etc. Repetitive or serious Investigator compliance issues may represent a need to initiate a corrective action plan with the Investigator and site, and in some cases, necessitate suspending enrollment at that site until the problem is resolved or ultimately terminating the Investigator's participation in the study. Medtronic may provide center-specific reports to Investigators summarizing information on deviations that occurred at the investigational site on a periodic basis.

10.10. Subject Withdrawal or Discontinuation

It is the subject's right to withdraw at any time from the study and for any reason without sanction, penalty or loss of benefits to which the subject is otherwise entitled, and without jeopardizing their future medical care. The Investigator may withdraw the subject at any time to protect the health, safety or welfare of the subject. At the last point of contact (if outside a study-required visit), every effort should be made to collect the status of any ongoing adverse events.

The subject may only be considered lost to follow-up after all efforts to obtain compliance are exhausted. At a minimum, four attempts must be made to contact the subject and documented in the subject's study records:

- 3 telephone attempts to the subject's last known phone number, and if unsuccessful,
- 1 certified letter from the PI to the subject's last known address

If the site is unable to reach the subject after the documented attempts, the site should make every attempt to verify the subject's vital status (alive or deceased).

All subjects will be encouraged to remain in the study through the last follow-up visit. Subjects who discontinue participation prematurely will be included in the analysis of results. If the subject discontinues participating in the study prior to completing the study requirements, the reason for withdrawal will be recorded in the subject's study records and on the appropriate eCRF.

Subject's enrolled in the study but do not receive the study device may be replaced in the study as long as the replacement does not go beyond the 22 subjects implanted at that site or the 110 study subject maximum.

10.11. Subject Exit from study

There are many scenarios in which a subject may exit the study. Table 6 below details how the data will be handled for each scenario.

Table 6. Study Exit Scenarios

Scenario	Follow-up Required	eCRFs Required
Subject enrolled (informed consent signed), but the study device never contacts subject, and no Mosaic or Hancock II valve with PEEK material is implanted	None	-Inclusion/Exclusion eCRF -Baseline eCRF (as applicable) -Study Exit eCRF
Subject enrolled, the study device comes into contact with the subject (i.e. passes the body plane) but no Mosaic or Hancock II valve with PEEK material is implanted	30 days post-attempted implant for safety only	-Eligibility eCRF -Baseline eCRF (including labs/echo) -Implant eCRF -AE/DD eCRF (as appropriate) -Study Exit eCRF
Subject enrolled, implanted with Mosaic or Hancock II valves with PEEK material, and exits the study early due to explant	Through the point of explant/study exit.	-All required/ unscheduled eCRFs through last visit completed -Valve Reintervention eCRF -AE/DD eCRF (as applicable) -Study Exit eCRF
Subject enrolled, implanted with Mosaic or Hancock II valves with PEEK material, and exits the study early due to any of the following: - Lost to Follow-up - Death - Withdrawal	Through point of death, withdrawal, or last visit completed	-All required/ unscheduled eCRFs through last visit completed -AE/DD eCRF (as applicable) -Study Exit eCRF
Subject enrolled, implanted and completes the study requirements	Through 3 year follow-up	-All required/ unscheduled eCRFs -AE/DD eCRF (as appropriate) -Study Exit eCRF

11. Risks and Benefits

11.1. Potential Risks

There are risks associated with any surgical procedure. Risks associated with the Mosaic or Hancock II valves with PEEK material are expected to be similar to the Mosaic and Hancock II valves with AHP stent material. These risks include but are not limited to the following:

- angina

- cardiac arrhythmia / dysrhythmias
- death
- endocarditis
- heart failure
- hemolysis
- hemolytic anemia
- hemorrhage, anticoagulant/antiplatelet-related
- infection other than endocarditis
- leak, transvalvular or paravalvular
- nonstructural dysfunction (obstructive pannus ingrowth, suture dehiscence, inappropriate sizing, other)
- structural deterioration (calcification, leaflet tear, stenosis, other)
- thromboembolism (includes myocardial infarction, stroke and peripheral embolic events)
- valve thrombosis

These complications could lead to:

- Reintervention
- Explant of the bioprosthesis
- Permanent disability
- Death

The Mosaic and Hancock II valves with PEEK material have not previously been studied in humans; however, pre-clinical design validation testing has been completed to verify substantial equivalence in expected valve performance. Residual risks of the Mosaic and Hancock II valves with PEEK material have been characterized as acceptable per ISO14971 and Medtronic standard operating procedures for risk management.

The expected rates of adverse device effects from tissue aortic and mitral valves are well characterized in the ANSI/AAMI/EN ISO 5840-2- "Cardiovascular implants- Cardiac valve prostheses Part 2: Surgically implanted heart valve substitutes", Table J1, Objective performance criteria (OPC) for surgical heart valve substitutes. Table 7 lists the highest anticipated rates for these OPC events. The OPCs are the average rates of valve related complications as assessed by linearized occurrence rates. It is expected that the rates of risks of the Mosaic and Hancock II valves with PEEK will be similar to Mosaic and Hancock II valves with AHP and to currently-market approved bioprosthetic aortic/mitral valves.

Table 7. Expected Occurrence of Valve Related Events per OPC

Adverse Event	**Bioprosthetic**	
	Aortic	**Mitral**
Thromboembolism	1.5%	1.3%
Valve Thrombosis	0.04%	0.03%
Major Haemorrhage - Anticoagulant related	0.6%	0.7%
Major Paravalvular Leak	0.3%	0.2%

Endocarditis	0.5%	0.4%

There are no expected additional risks due to subject participation in the study. Preoperative evaluation and close postoperative monitoring will minimize foreseeable risk and discomfort. Interactions with concomitant therapy may exist. See the IFU for a list of contraindications.

The following measures will be implemented to minimize risks to study subjects:

- Investigators will have expertise in aortic and/or mitral heart valve replacement procedures.
- Investigative sites will have comprehensive cardiology and surgery programs.
- Investigators will be trained on the use of the Mosaic and Hancock II valves with PEEK material and accessories.
- Instructions for Use are provided with each Mosaic and Hancock II device to ensure consistent use of the device within pretested parameters.
- Subjects receiving the Mosaic or Hancock II valves with PEEK material will be rigorously followed over the course of the study by appropriately trained personnel. The protocol includes regular follow-up visits to assess device safety. These visits will enable detection of deterioration in Mosaic and Hancock II valves with PEEK material function should it occur, and allow appropriate intervention. The safety events will be closely reviewed by a panel of expert physicians (Clinical Events Committee).

Potential treatments for the foreseeable risks may include medication, surgery, medical monitoring or other applicable treatments, and will be provided at the discretion of the Investigator.

Any unanticipated or unforeseen complications will be reported by the PI (or authorized designee) to the Ethics Board and to Medtronic. Medtronic will in turn report any necessary findings to the appropriate regulatory agencies/bodies in each of the respective geographies.

11.2. Potential Benefits

Potential benefits from use of the device are similar to those associated with the previous Mosaic and Hancock II valves with AHP stent material. The primary benefit is restoration of heart blood flow control by replacement of the diseased heart valve. The chosen porcine tissue has proven durable performance, as demonstrated in currently approved valves.[6]

The Mosaic and Hancock II valves with PEEK material may offer the following benefits:

- The Mosaic valve tissue is treated with an alpha amino oleic acid (AOA™) anti-mineralization process that has been shown to mitigate calcification of bioprosthetic valves.
- Wide range of available sizes
- No change to implantation methods, principle of operation and condition of use should provide seamless transition in normal clinical practice.

There is no direct benefit associated to participation in this study, but the information obtained during this study will be used scientifically. The results of this study can help physicians understand the safety and clinical performance of the heart valve.

11.3. Risk-Benefit Rationale

It has been demonstrated that implantation of aortic and mitral tissue valves can be performed safely, and that these devices provide competent valve function. The Mosaic and Hancock II valves with PEEK

material have undergone extensive pre-clinical testing and have demonstrated comparable performance to the Mosaic and Hancock II valves with AHP stent material.

Given the poor prognosis of subjects with aortic or mitral valve deficiencies, and the expectation that risks of the Mosaic and Hancock II valves with PEEK material are similar to current market-released aortic and mitral tissue valves, the potential benefits outweigh the risks and the investigation of this valve is justified.

12. Adverse Event Assessments

12.1. Definitions/Classifications

12.1.1. Definitions

For the purposes of this post market study, each adverse event will be classified according to ISO 14155:2011 definitions and are provided in Table 8. Where the definition indicates "device", it refers to the Mosaic and/or Hancock II devices used in the study.

Table 8. Definitions of Adverse Events for the HAMMOCK PAS Study

Event Type	Definition
Adverse Event (AE) (EN ISO14155:2011 3.2)	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 investigational medical device NOTE 1 This definition includes events related to the investigational medical device or the comparator. NOTE 2 This definition includes events related to the procedures involved. NOTE 3 For users or other persons, this definition is restricted to events related to investigational medical devices.
Serious Adverse Event (SAE) (EN ISO14155:2011 3.37)	Adverse event that a) led to death, b) led to a serious deterioration in the health of the subject, resulting in 1) a life-threatening illness or injury, or 2) a permanent impairment of a body structure or a body function, or 3) in-patient or prolonged hospitalization, or 4) medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function, c) led to foetal distress, foetal death or a congenital abnormality or birth defect. *NOTE: Planned hospitalization for a pre-existing condition, or a procedure required by the CIP, without serious deterioration in health, is not considered a serious adverse event.*
Adverse Device Effect (ADE) (EN ISO14155:2011 3.1)	Adverse event related to the use of an investigational medical device. *NOTE 1: This definition includes adverse events resulting from insufficient or inadequate instructions for use, deployment, implantation, installation, or operation,*

Event Type	Definition
	or any malfunction of the investigational medical device. *NOTE 2: This definition includes any event resulting from an error use or from intentional misuse of the investigational medical device.*
Serious Adverse Device Effect (SADE) (EN ISO14155:2011 3.36)	Adverse device effect that has resulted in any of the consequences characteristic of a Serious Adverse Event.
Device Deficiency (EN ISO14155:2011 3.15)	Inadequacy of a medical device with respect to its identity, quality, durability, reliability, safety or performance. *NOTE: Device deficiencies include malfunctions, use errors, and inadequate labeling.*
Device Deficiency with SADE potential (EN ISO14155:2011 6.4.2)	Device deficiencies that did not lead to an adverse event but could have led to a medical occurrence a) if either suitable action had not been taken, b) if intervention had not been made, or c) if circumstances had been less fortunate, shall be reported as specified in 8.2.5 and 9.8 in ISO14155:2011.
Unanticipated Serious Adverse Device Effect (USADE) (EN ISO14155:2011 3.42)	Serious adverse device effect which by its nature, incidence, severity or outcome has not been identified in the current version of the risk analysis report NOTE Anticipated serious adverse device effect (ASADE) is an effect which by its nature, incidence, severity or outcome has been identified in the risk analysis report.

12.1.2. Evaluation and Documentation of Adverse Events and Device Deficiencies

Investigators are required to evaluate and document in the medical record all AEs and Device Deficiencies (per the definition in Table 8) observed in study subjects from the time they are enrolled until they are no longer participating in the trial. Regarding Adverse Event collection, the study is deviating from ISO 14155:2011 as in the scope of the study Investigators are required to report the following reportable Adverse Events to Medtronic: all Serious Adverse Events, all device and procedure related Adverse Events and all Device Deficiencies.

All reportable Adverse Events / Device Deficiencies that occur from subject enrollment through subject exit need to be reported to Medtronic via the appropriate eCRFs.

In addition, for all deaths and potential primary safety endpoint-related adverse events, sites should submit relevant, de-identified source documents to Medtronic for the Clinical Events Committee (CEC) members to use in their adjudication of the event. The CEC may request source documentation on additional events, at their discretion and according to the CEC Charter. Additional information regarding the CEC is detailed in Section 13.

The events listed in Table 9 are expected for patients undergoing cardiac surgery, and do not need to be reported as an AE, unless they occur outside of the stated timeframe, are otherwise considered to be an AE according to the treating Investigator, or are suspected or confirmed to be device-related.

Table 9. Non-Reportable Medical Occurrences Associated With Index Procedure

Body category	Occurrence	Timeframe (hours) from the Index Procedure
Hematologic	Blood transfusion and anemia occurring during the index procedure within expected ranges (part of the regular hospital protocol)	0
Hematologic	Any bleeding during the index procedure	0
Hematologic	Any bleeding after index procedure with < 3 units blood transfusion, or < 1 liter blood loss	24
Cardiac	Short transient episode of arrhythmia (including ventricular fibrillation) during index procedure	0
Central nervous system	Confusion, anxiety and/or disorientation (other than TIA/stroke) starting within 48 hours with or without medical intervention	120 (5 days)
Central nervous system	Temporary change in mental status (other than TIA/stroke) not requiring additional medical interventions or new medical assessments (e.g. CT)	72
Central nervous system	Dizziness and/or lightheadedness with or without treatment	24
Central nervous system	Headache with or without treatment	72
Central nervous system	Sleep problems or insomnia with or without treatment	120 (5 days)
Respiratory/pulmonary	Mild dyspnea or cough with or without treatment	72
Respiratory	Oxygen supply after extubation / "forced breathing therapy"	48
Gastrointestinal	Diarrhea with or without treatment	48
Gastrointestinal	Obstipation / Constipation with or without treatment	72
Gastrointestinal	Anesthesia-related nausea and/or vomiting with or without treatment	24
Body Temperature	Low-grade fever (<101.3°F or <38.5°C) without confirmed infection	48
Body Temperature	Low body temperature	6
Pain	Pain (e.g. back, shoulder) related to laying on the procedure table with or without treatment	72
Pain	Incisional pain (pain at access site) with or without standard treatment and patient not returning to clinic to have additional treatment	No time limit
Pain	Pain in throat and/or trachea due to intubation	72
Skin and subcutaneous System	Mild to moderate bruising or ecchymosis	168 (7 days)
Respiratory	Atelectasis / Pleural Effusion not requiring punctuation	168 (7 days)

Body category	Occurrence	Timeframe (hours) from the Index Procedure
General	Edema resulting in weight increase up to 4 kg / 9lbs from baseline	168 (7 days)

For all reportable events, the general procedure for Investigator reporting any adverse event is as follows:

- Report the event to Medtronic as soon as possible but no later than the timeframes outlined in Table 11. Sites will be provided with the contact information of the appropriate Medtronic designee.
- Complete all sections of the Adverse Event/Device Deficiency eCRF.
- Each unique event/diagnosis must be documented separately.
- Documented pre-existing conditions are not considered to be reportable AEs unless there is a change in the nature or severity of the condition.
- The Adverse Event eCRF must be reviewed and approved by the Investigator.

The following information should be collected on the Adverse Event eCRF:

- AE diagnosis
- Date of onset or first observation
- Date of investigational site study personnel's first awareness of the event
- Description of the event
- Seriousness of the event
- Causal relationship of the event to the Mosaic or Hancock II valves with PEEK material
- Causal relationship of the event to the Mosaic or Hancock II valve implant procedure
- Treatment required or action taken, including any medical or surgical intervention and date of intervention
- Outcome or status of the event (any reported event should be followed until it has resolved, has a stable level of sequelae, or is no longer clinically significant in the Investigator's opinion)
- Date of Resolution

For all deaths, Investigators should assess and document the following information on the appropriate eCRFs:

- Date of death
- Primary death category
- Causal relationship of the event to the surgical valve
- Causal relationship of the event to the implant procedure

12.1.3. Classification of Causal Relationships

For each reported AE, the causal relationship between the AE and the study devices and implant procedure will be classified as not related, unlikely, possible, probable, causal relationship. The causal relationships are defined in Table 10**Error! Reference source not found.**.

Table 10. Adverse Event Causal Relationship Definitions

Related to	Definition
Mosaic or Hancock II valves with PEEK material	Any AE involving the function of the device, or the presence of the device in the body. Included in this category are events that are directly attributed to the device.
Mosaic or Hancock II valves with PEEK material implant procedure	Any AE that results from the implant procedure of the device through 30 days post-implant. Events in this category are directly related to the general procedural sequelae.

12.2. Reporting of Adverse Events

Reportable adverse events as listed in section 12.1.2 are required to be reported to Medtronic via the Adverse Event or Device Deficiency eCRF, as soon as possible after the event occurs, but no later than the timeframes listed in Table 11.

Table 11. Required Timeframes for Adverse Event Reporting To Medtronic

Event Type	Timeframe for Reporting
Serious Adverse Event (SAE)	Immediately, but no later than 3 calendar days after the investigational site study personnel's awareness of the event
Serious Adverse Device Effect (SADE)	Immediately, but no later than 3 calendar days after the investigational site study personnel's awareness of the event
Device Deficiency that might have led to an SADE	Immediately, but no later than 3 calendar days after the investigational site study personnel's awareness of the event
Adverse Device Effect (ADE) including Device or Procedure Related Adverse Events	Immediately, but no later than 10 calendar days after the investigational site study personnel's awareness of the event
Unanticipated Adverse Serious Device Effects (USADE)	USADEs must be submitted as soon as possible, but no later than 3 calendar days after the investigational site study personnel's awareness of the effect
Device Deficiency	No later than 10 calendar days after the investigational site study personnel's awareness of the event

In addition, Investigators are obligated to report adverse events in accordance with the requirements of their reviewing Ethics Board and local regulations.

Investigators should contact the Medtronic study manager or site manager if they have any questions regarding reportable AEs. Medtronic will maintain a listing of current study contact details and provide to each site.

12.2.1. Documentation and Reporting of Device Deficiencies

Device deficiency information will be collected throughout the study and reported to Medtronic. For Device deficiencies that lead to an ADE or SADE, these must also be reported on the AE eCRF according to reporting requirements.

Device deficiencies that did not lead to an AE should be reported only on a Device Deficiency eCRF (one for each device deficiency).

Device deficiencies that did not lead to an adverse event but might have led to an SADE if a) a suitable action had not been taken, or b) an intervention had not been made, or c) circumstances had been less fortunate, should be reported to Medtronic immediately of the site's first learning of the event on a Device Deficiency eCRF.

Any study valve involved with a device deficiency should be returned to Medtronic (unless implanted) for analysis.

13. Data Review Committees

Due to the post market status of this study a Data Monitoring Committee (DMC) will not be assembled.

The independent Contract Research Organization (CRO) Baim Institute for Clinical Research, 930 Commonwealth Avenue, Boston, MA 02215 USA, will be established as the Clinical Events Committee (CEC) prior to the first enrollment of the study. The purpose of the CEC is to provide an independent medical review and classify/adjudicate, at a minimum, all deaths and potential primary safety endpoint events for seriousness and relatedness to the study device/procedure according to definitions and processes outlined in the protocol and the CEC charter. The CEC will consist of qualified cardiologists, and cardiothoracic surgeons (including a chairperson), who are not participants in the study. Additional specialists, such as echocardiologists, may also be selected as part of the CEC.

Prior to the onset of the study, a CEC charter will be drafted to establish explicit rules outlining the minimum amount of data required and the algorithm followed in order to classify/adjudicate a study endpoint related clinical event. The charter will be approved by Medtronic and the CEC members.

All valve related deaths and potential primary safety endpoint events will be reviewed and adjudicated by the CEC. All other events will be reviewed and classified by the sponsor, by qualified internal Medtronic safety individual(s) to ensure they should not be adjudicated by the full CEC and that the events are appropriately classified by the Investigator.

CEC decisions will be documented in meeting minutes, which will be maintained in the study master file.

Additional details about the CEC will be outlined in the CEC charter.

14. Statistical Design and Methods

Statistical analysis will be performed by Medtronic employed statisticians or their designated representatives. A separate Statistical Analysis Plan (SAP) will be developed to further describe pre-specified statistical methods, data handling rules, and analyses that will be employed. Any deviation from the original statistical analysis plan will be reported in the final study report, along with justification for the deviation(s).

The safety and clinical performance analyses will be conducted on those subjects implanted with the Mosaic and Hancock II valves with PEEK material (As Treated population).

Additional exploratory analyses of the data may be conducted as deemed appropriate.

14.1. Analysis Set

Implanted Population

The implanted population consists of all enrolled subjects who are actually implanted with a Mosaic or Hancock II device. To be considered implanted, the subject's device disposition form must show at least one device with a final disposition of "Implanted." Time zero begins at the date of the procedure.

The safety and clinical performance analyses will be conducted on those subjects implanted with the Mosaic and Hancock II valves with PEEK material (implanted population).

Additional exploratory analyses of the data may be conducted as deemed appropriate.

14.2. Primary Objectives

The primary objective of the study is to characterize the freedom from valve related deaths, re-intervention of, or explants related to the Mosaic and Hancock II valves with PEEK stent material in a patient population undergoing aortic or mitral valve replacement of his/her native aortic or mitral valve, at 1 year post implant. All subjects will be followed and evaluated annually up to 3 years.

14.2.1. Primary Endpoints

The primary endpoints are the following events related to the Mosaic and Hancock II valves with PEEK stent material:

- valve related death
- re-intervention on the study device
- explant of the study device

14.2.2. Sample Size

A sample size of 89 at 1 year will provide a one-sided 95% confidence interval width of 5%, when the sample event free proportion assumed to be 97% at 1 year post implant. Considering the possible attrition rate assumed to be ≤10% in the first year, a minimum of 100 subjects will be implanted.

14.2.3. Analysis Methods

No specific hypotheses have been set for the overall analysis of freedom from deaths, re-intervention, or explant related to the Mosaic and Hancock II valves with PEEK stent material. Historical control data are provided below for qualitative comparison.

1 year Endpoint	Control Value Freedom from ± Standard Error
Valve-related Death	
Mosaic[1]	98.6 ± 0.8
Hancock II[2]	94.6 ± 2.4
Valve Related Reoperation	
Mosaic[1]	99.1 ± 0.6
Hancock II[2]	100.0 ± 3.6
Valve-related Explant	
Mosaic[1]	99.1 ± 0.6
Hancock II[2]	100.0 ± 3.6

[1]Mosaic Mitral Bioprosthesis 16-year clinical compendium
[2]Medtronic Hancock II Long-Term Clinical Study MVR results provided in Instructions for Use

Kaplan-Meier method will be used for the time to the first valve related death, re-intervention of the study device, or explant related to the Mosaic and Hancock II valves with PEEK stent material at 1 year after procedure. Subjects not experiencing the event through 1 year after procedure will be censored. One year is defined at time point of 365 days post procedure. The product-limit estimate of the event-free rate (or event rate), the number of subjects at risk, the number of subjects with event, the number of subjects censored, and the log-log transformed lower one-sided 95% confidence interval using the Greenwood standard error will be presented. Subjects will be censored at their last visit, or death/explant/exit.

14.3. Secondary Objectives

The performance objective is to confirm the clinical performance of the Mosaic and Hancock II valves with PEEK material at one year post implant. All subjects will be followed and evaluated annually up to 3 years.

14.3.1. Secondary Endpoints

The clinical performance endpoints are:

- NYHA Functional Classification (at 1 year and annually thereafter through 3 years)
- Clinically acceptable hemodynamic performance as measured by the following hemodynamic measurements obtained from echocardiography at discharge or ≤30 days (whichever comes first), 1 year and annually thereafter through 3 years):
- effective orifice area (EOA)
- effective orifice area index (EOAI)
- peak pressure gradient
- mean pressure gradient
- performance index
- cardiac output
- cardiac index
- valve regurgitation

No specific hypotheses have been set for the analysis of hemodynamic performance of Mosaic and Hancock II valves containing PEEK stent material at 1 year post-implant. No sample size determination is based on these secondary endpoints.

14.3.1.1. Analysis Methods

NYHA functional classification and echocardiographic hemodynamic data will be summarized using descriptive statistics for continuous variables and frequency tables for discrete variables. NYHA functional class will be evaluated based on the percentage of subjects in each specific NYHA class at each follow-up time-point.

Hemodynamic performance will be qualitatively compared with historical clinical performance data for Mosaic and Hancock II valves from literature as well as current guidelines for the treatment of aortic and mitral valve disease to evaluate clinically acceptable performance.

14.4. Additional Analysis Information

14.4.1. General Summaries

Baseline demographic and clinical variables will be summarized. Continuous variables will be summarized as means, medians, standard deviations and ranges. Categorical variables will be summarized as frequencies and percentages.

14.4.2. Missing Data

Every effort will be undertaken to minimize missing data. Missing (due to withdrawal, missing follow-up or loss-to-follow up etc.), unused and spurious data will remain identifiable in the database. The number of subjects included in the analysis will be reported so the impact of missing data can be assessed. Unless otherwise specified in each objective, no statistical techniques will be used to impute missing data.

14.4.3. Minimizing Bias

Sponsor shall avoid improper influence on, or inducement of, the subject, monitor, any investigator(s) or other parties participating in, or contributing to, the clinical study.

Selection of subjects, treatment of subjects and evaluation of study data are potential sources of bias. Methods incorporated in the study design to minimize potential bias include (but are not limited to):

- For sites that are participating in other Aortic or Mitral valve studies which may have similar enrollment criteria as the HAMMOCK PAS study, a written process for avoiding selection bias is strongly recommended.
- Demographics and medical history will be collected at baseline in order to later assess possible characteristics that may influence endpoints
- Data collection requirements and study procedures will be standardized across all geographies
- All geographies will follow the same version of the CIP and eCRFs
- No more than 20% of expected implants may come from a single site
- All study Investigators will be required to meet the requirements of 21CFR Part 54, Financial Disclosure by Clinical Investigators
- All study site and Medtronic personnel will be trained using standardized training materials
- Regular monitoring visits will be conducted to verify adherence to the CIP and source data
- An independent Clinical Events Committee (CEC) will be utilized to regularly review and adjudicate reported adverse events

15. Ethics

15.1. Statement(s) of Compliance

The HAMMOCK PAS study will be conducted in compliance with the protocol, and designed to reflect the principles of International Conference on Harmonization Guidelines on Good Clinical Practice (GCP), Declaration of Helsinki, and ISO 14155:2011. These include the protection of the rights, safety and well-being of human subjects, controls to ensure the scientific conduct and credibility of the clinical investigation and the definition of responsibilities of the sponsor and Investigators. Pediatric, legally incompetent, or otherwise vulnerable patients, such that they cannot provide informed consent, are not eligible for the trial.

The principles of the Declaration of Helsinki are implemented in this study by means of the Informed Consent (IC) process, Ethics Board approval, study training, clinical study registration, pre-clinical testing, risk benefit assessment, and publication policy.

Regarding Adverse Event collection, the study is deviating from ISO 14155:2011 as Adverse Events collection is limited to all Serious Adverse Events, all device and procedure related Adverse Events and all Device Deficiencies.

Regulatory authority notification/approval to conduct the study is not required in the US; however competent authority approval is required in Europe. Investigational sites will not be activated, nor begin enrolling subjects until IRB/EC and regulatory authority approvals/notification, as appropriate, are received (as appropriate). Additionally, any requirements imposed by a local regulatory agency or Ethics Board shall be followed, as appropriate.

16. Study Administration

16.1. Monitoring

Monitoring and monitoring oversight will be provided by Medtronic (Mounds View, MN, USA, and Maastricht, the Netherlands). Representatives of Medtronic (i.e. contractors and designees) may also act as the study monitors to the site. A list of the study monitors will be kept separate from this document, and Medtronic will provide updated contact lists to the investigative sites.

Monitoring visits will be conducted at the start, during and at the closure of the clinical study in accordance with Medtronic SOPs and the study-specific Monitoring Plan. Frequency and timing of monitoring visits shall be determined by the sponsor for each site based on enrollment rate and volume, study compliance and findings from previous visits.

A site initiation visit will be performed to prepare the site and will include training and collection of the required documentation such as Curriculum Vitaes and Financial Disclosures.

Specific monitoring requirements are detailed in the study-specific Monitoring Plan. In order to ensure a high degree of data quality, all enrolling clinical centers will be monitored frequently. The aim is at minimum to source data verify 90% of primary endpoint data collected in the study. In addition, during the monitoring visits, 100% of available Informed Consents of the enrolled subjects at the center will be initially verified, with follow-up verification completed for Informed Consents of the enrolled subjects at the center who are planned for review during a monitoring visit. The PI should be available during these monitoring visits to discuss study status and Monitoring Action Items.

Medtronic or designee will conduct monitoring visits to monitor compliance with the protocol, clinical trial agreement, applicable regulations and adherence to the data collection procedures, to assess the accuracy and completeness of submitted clinical data, and to verify that records and documents are being properly maintained for the duration of the study.

The Investigator must provide adequate oversight to ensure accuracy, completeness and timeliness of the data reported in the eCRFs and in all other required reports. Data reported on the eCRFs which are derived from source documents must be consistent with the source documents and discrepancies need to be justified in a documented rationale, signed and dated by the PI, and filed in the subject's medical file.

All monitoring activities will be documented and will include a summary of what the monitor reviewed and any observations with regard to the completion of previous or newly identified action items, significant findings, facts, deviations, conclusions, and recommended actions to be taken to secure compliance.

16.2. Data Management

Only authorized persons can complete eCRFs. eCRFs shall be signed by Investigators (physicians only) as specified on the Delegated Task List included in the Investigator Site File.

The Electronic Data Capture (EDC) system maintains an audit trail on entries, changes or corrections in eCRFs. If a person is only authorized to complete eCRFs or to make changes to an already signed eCRF, the Investigator shall re-sign this eCRF.

Data management will be done according to Medtronic SOPs and the Data Management Plan for this clinical study. These documents will be made available on request. All collected data will be reviewed for completeness, correctness and consistency. In case of issues, queries will be sent to the Investigator to complete, correct or comment the data.

16.3. Direct Access to Source Data/Documents

The Investigator must ensure the availability of original source documents from which the information on the eCRFs was derived. Where printouts of electronic medical records, are provided as source documents, or where copies of source documents are retained as source documents, they should be signed and dated by a member of the investigational site team indicating they are a true reproduction of the original source document (Certified Copies).

Direct access to source documents per applicable regulations must be made available for monitoring or auditing by the sponsor's representative or representatives of the competent authorities and other applicable regulatory agencies.

16.4. Confidentiality

All information and data sent to parties involved in study conduct concerning subjects or their participation in this study will be considered confidential. Study sites will assign a unique subject ID number (SID) to each subject. Records of the subject/SID relationship will be maintained by the study site. The SID number is to be recorded on all study documents to link them to the subject's medical records at the site.

Confidentiality of data will be observed by all parties involved at all times throughout the clinical investigation. All data shall be secured against unauthorized access. The privacy of each subject and confidentiality of his/her information shall be preserved in reports and when publishing any data.

In the United States, "Protected Health Information" (PHI) will be maintained in compliance with the Health Insurance Portability and Accountability Act of 1996 (HIPAA). In Europe, subject data shall be handled in accordance with EU Data Privacy Directive: 95/46/EC and local regulations.

To maintain confidentiality, the subject's name or any other PHI should not be recorded on any study document other than the informed consent form, as required by EN ISO5840: 2009. This scenario will be covered in the Patient Information-Informed Consent Form. In the event a subject's name/PHI is included for any reason, it will be blinded; as applicable. In the event of inability to blind the identification (e.g., digital media), it will be handled in a confidential manner by the authorized personnel.

Data relating to the study might be made available to third parties (for example in case of an audit performed by regulatory authorities), provided the data are treated as confidential and that the subject's privacy is guaranteed. No identifiable subject information will be published.

16.5. CIP Amendments

Any revisions or amendments to the CIP, if required, or Informed Consent document, along with a statement of justification for the changes, will be submitted to all affected governing Ethics Boards and competent authorities if required by local law, according to applicable regulations. If the CIP is amended, a review of the eCRFs will be completed to determine if amendment to the forms is necessary. All amendments to the CIP shall be agreed between the sponsor and the PI(s). Approval by Ethics Board must be obtained prior to implementing a CIP revision at the site.

16.6. Record Retention

All study-related documents must be retained for a period of at least 2 years after the last approval of a marketing application (or longer if required by local law) and until there are no pending or contemplated marketing applications in an ICH region, or at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational device. The sponsor will inform the Investigator/site when these documents are no longer required to be retained.

No study document or image will be destroyed without prior written agreement between the sponsor and the Investigator. Measures shall be taken to prevent accidental or premature destruction of documents. Should the Investigator wish to assign the study records to another party or move them to another location, advance written notice must be given to the sponsor.

The sponsor will retain the study records for the life of Medtronic, according to Medtronic Corporate Policy and Record Retention Schedule.

Medtronic will provide a final written report of the trial results according to applicable regulations, and will include:

- Identification of the device(s)
- Description of the methodology and design of the clinical investigation
- Summary of the deviations from the CIP
- Statistical analysis of the trial data
- Critical appraisal of the aims of the trial

Medtronic will submit this final report to the PIs for review and comment, and shall document and disseminate discrepant comments to all trial PIs. The coordinating Investigators will provide their signatures, indicating their agreement with the content of the final report.

All required trial reports will be submitted to regulatory authorities per local reporting requirements/regulations.

16.7. Publication and Use of Information

The study will be registered at http://clinicaltrials.gov before first enrollment in the study. Study data and results will be made available as required per regulations.

Other publication of the study results is not planned. Should a need for publication be identified, Medtronic will develop a separate publication plan that will provide detailed information about a publication committee, if applicable, authorship, publication proposals, and handling requests for data.

16.8. Trial Insurance / Subject Indemnification

Medtronic, Inc. (including all wholly owned subsidiaries) maintains appropriate clinical trial liability insurance coverage as required under applicable laws and regulations and will comply with applicable law and custom concerning specific insurance coverage. If required, a Clinical Trial Insurance statement/certificate will be provided to the Ethics Board.

Medtronic will provide subject indemnification according to local laws where this trial will be conducted.

16.9. Suspension or Early Termination

16.9.1. Criteria for Study-Wide Termination or Suspension

Possible reasons for considering study suspension or termination of the study for all centers include but are not limited to:

- AEs and device deficiencies associated with the system or product under investigation which might endanger the safety or welfare of subjects
- Observed/suspected performance different from the product's design intent
- Decision by Medtronic or regulatory body (medically/ethically justifiable) where the study is operating under regulatory body authority

16.9.2. Criteria for Investigator/Center Termination or Suspension

Possible reasons for clinical Investigator or center termination or suspension include but are not limited to:

- Failure to obtain initial Ethics Board approval or annual renewal of the study
- Consistent non-compliance to the CIP (e.g. failure to adhere to eligibility criteria, failure to follow subjects per scheduled follow-ups, etc.)
- Lack of enrollment
- Noncompliance to regulations and the terms of the Clinical Study Agreement (e.g. failure to submit data in a timely manner, failure to follow-up on data queries and monitoring findings in a timely manner, etc.)
- Ethics Board suspension of the center
- Fraud or fraudulent misconduct (as defined by local law and regulations)
- Investigator request (e.g. no longer able to support the study)

16.9.3. Procedures for Planned Study Closure, Termination, or Suspension

Medtronic will promptly inform the clinical investigators of the reasons for a study termination or suspension and inform the regulatory authority (ies) (where required per regulatory requirements).

16.9.3.1. Medtronic - Initiated

In the case of study termination or suspension for reasons other than a temporary Ethics Board approval lapse, the investigator will promptly inform the Ethics Board.

In the case of study termination, the investigator must inform the subjects and may inform the personal physician of the subjects to ensure appropriate care and follow-up is provided.

In the case of a study suspension, subject enrollment must stop until the suspension is lifted by Medtronic. Subjects already enrolled should continue to be followed out of consideration of their safety, rights, and welfare.

16.9.3.2. Investigator - Initiated

The investigator will promptly inform:

- Medtronic and provide a detailed written explanation of the termination or suspension
- The institution (where required per regulatory requirements)
- The Ethics Board
- The subjects and may inform the personal physicians of the subjects to ensure appropriate care and follow-up is provided.

In the case of a study suspension:

- Subject enrollment must stop until the suspension is lifted
- Subjects already enrolled should continue to be followed out of consideration of their safety, rights, and welfare.

16.9.3.3. Ethics Board - Initiated

The investigator will promptly inform:

- Medtronic and provide a detailed written explanation of the termination or suspension within 5 business days
- The institution (where required per regulatory requirements)
- The subjects and may inform the personal physicians of the subjects, with the rationale for the study termination or suspension.

In the case of a study suspension:

- Subject enrollment must stop until the Ethics Board suspension is lifted
- Subjects already enrolled should continue to be followed in accordance with Ethics Board policy or its determination that an overriding safety concern or ethical issue is involved.

17. References

[1] Hancock II bioprosthesis for aortic valve replacement: The gold standard of bioprosthetic valves durability. David T, Armstrong S, Maganti M. Ann Thorac Surg. 2010; 90:775-81.

[2] The fate of Hancock II porcine valve recipients 25 years after implant. Valfre C, Ius P, Minniti G, Salvador L, Bottio, Cesari F, Rizzoli G, Gerosa G. European Journal of Cardio-thoracic Surg. 2010; 38:141-46.

[3] Medtronic Mosaic porcine bioprosthesis: Assessment of 12-year performance. Jamieson W, Reiss F, Raudkivi P, Metras J, Busse E, Goldstein J, Fradet G. J Thorac Cardiovasc Surg. 2011;142:302-307.

[4] Aortic valve replacement with the Medtronic Mosaic Bioprosthesis: A 13-Year Follow-up. Celient M, Ravenni G, Milano A, Pratali S, Scioti G, Nardi C, Bortolotti U. Ann Thorac Surg. 2012;93:510-515.

[5] Flameng W, Rega F, Vercalsteren M, Herijgers P, Meuris B. Antimineralization treatment and patient-prosthesis mismatch are major determinants of the onset and incidence of structural valve degeneration in bioprosthetic heart valves. J Thorac Cardiovasc Surg. 2014 Apr;147(4):1219-24. doi: 10.1016/j.jtcvs.2013.03.025. Epub 2013 Apr 25.

[6] Medtronic internal study data: Mosaic Aortic 17 year compendium.

18. Appendices

18.1. MASTER Informed Consent Template

NOTE: Refer to the most current version of the master informed consent form template provided under separate cover.

18.2. Hancock II IFU

NOTE: Refer to the most current version of the instructions for use for the Hancock II device provided under separate cover or packaged with the device.

18.3. Mosaic IFU

NOTE: Refer to the most current version of the instructions for use for the Mosaic device provided under separate cover or packaged with the device.

18.4. Case Report Forms

NOTE: Refer to the most current version of the HAMMOCK PAS case report forms provided under separate cover.

18.5. Definitions for the HAMMOCK PAS

18.5.1. Baseline

The definitions provided in this section are from the STS Risk Score Dictionary[vii], and should be applied when assessing baseline medical history and when conducting the baseline STS Risk Score. Please see Trial Definitions in Section 18.5.2 for definitions applied to the trial from procedure through study exit. The entire STS Risk Calculator Dictionary can be found at http://www.sts.org under the STS National Database tab, Database Managers section.

Factor	Baseline/STS Definitions
Arrhythmia	History or preoperative arrhythmia (sustained ventricular tachycardia, ventricular fibrillation, atrial fibrillation, atrial flutter, third degree heart block) that has been treated with any of the following modalities: • ablation therapy • AICD • pacemaker • pharmacologic treatment • electro cardioversion
Atrial fibrillation/atrial flutter	Presence of atrial fibrillation or flutter within two weeks of the procedure
Cardiac presentation on admission and at time of surgery	Indicate the patient's cardiac symptoms at the time of this admission. Cardiac presentation is not for angina only. Indicate the patient's cardiac presentation / symptoms**.** Choose the worst status. If the patient presents with atypical symptoms of myocardial ischemia (i.e. only shortness of breath, upper abdominal pain, left arm pain, etc.) that is known and documented to be myocardial ischemia, and is considered to be an anginal equivalent, code the selection that fits their presentation. If these symptoms are not thought to be or have not been proven to be the anginal equivalent, code "No Symptoms". **Time Frame:** The highest value at the time of admission. If this is a subsequent episode of care (within 7 days), do not code the CAD Presentation from the previous episode of care. • No symptoms – No angina, no acute STEMI, non-STEMI, no anginal equivalent, and no other atypical chest pain. • Stable angina without a change in frequency or pattern for the 6 weeks prior. Angina is controlled by rest and/or oral or transcutaneous medications. • Unstable angina: There are three principal presentations of unstable angina: • Rest angina (occurring at rest and prolonged, usually >20 minutes) • New-onset angina (within the past 2 months, of at least Canadian Cardiovascular Society Class III severity); or • Increasing angina (previously diagnosed angina that has become

Factor	Baseline/STS Definitions
	distinctly more frequent, longer in duration, or increased by 1 or more Canadian Cardiovascular Society class to at least CCS III severity). • Non-STEMI The patient was hospitalized for a non-ST elevation myocardial infarction (STEMI) as documented in the medical record. Non-STEMIs are characterized by the presence of both criteria: a. Cardiac biomarkers (creatinine kinase-myocardial band, Troponin T or I) exceed the upper limit of normal according to the individual hospital. Laboratory confirmation of myocardial necrosis; laboratory parameters with a clinical presentation which is consistent or suggestive of ischemia. ECG changes and/or ischemic symptoms may or may not be present b. Absence of ECG changes diagnostic of a STEMI (see STEMI). • ST-Elevation MI (STEMI) or equivalent. The patient presented with a ST elevation myocardial infarction (STEMI) or its equivalent as documented in the medical record. STEMIs are characterized by the presence of **both criteria**: ECG evidence of STEMI: New or presumed new ST-segment elevation or new left bundle branch block not documented to be resolved within 20 minutes. ST-segment elevation is defined by new or presumed new sustained ST-segment elevation at the J-point in two contiguous ECG leads with the cut-off points: ≥0.2 mV in men or ≥ 0.15mV in women in leads V2- V3 and/or ≥ 0.1 mV in other leads and lasting greater than or equal to 20 minutes. If no exact ST-elevation measurement is recorded in the medical chart, physician's written documentation of ST-elevation or Q waves is acceptable. If only one ECG is performed, then the assumption that the ST elevation persisted at least the required 20 minutes is acceptable. Left bundle branch block (LBBB) refers to new or presumed new LBBB on the initial ECG. Cardiac biomarkers (creatinine kinase-myocardial band, Troponin T or I) exceed the upper limit of normal according to the individual hospital's laboratory parameters and a clinical presentation which is consistent or suggestive of ischemia. Note: For purposes of the Registry, ST elevation in the posterior chest leads (V7 through V9), or ST depression that is maximal in V1-3, without ST- segment elevation in other leads, demonstrating posterobasal myocardial infarction, is considered a STEMI equivalent. • Anginal Equivalent - An anginal equivalent is a symptom such as shortness of breath (dyspnea), diaphoresis, extreme fatigue, or belching, occurring in a patient at high cardiac risk. Anginal equivalents are considered to be symptoms of myocardial ischemia. Anginal equivalents are considered to have the same importance as angina pectoris in patients presenting with elevation of cardiac enzymes or certain EKG changes which are diagnostic of myocardial ischemia. For the patient with diabetes who presents with "silent angina", code

Factor	Baseline/STS Definitions
	anginal equivalent. • Other – Aortic dissections, sudden death, heart block, arrhythmia, syncope or heart failure.
Cardiogenic shock	Cardiogenic shock is defined as a sustained (>30 min) episode of hypoperfusion evidenced by systolic blood pressure <90 mm Hg and/or, if available, cardiac index <2.2 L/min per square meter determined to be secondary to cardiac dysfunction and/or the requirement for parenteral inotropic or vasopressor agents or mechanical support (e.g., IABP, extracorporeal circulation, VADs) to maintain blood pressure and cardiac index above those specified levels. Note: Transient episodes of hypotension reversed with IV fluid or atropine do not constitute cardiogenic shock. The hemodynamic compromise (with or without extraordinary supportive therapy) must persist for at least 30 min.
Cerebrovascular accident	Indicate whether the patient has a history of stroke. Stroke is an acute episode of focal or global neurological dysfunction caused by brain, spinal cord, or retinal vascular injury as a result of hemorrhage or infarction, where the neurological dysfunction lasts for greater than 24 hours. ≤ 30 days is recent >30 days is remote
Cerebrovascular disease	Indicate whether the patient has a current or previous history of any of the following: A. Stroke: Stroke is an acute episode of focal or global neurological dysfunction caused by brain, spinal cord, or retinal vascular injury as a result of hemorrhage or infarction, where the neurological dysfunction lasts for greater than 24 hours. B. TIA: is defined as a transient episode of focal neurological dysfunction caused by brain, spinal cord, or retinal ischemia, without acute infarction, where the neurological dysfunction resolves within 24 hours. C. Noninvasive or invasive arterial imaging test demonstrating >=50% stenosis of any of the major extracranial or intracranial vessels to the brain. D. Previous cervical or cerebral artery revascularization surgery or percutaneous intervention. • This does not include chronic (nonvascular) neurological diseases or other acute neurological insults such as metabolic and anoxic ischemic encephalopathy.
Chronic lung disease	Indicate whether the patient has chronic lung disease, and the severity level according to the following classification: 1) None 2) Mild: FEV1 60% to 75% of predicted, and/or on chronic inhaled or oral bronchodilator therapy. 3) Moderate: FEV1 50% to 59% of predicted, and/or on chronic steroid therapy aimed at lung disease. 4) Severe: FEV1 < 50% and/or Room Air pO <60 or pCO2 > 50.

Factor	Baseline/STS Definitions
	5) CLD present, severity not documented 6) Unknown A history of chronic inhalation reactive disease (asbestosis, mesothelioma, black lung disease or pneumoconiosis) may qualify as chronic lung disease. Radiation induced pneumonitis or radiation fibrosis also qualifies as chronic lung disease. (if above criteria is met) A history of atelectasis is a transient condition and does not qualify. Chronic lung disease can include patients with chronic obstructive pulmonary disease, chronic bronchitis, or emphysema. It can also include a patient who is currently being chronically treated with inhaled or oral pharmacological therapy (e.g., beta-adrenergic agonist, anti-inflammatory agent, leukotriene receptor antagonist, or steroid). Patients with asthma or seasonal allergies are not considered to have chronic lung disease. Patients on home oxygen without documentation of COPD or PFT testing are coded as unknown.
Diabetes	History of diabetes diagnosed and/or treated by a healthcare provider. The American Diabetes Association criteria include documentation of the following: 1. Hemoglobin A1c >=6.5%; or 2. Fasting plasma glucose >=126 mg/dL (7.0 mmol/L); or 3. 2-h Plasma glucose >=200 mg/dL (11.1 mmol/L) during an oral glucose tolerance test; or 4. In a patient with classic symptoms of hyperglycemia or hyperglycemic crisis, a random plasma glucose >=200 mg/dL (11.1 mmol/L) This does not include gestational diabetes.
Dialysis	Indicate if subject is currently undergoing dialysis
Hypertension	Any of the following: • documented history of hypertension diagnosed and treated with medication, diet and/or exercise, • prior documentation of blood pressure >140 mmHg systolic or 90 mmHg diastolic for patients without diabetes or chronic kidney disease, or prior documentation of blood pressure >130 mmHg systolic or 80 mmHg diastolic on at least 2 occasions for patients with diabetes or chronic kidney disease • currently on pharmacologic therapy to control hypertension
Immunocompromised	Indicate whether subject is immunocompromised due to immunosuppressive medication therapy within 30 days preceding the operative procedure or an existing medical condition. This includes, but is not limited to systemic steroid therapy, anti-rejection medications and chemotherapy. This does not include topical steroid applications, one time systemic therapy inhaled steroid therapy or pre-procedure steroid protocol.
Infective endocarditis	Indicate whether the patient has a history of endocarditis: Endocarditis must meet at least 1 of the following criteria:

Factor	Baseline/STS Definitions
	1. Patient has organisms cultured from valve or vegetation. 2. Patient has 2 or more of the following signs or symptoms: fever (>38°C), new or changing murmur*, embolic phenomena*, skin manifestations* (i.e., petechiae, splinter hemorrhages, painful subcutaneous nodules), congestive heart failure*, or cardiac conduction abnormality* * With no other recognized cause and at least 1 of the following: a. organisms cultured from 2 or more blood cultures b. organisms seen on Gram's stain of valve when culture is negative or not done c. valvular vegetation seen during an invasive procedure or autopsy d. positive laboratory test on blood or urine (e.g., antigen tests for H influenzae, S pneumoniae, N meningitidis, or Group B Streptococcus) e. evidence of new vegetation seen on echocardiogram and if diagnosis is made antemortem, physician institutes appropriate antimicrobial therapy. Marantic Endocarditis (Lupus) should not be coded as infectious endocarditis.
Liver Disease	Indicate whether the patient has a history of hepatitis B, hepatitis C, cirrhosis, portal hypertension, esophageal varices, chronic alcohol abuse or congestive hepatopathy. Exclude NASH in the absence of cirrhosis. Hepatitis A is a transient condition- do not code as liver disease
Myocardial infarction	History of documented myocardial infarction at any time prior to surgery
Number of diseased vessels	The number of diseased major native coronary vessel systems: LAD system, Circumflex system, and/or Right system with >= 50% narrowing of any vessel preoperatively. NOTE: Left main disease (>=50%) is counted as TWO vessels (LAD and Circumflex, which may include a Ramus Intermedius). (E.g., left main and RCA would count as three total)
Peripheral Arterial Disease	History of peripheral arterial disease (includes upper and lower extremity, renal, mesenteric, and abdominal aortic systems). This can include: • claudication , either with exertion or at rest • amputation for arterial vascular insufficiency • vascular reconstruction, bypass surgery, or percutaneous intervention to the extremities (excluding dialysis fistulas and vein stripping) • documented aortic aneurysm with or without repair • positive noninvasive test (e.g., ankle brachial index =< 0.9, ultrasound, magnetic resonance or computed tomography imaging of > 50% diameter stenosis in any peripheral artery, i.e., renal, subclavian, femoral, iliac) or angiographic imaging. *Excludes disease in the carotid or cerebrovascular arteries or thoracic aorta. Does not include DVT.
Status of the procedure	**Elective:** The patient's cardiac function has been stable in the days or weeks prior to the operation. The procedure could be deferred without increased risk of compromised cardiac outcome.

Factor	Baseline/STS Definitions
	Urgent: Procedure required during same hospitalization in order to minimize chance of further clinical deterioration. Examples include but are not limited to: Worsening, sudden chest pain, CHF, acute myocardial infarction (AMI), anatomy, IABP, unstable angina (USA) with intravenous (IV) nitroglycerin (NTG) or rest angina. **Emergent**: Patients requiring emergency operations will have ongoing, refractory (difficult, complicated, and/or unmanageable) unrelenting cardiac compromise, with or without hemodynamic instability, and not responsive to any form of therapy except cardiac surgery. An emergency procedure is one in which there should be no delay in providing operative intervention. The patient's clinical status includes any of the following: a. Ischemic dysfunction (any of the following): (1) Ongoing ischemia including rest angina despite maximal medical therapy (medical and/or IABP)); (2) Acute Evolving Myocardial Infarction within 24 hours before surgery; or (3) pulmonary edema requiring intubation. b. Mechanical dysfunction (either of the following): (1) shock with circulatory support; or (2) shock without circulatory support. **Emergent Salvage:** The patient is undergoing CPR en route to the OR or prior to anesthesia induction.

18.5.2. Trial Definitions

The trial definitions in this section should be used when recording data from procedure through study exit.

18.5.2.1. NYHA Functional Classification

The New York Heart Association (NYHA) Functional Classification is a system for defining cardiac disease and related functional limitations into four broad categorizations as defined in the table below.

Classification	Description
Class I	Patients with cardiac disease, but without resulting limitations of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnea, or anginal pain.
Class II	Patients with cardiac disease resulting in slight limitation of physical activity. Patients are comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnea, or anginal pain.
Class III	Patients with cardiac disease resulting in marked limitation of physical activity. Patients are comfortable at rest. Less than ordinary physical activity causes fatigue, palpitation, dyspnea, or anginal pain.
Class IV	Patients with cardiac disease resulting in inability to perform any physical activity without discomfort. Symptoms of cardiac insufficiency or of the anginal syndrome may be present even at rest. If any physical activity is undertaken, discomfort is increased.

18.5.2.2. Endpoint Related Events

Death	**All-Cause Mortality** All deaths from any cause after a valve intervention.
	Cardiac Death All deaths resulting from cardiac causes. This category includes valve-related mortality, sudden unexplained deaths, and deaths from non-valve-related cardiac causes (e.g., heart failure, acute myocardial infarction, or documented arrhythmias).
	Valve-related mortality Any death caused by structural valve deterioration, nonstructural dysfunction, valve thrombosis, embolism, bleeding event, or operated valve endocarditis; death related to reintervention on the study valve; or sudden, unexplained death. Deaths caused by heart failure in patients with advanced myocardial disease and satisfactorily functioning cardiac valves are not counted. Specific causes of valve-related deaths should be reported.
	Sudden, unexplained death Death in which the cause has not been determined by clinical investigation or autopsy findings and the relationship to the study valve is undefined.
	Non-Cardiac Death All deaths due to any cause, excluding cardiac death, sudden, unexplained death, or study valve-related mortality.
Explant	Reintervention to remove of the study valve for any reason. Does not include peri-procedural removal during the index procedure.
Reintervention [viii]	Following the completion of the index procedure, defined as the subject leaving the operating theater with an implanted Mosaic or Hancock II valve; Any surgical or percutaneous interventional catheter procedure that repairs, otherwise alters or adjusts, or replaces a previously implanted Mosaic or Hancock II valve bioprosthesis. In addition to surgical reoperations, balloon dilatation, interventional manipulation, repositioning, or retrieval, and other catheter-based interventions for valve –related complications are also considered reinterventions. Report indications for reintervention; surgical and percutaneous catheter reinterventions should be listed separately.

18.5.2.3. Valve-Related Adverse Events

Term	Valve-Related Adverse Event Definition
Prosthetic Valve Endocarditis [viii]	Infection involving a heart valve substitute. Diagnosis is based on customary clinical criteria, including an appropriate combination of positive blood cultures, clinical signs (fever, new or altered cardiac murmurs, splenomegaly, systemic embolus, or immunopathologic lesions), and/or histologic confirmation of endocarditis at reoperation or autopsy. Morbidity associated with active infection such as valve thrombosis, embolus, or paravalvular leak is included under this category and is not included in other categories of morbidity. • The Modified Duke Criteria for Endocarditis [ix] may be used to diagnose endocarditis events for the HAMMOCK PAS study, in the absence of reoperation or autopsy. These criteria are provided for reference in Section 18.5.3 of this appendix.
Hemolysis	Hemolysis is defined as laboratory evidence of red blood cell destruction attributable to the Mosaic or Hancock II valve. Hemolysis will be diagnosed by plasma free hemoglobin higher than the upper limit of the normal range (to be determined by the lab), or plasma free hemoglobin > 40mg/dl on 2 consecutive measurements within 24 hours. However, if plasma free hemoglobin results are inconclusive or not available, serum lactate dehydrogenase, haptoglobin and reticulocyte count may be used together to diagnose hemolysis. Severity of hemolysis is classified as clinically significant (requires intervention (i.e., long-term iron supplement, transfusion, or replacement of bioprosthesis)) or not clinically significant (does not require intervention) Events which are excluded are those due to liver disease or systemic infection. If the event is secondary to endocarditis, hemorrhage, perivalvular leak, thromboembolism, thrombosis, it should be reported as such.
Hemorrhage (bleeding)	Any episode of internal or external bleeding. These events are reported as major or minor as defined below: **Major:** An episode of internal or external bleeding with more than or equal than 1 liter blood loss which causes death, hospitalization, or permanent injury (e.g., vision loss) or necessitates transfusion 3 or more units of blood, pericardiocentesis, or reoperation. **Minor:** All other episodes of internal or external loss of blood after 24 hours from index procedure. Examples include nosebleeds that require nose packing as outpatient or ER visit, hematomas due to trauma or surgery that do not require transfusion, or minor ocular hemorrhage. Excluded from this definition are bleeding events associated with major trauma or a major operation. Bleeding events occurring during the index procedure, including any bleeding within 24 hours of index procedure with less than 3 units' blood transfusion, or less than 1 liter blood loss are excluded.
	Anticoagulant/antiplatelet-related hemorrhage All major or minor hemorrhage events in subjects who are receiving anticoagulants and/or antiplatelet drugs

Term	Valve-Related Adverse Event Definition
Nonstructural dysfunction	Abnormality resulting in stenosis or regurgitation of the heart valve substitute that is not intrinsic to the valve itself. The diagnosis should be confirmed by examination of the explanted or damaged valve. Examples include: • Entrapment by pannus (ingrowth of tissue into the heart valve substitute which may interfere with normal functioning) or suture • Paravalvular leak (clinically or hemodynamically detectable defect between the heart valve substitute and the patient's annulus), • Inappropriate sizing, • Significant hemolytic anemia This dysfunction is exclusive of valve thrombosis, systemic embolus, or infection diagnosed at re-operation, autopsy, or in vivo investigation.
Paravalvular leak	Any evidence of leakage of blood around the prosthesis between the sewing ring and the native annulus. Paravalvular leaks will be graded for severity of the regurgitation using the ASE Aortic Valve Regurgitation scale (see Section 2.4) and will be classified as: **Minor leaks**: does not require surgical or percutaneous intervention **Major leaks**: requires surgical or percutaneous intervention Clinically significant paravalvular leak (PVL that is moderate or greater in severity as assessed by the ASE Aortic Valve Regurgitation scale (see Section 2.4) and/or requires reintervention) as assessed by the site should be reported as an adverse event. If the event is secondary due to endocarditis, it must be reported as such. Secondary events related to paravalvular leak (hemolysis, thromboembolism, or thrombosis) should be also be recorded as such. For study progress reports and regulatory submission, all paravalvular leak regardless of severity will additionally be summarized as assessed by the Echocardiography Core Lab for each subject at each visit.
Structural Valve Deterioration [viii]	Change to the function of a heart valve substitute resulting from an intrinsic abnormality that causes stenosis or regurgitation. The diagnosis should be confirmed by examination of the explanted or damaged valve. It includes intrinsic changes such as wear, fatigue failure, stress fracture, calcification, leaflet tear, and stent creep. • This definition excludes paravalvular leak infection or pannus overgrowth, or thrombosis of the heart valve substitute as determined by reoperation, autopsy, or in vivo investigation.

Term	Valve-Related Adverse Event Definition
Thromboembolism [viii]	Clot or other particulate matter, not associated with infection, originating on or near the heart valve substitute and transported to another part of the body. Diagnosis may be indicated by: • A new, permanent or transient, focal or global neurologic deficit (exclusive of hemorrhage) • Any peripheral arterial embolus unless proved to have resulted from another cause (e.g., atrial myxoma); • Acute myocardial infarction that occurs after operation in patients with known normal coronary arteries. Events which are excluded are: • Neurologic deficit resulting from hemorrhage • Patients who do not awaken post-operatively or who awaken with a stroke or myocardial infarction are excluded. • Any peripheral arterial emboli proven to have originated from another cause (e.g., atrial myxoma), pulmonary emboli, or events due to proven ischemic disease of the extremities. • Acute myocardial infarction that occurs after operation in with known coronary artery disease. If the event is secondary to hemorrhage, paravalvular leak or endocarditis, it should be reported as such. Secondary events related to thromboembolism should also be recorded as such.
Thromboembolism, cont.	Neurologic events: [viii] **Any central, new neurological deficit, whether temporary or permanent, focal or global, that occurs after the patient emerges from anesthesia.** • **Transient ischemic attack** (TIA) is a fully reversible neurologic event that lasts less than or equal to 24 hours. If radiographic imaging demonstrates an acute central neurologic lesion (cerebral infarction with transient symptoms"), the event should be reported as a stroke. Multiple or repeated transient events occurring during a short period (a burst or cluster) should be reported as one event and documented as a cluster. • **Stroke** (CVA) is a neurologic deficit lasting more than 24 hours, or lasting 24 hours or less with brain imaging study showing infarction.
	Peripheral embolic events: [ix] **An operative, autopsy, or clinically documented embolus that produces symptoms from complete or partial obstruction of a peripheral (noncerebral) artery.**
	Acute myocardial infarction: [ix] An area of coagulation necrosis resulting from impaired oxygenation of the myocardium.

Term	Valve-Related Adverse Event Definition
Valve Thrombosis	Blood clot not associated with infection, causing dysfunction of the heart valve substitute. Diagnosis may be proven by operation, autopsy, or clinical investigation (e.g., echocardiography, angiocardiography, or MRI)

18.5.3. Modified Duke Criteria for Endocarditis

The Modified Duke Criteria for Endocarditis [ix] may be used to diagnose endocarditis events for the HAMMOCK PAS study, in the absence of reoperation or autopsy.

Criteria	Definite Infective Endocarditis	Possible Infective Endocarditis	Not Infective Endocarditis
• Pathologic			
Histologic	Vegetation or intracardiac abscess present, confirmed by histology showing active endocarditis	Short of definite, but not rejected	No pathologic evidence of infective endocarditis with antibiotic therapy for 4 days or less
• Or			
Bacteria	Demonstrated by culture or histology in a vegetation, or in a vegetation that has embolized, or in an intracardiac abscess	Short of definite, but not rejected	No pathologic evidence of infective endocarditis with antibiotic therapy for 4 days or less
• Clinical - any one of following:			
Major criteria	2 criteria met	Does not apply	• Resolution of manifestations of endocarditis, with antibiotic therapy for 4 days or less, **or** firm alternate diagnosis for manifestations of endocarditis. Does not meet criteria for possible infective endocarditis
Minor criteria	5 criteria met	3 criteria met	
Major and minor	1 major + 3 minor	1 major and 1 minor	

Major Criteria
A. Supportive laboratory evidence ▪ Typical microorganism for infective endocarditis from two separate blood cultures: viridans streptococci, Staphylococcus aureus, Streptococcus bovis, HACEK group (Haemophilus spp. Actinobacillus actinomycetemcomitans, Cardiobacterium hominis, Eikenella spp., and Kingella kingae) **or** ▪ Community-acquired enterococci, in the absence of a primary focus ▪ Persistently positive blood culture, defined as recovery of a microorganism consistent with infective endocarditis from blood cultures drawn more than 12 hours apart **or** ▪ Persistently positive blood culture, defined as recovery of a microorganism consistent with infective endocarditis from all of three or a majority of four or more separate blood cultures, with first and last drawn at least 1 hour apart. ▪ Single positive blood culture for *Coxiella burnetti* or phase I antibody titer >1:800
B. Evidence of endocardial involvement Echocardiogram supportive of infective endocarditis. **1. Type of study** **TEE recommended as first test in the following patients**: a) prosthetic valve endocarditis; **or** b) those with at least "possible" endocarditis by clinical criteria; **or** c) those with suspected complicated endocarditis, such as paravalvular abscess. **TTE recommended as first test in all other patients** 2. Definition of positive findings • oscillating intracardiac mass, on valve or supporting structures, or in the path of regurgitant jets, or on implanted material, in the absence of an alternative anatomic explanation **or** myocardial abscess **or** new partial dehiscence of prosthetic valve
• C. New valvular regurgitation (increase or change in pre-existing murmur not sufficient)
Minor Criteria
Predisposing heart condition or intravenous drug use
Fever >= 38.0 C (100.4 F)
Vascular phenomena: major arterial emboli, septic pulmonary infarcts, mycotic aneurysm, intracranial hemorrhage, conjunctival hemorrhage, Janeway lesions
Immunologic phenomena: glomerulonephritis, Osler's nodes, Roth spots, rheumatoid factor
• Positive blood culture not meeting major criterion as noted previously (excluding single positive cultures for coagulase-negative staphylococci and organisms that do not cause endocarditis) or serologic evidence of active infection with organism consistent with infective endocarditis

18.5.4. Aortic Valve Regurgitation

One of the endpoints for the HAMMOCK PAS is paravalvular leak of the study valve. Severity of any paravalvular leak will be measured using the ASE recommended parameters to assess Aortic Regurgitation (AR) severity [x], as outlined in the table below.

Parameter	Mild	Moderate	Severe
Valve structure and motion			
Mechanical or bioprosthetic	Usually normal	Abnormal[2]	Abnormal[2]
Structural parameters			
LV size	Normal[3]	Normal or mildly dilated[3]	Dilated[3]
Doppler parameters (qualitative or semi-quantitative)			
Jet width in central jets (% LVOT diameter): color[1]	Narrow (≤25%)	Intermediate (26% - 64%)	Large (≥65%)
Jet density: CW Doppler	Incomplete or faint	Dense	Dense
Jet deceleration rate (PHT, ms): CW Doppler[4]	Slow (>500)	Variable (200 – 500)	Steep (<200)
LVOT flow vs pulmonary flow: PW Doppler	Slightly increased	Intermediate	Greatly increased
Diastolic flow reversal in descending aorta: PW Doppler	Absent or brief early diastolic	Intermediate	Prominent, holodiastolic
Circumferential extent of prosthetic paravalvular regurgitation (%)	<10	10 – 19	≥20
Doppler Parameters (quantitative)			
Regurgitant volume (ml/beat)	<30	30 – 59	≥60
Regurgitant fraction (%)	<30	30 – 49	≥50

Notes:
PHT = pressure half-time
[1] Parameter applicable to central jets, and is less accurate in eccentric jets; Nyquist limit of 50 – 60 cm/sec.
[2] Abnormal mechanical valves, for example, immobile occluder (valvular regurgitation), dehiscence or rocking (paravalvular regurgitation); abnormal biologic valves, for example, leaflet thickening or prolapse (valvular), dehiscence or rocking (paravalvular regurgitation).
[3] Applies to chronic, late postoperative AR in the absence of other etiologies.
[4] Influenced by LV compliance.
Not well validated and may overestimate severity compared with quantitative Doppler

18.5.5. Mitral Valve Regurgitation

One of the endpoints for the HAMMOCK PAS is paravalvular leak of the study valve. Severity of any paravalvular leak will be measured using the ASE recommended parameters to assess Aortic Regurgitation (AR) severity [xi], as outlined in the table below.

Parameter	Mild	Moderate	Severe
Structural parameters			
LV size	Normal[1]	Normal or dilated	Usually dilated[3]
Prosthetic valve [5]	Usually normal	Abnormal[6]	Abnormal[6]
Doppler parameters			
Color flow jet area [5 7]	Small, central jet (usually <4 cm2 or <20% of LA area)	Variable	Large central jet (usually >8 cm2 or >40% of LA area) or variable size wall-impinging jet swirling in left atrium
Flow convergence[8]	None or minimal	Intermediate	Large
Jet density: CW Doppler [5]	Incomplete or faint	Dense	Dense
Jet contour: CW Doppler [5]	Parabolic	Usually parabolic	Early peaking, triangular
Pulmonary venous flow [5]	Systolic dominance[4]	Systolic blunting[4]	Systolic flow reversal[2]
Quantitative Parameters [9]			
VC width (cm) [5]	<0.3	0.3 – 0.59	≥0.6
R vol (mL/beat)	<30	30 – 59	≥60
RF (%)	<30	30 – 49	≥50
EROA (cm2)	<0.20	0.20 – 0.49	≥0.50

Notes:
EROA, Effective regurgitant orifice area; RF, regurgitant fraction; R vol, regurgitant volume; VC, vena contracta.
[1] LV size applied only to chronic lesions.
[2] Pulmonary venous systolic flow reversal is specific but not sensitive for severe MR.
[3] In the absence of other etiologies of LV enlargement and acute MR.
[4] Unless other reasons for systolic blunting (eg, atrial fibrillation, elevated LA pressure).
[5] Parameter may be best evaluated or obtained with TEE, particularly in mechanical valves.
[6] Abnormal mechanical valves, for example, immobile occluder (valvular regurgitation), dehiscence or rocking (paravalvular regurgitation); abnormal biologic valves, for example, leaflet thickening or prolapse (valvular), dehiscence or rocking (paravalvular regurgitation).
[7] At a Nyquist limit of 50 to 60 cm/s.
[8] Minimal and large flow convergence defined as a flow convergence radius <0.4 and $0.9 cm for central jets, respectively, with a baseline shift at a Nyquist limit of 40 cm/s; cutoffs for eccentric jets may be higher.
[9] These quantitative parameters are less well validated than in native MR.

18.6. Investigational Sites

A listing of the investigational sites, name, address and professional position of PI's and coordinating investigator(s) if assigned) will be provided under separate cover.

18.6.1. Site Selection

The following criteria will be used to select investigators and sites for participation:

- Experience in cardiothoracic surgery and surgical aortic and/or mitral valve replacement
- The presence or capacity of establishing an investigative team capable of managing the duties of the clinical trial
- Access to the necessary cardiovascular facilities and services to complete protocol required study procedures and follow-up.
- Availability of the study device(s)
- A sufficient patient population to meet enrollment expectations (estimated treatment of 10 subjects at each site, with a maximum of 20 treated subjects (or 20% of the total trial population)
- Willingness to comply with the requirements described in this CIP

A listing of Investigators and investigative centers/sites will be provided under separate cover.

18.6.2. Research Agreement and Financial Disclosure

A Clinical Investigation Agreement shall be signed by the participating investigational site and/or the PI at each investigational site per the local legal requirements, and returned to Medtronic prior to trial activation. The Investigator is required to indicate their approval of the CIP (and any subsequent amendments), by signing and dating the agreement. All Investigators will be asked to complete financial disclosure statements provided by Medtronic prior to their participation in the trial.

18.6.3. Training of Investigative Staff

Medtronic will provide training to the investigative team, according to the Training Plan, on the trial Requirements as applicable. Training required per local law/regulation will occur prior to site activation at each site.

Site personnel (including new personnel) must be trained and activated by Medtronic prior to performing any protocol related duties.

18.6.4. Site Activation

Investigational sites will receive a formal letter of site activation, upon receipt of or completion of the following:

- Curriculum vitae of the Principal and Sub-investigators and all key site staff
- A signed research agreement
- A signed Investigator statement
- Financial disclosure from the Investigators
- Competent Authority (as applicable to the geography)
- A copy of the IRB/Ethics Board approval letter, along with the voting roster
- The IRB/Ethics Board approved informed consent form

- Documented training of the investigative team
- Delegated Task List
- Lab certificate and lab normal values/ranges

18.7. Other Institutions

18.7.1. Echocardiography Core Lab

The Echocardiography Core Laboratory (Echo Core Lab) is responsible for developing protocol requirements, reviewing echo exams, interpreting subject echo data, and providing feedback on the quality of the echo exams to participating sites. The Echo Core Lab will review, analyze, and record data on the Echo Core Lab Assessment eCRF. The Echo Core Lab Cardiologist's interpretation of all echocardiograms will be used for the data analyses. All transthoracic echocardiography recordings will be evaluated by the team of Dr. Neil J. Weissman at:

Cardiovascular Core Labs
MedStar Health Research Institute
100 Irving Street, NW
East Building, Room 5123
Washington, DC 20010 USA
Phone: +1-202-877-0223
Fax: +1-202-877-0206

Details of the Echocardiography methods and the procedure for sending TTE is provided in an Echocardiographic Procedures Manual provided under separate cover.

18.7.2. Pathology Core Lab

All explanted study valves will be independently analyzed by:

CVPath Institute, Inc.,
19 Firstfield Road,
Gaithersburg, MD 20878

Details of the procedure for sending explanted valves provided under separate cover.

18.7.3. Clinical Events Committee

Details of the clinical events committee provided under separate cover.

[vii] http://www.sts.org
[viii] ANSI/AAMI/ISO 5840:2005. Cardiovascular implants- Cardiac valve prostheses.
[ix] Li JS, Sexton DJ, Michk N, Nettles, R, Fowler VG Jr, Ryan T, et al. Proposed modifications to the Duke criteria for the diagnosis of infectious endocarditis. Clin Infect Dis. 2000; 30:633-8.
[x] Zoghbi WA, Chambers JB, Dumesnil JG, et al. Recommendations for Evaluation of Prosthetic Valves with Echocardiography and Doppler Ultrasound. J Am Soc Echocardiogr 2009; 975-1014.
[xi] Zoghbi WA, Chambers JB, Dumesnil JG, et al. Recommendations for Evaluation of Prosthetic Valves with Echocardiography and Doppler Ultrasound. J Am Soc Echocardiogr 2009; 975-1014.