Bicuspid aortic valve replacement: EvaLuatIon of transcathetEr VERsus Surgery (BELIEVERS) Trial

Protocol ID: BAV2025-4770

National Clinical Trial (NCT) Identified Number:

NCT07413965

Sponsor: Cedars-Sinai Medical Center

Principal Investigator: Raj Makkar, MD

Funded by: Patient-Centered Outcomes Research Institute (PCORI)

Version Number: v2.0

31st March, 2026

Collaborating Institutions and Researchers	Marcio Diniz, PhD Data Coordinating Center (DCC) Icahn School of Medicine at Mount Sinai 1 Gustave L. Levy PL New York NY 10029 Philippe Pibarot, MD Universite Laval, Institute Universitaire de Cardiologie et De Pneumology 2725 Sainte-Foy Road, Quebec, Canada G1C 4G5

Summary of Changes from Previous Version:

Affected Section(s)	Summary of Revisions Made	Rationale
Multiple	Edits throughout Protocol for clarification.	Edits (for protocol clarification rather than substantive) following review with Steering Committee and Data Coordinating Center.

PROTOCOL TITLE: Bicuspid aortic valve replacement: EvaLuatIon of transcathetEr VERsus Surgery (BELIEVERS) Trial

Clinical Coordinating Center (CCC) Principal Investigator: Raj Makkar, MD
Sponsor: Cedars-Sinai Medical Center

Data Coordinating Center (DCC) Principal Investigator: Marcio Diniz, PhD

Protocol Version: 2.0
Version Date: 31-Mar-2026

Declaration of Investigator
I confirm that I have read the above-mentioned protocol and its attachments. I agree to conduct the described trial in compliance with all stipulations of the protocol, regulations and ICH E6 Guideline for Good Clinical Practice (GCP).

CCC Principal Investigator: Raj Makkar, MD

Principal Investigator Signature: _____Date: _____

DCC Principal Investigator: Marcio Diniz, PhD

Principal Investigator Signature: _____Date:_____

Institution/Site #: _____

Principal Investigator Name: _____

Principal Investigator Signature: _____Date:_____

Table of Contents

STATEMENT OF COMPLIANCE

The trial will be carried out in accordance with International Conference on Harmonization Good Clinical Practice (ICH GCP) and the following:

- United States (US) Code of Federal Regulations (CFR) applicable to clinical studies (45 CFR Part 46, 21 CFR Part 50, 21 CFR Part 56, 21 CFR Part 312, and/or 21 CFR Part812)

Investigators and clinical trial staff who are responsible for the conduct, management, or oversight of the trial have completed Human Patients Protection and ICH GCP Training.

The protocol, informed consent form(s), recruitment materials, and all patient materials will be submitted to the Institutional Review Board (IRB) for review and approval. Approval of both the protocol and the consent form must be obtained before any patient is enrolled. Any amendment to the protocol will require review and approval by the IRB before the changes are implemented to the study. In addition, all changes to the consent form will be IRB-approved; a determination will be made regarding whether a new consent needs to be obtained from patients who provided consent, using a previously approved consent form.

1 PROTOCOL SUMMARY

1.1 SYNOPSIS

Title:	**Bicuspid aortic valve replacement: EvaLuatIon of transcathetEr VERsus Surgery (BELIEVERS) Trial**
Study Description:	The study is a multicenter, randomized superiority trial of **standard of care** therapies for **severe aortic stenosis** (AS) in patients with a bicuspid aortic valve (BAV). Namely, the therapies to which patients will be randomized will be **transcatheter** aortic valve replacement (TAVR) or **surgical** aortic valve replacement (SAVR), in patients deemed clinically suitable for both **following patient selection committee review**. The null hypothesis is that there is **no difference between TAVR and SAVR** in relation to the hierarchical primary composite endpoint. The alternate hypothesis is that **TAVR differs from SAVR**. The test for superiority is two-sided, such that SAVR or TAVR superiority could be demonstrated. Patients deemed suitable for randomization at the individual level by a local heart team will be **affirmed by the patient selection committee**. Patients deemed **unsuitable for randomization** but **meet inclusion criteria** and ultimately undergo SAVR or TAVR are of interest and will be entered into the SAVR and TAVR registry cohorts.
Objectives:	The overarching goal of this study is to provide an evidence base for a structured and consistent image-guided precision-medicine based approach to guide patients and their providers to the most appropriate therapy for valve replacement for their particular BAV anatomy, weighing their "TAVR risk" (figure 1; predominantly driven by anatomical factors) with their "SAVR risk" (predominantly driven by clinical factors).

Endpoints: Please see Table 1 below.

Study Population: Sample size: 1200 randomized patients required for 85% power to detect a difference (two-sided superiority)**.**

Patients at 50 years of age or older at time of consent with severe aortic stenosis (AS) and a bicuspid aortic valve (BAV) deemed suitable for a bioprosthesis by a local heart team (unsuitable or patient declined a mechanical valve or Ross procedure, following demonstration of evidence-based shared decision making with a validated decision-aid(1)).

Description of Sites/Facilities Enrolling Patients: At least 60 sites that perform both TAVR and SAVR are initially planned in the United States and Canada**.**

Description of Study Intervention: The study intervention is aortic valve replacement by TAVR or SAVR that are commercially available and standard of care devices. Patients will be randomized 1:1 to TAVR or SAVR using permuted block randomization with varying block size **stratified by (1) sex** and (2) low or intermediate/high SAVR (clinical) risk, (3) planned TAVR type (in the event of randomization to TAVR). Local heart team assessments of ***clinical risk*** assessment and ***anatomical risk*** assessment by CT corelab will be provided to the patient selection committee for final adjudication of ***TAVR and SAVR risk***. For the patient to be suitable for randomization, there must be relative equipoise, defined as follows: the TAVR and SAVR risk strata, as per final adjudication by the patient selection committee based on site-reported (SAVR risk) and CT Corelab analyzed qualitative and quantitative data (TAVR risk), must not deviate by more than one risk stratum. For instance, a low SAVR risk patient cannot be randomized if the TAVR risk is deemed high, and vice versa. However, an intermediate SAVR risk patient could be randomized if the TAVR risk is low or high and vice versa. It is anticipated that the feasibility phase (around 20 sites) will enroll 10% of the full-scale study phase of 1200 randomized patients (1200 clinical trial patients from at least 60 and up to 80 sites).

Study Duration: Estimated time from when the study opens to enrollment until completion of data analyses: 120 months. The current PCORI funding will cover the first 6.5 years, additional funding was secured for the remaining 3.5 years. Protocol will be revised as appropriate, at the end of the 6.5-year period, to reflect non-PCORI funding.

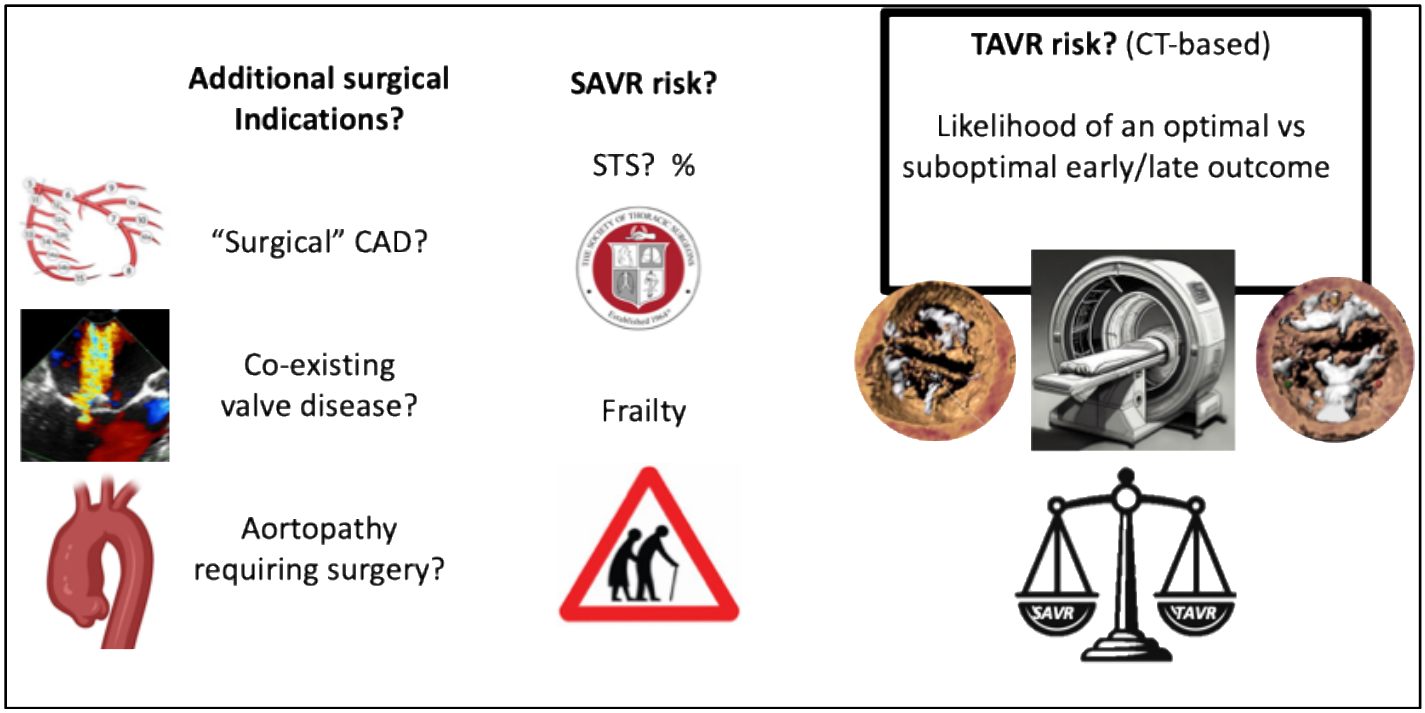
Patient Duration: Time it will take for each individual patient to complete all patient visits: Follow-up is planned annually to 10 years. This will include standard of care clinic visit (in person or virtual) and a standard of care echocardiogram**.**

Table 1. Primary, Secondary, Safety and Exploratory Outcomes				
Primary or Secondary	**Name of Outcome**	**Specific measure to be used**	**Timepoints**	**Estimated power (if applicable)**
Primary	**A hierarchical composite of: (1) death, (2) disabling stroke, (3) non-disabling stroke, (4) valve reintervention, (5) rehospitalization†, (6) unfavorable KCCQ (VARC-3*)**	Hierarchical categorical using Win ratio (superiority)	**Assessed at latest available annual follow-up (6y duration PCORI funded)**	**>85%**
Key Secondary	Hierarchical composite of (1) death (2) time averaged KCCQ score.	Win ratio	**Survival status assessed at latest available annual follow-up. KCCQ will be assessed as a time-average over patient follow-up**	>95%
Secondary	Time averaged Kansas City Cardiomyopathy Questionnaire (KCCQ) status (continuous)	KCCQ questionnaire	Time average over all patient follow-up	>95%
Secondary	Kansas City Cardiomyopathy Questionnaire (KCCQ) status (continuous)	KCCQ questionnaire	From baseline to 1, 12, 24, 36, 48, 60, 72, 84, 96, 108, 120 months	Not powered
Secondary	CV rehospitalization days (count)	CRF: clinical events assessed by direct follow-up	Event driven	Not powered
Secondary	Short Form-12 (SF-12) Health Survey (continuous)	SF-12 questionnaire	From baseline to 1, 12, 24, 36, 48, 60, 72, 84, 96, 108, 120 months	Not powered
Secondary	New York Heart Association (NYHA) status (categorical)	NYHA clinical scale	From baseline to discharge, 1, 12, 24, 36, 48,60, 72, 84, 96, 108, 120 months	Not powered
Secondary	6 min walk test (continuous)	6 min walk test distance	From baseline to 1, 12	Not powered
Secondary	Depression score (continuous)	PHQ-9 score	From baseline to 1, 12, 24, 36, 48, 60, 72, 84, 96, 108, 120 months	Not powered
Secondary	Time-to-recovery to baseline (categorical)	QOR-15 scale	From baseline to discharge, 1, 12 months	Not powered
Secondary	Death (time-to-event)	CRF: clinical events assessed by direct follow-up	Event driven	Not powered
Secondary	Cardiovascular death (time-to-event)	CRF: clinical events assessed by direct follow-up	Event driven	Not powered
Secondary	All stroke (time-to-first event) Ischemic, hemorrhagic, not otherwise specified	CRF: clinical events assessed by direct follow-up	Event driven	Not powered
Secondary	Disabling stroke (time-to-first event,)	CRF: clinical events assessed by direct follow-up	Event driven	Not powered
Secondary	Rehospitalization (*valve-, procedure-, or HF-related)*; (time-to-first event)	CRF: clinical events assessed by direct follow-up	Event driven	Not powered
Secondary	Death/stroke/rehospitalization; (time-to-first event)	CRF: clinical events assessed by direct follow-up	Event driven	Not powered
Secondary	Aortic dissection (time-to-first event)	CRF: clinical events assessed by direct follow-up	Event driven	Not powered
Secondary	Need for surgery of the aorta (time-to-event)	CRF: clinical events assessed by direct follow-up	Event driven	Not powered

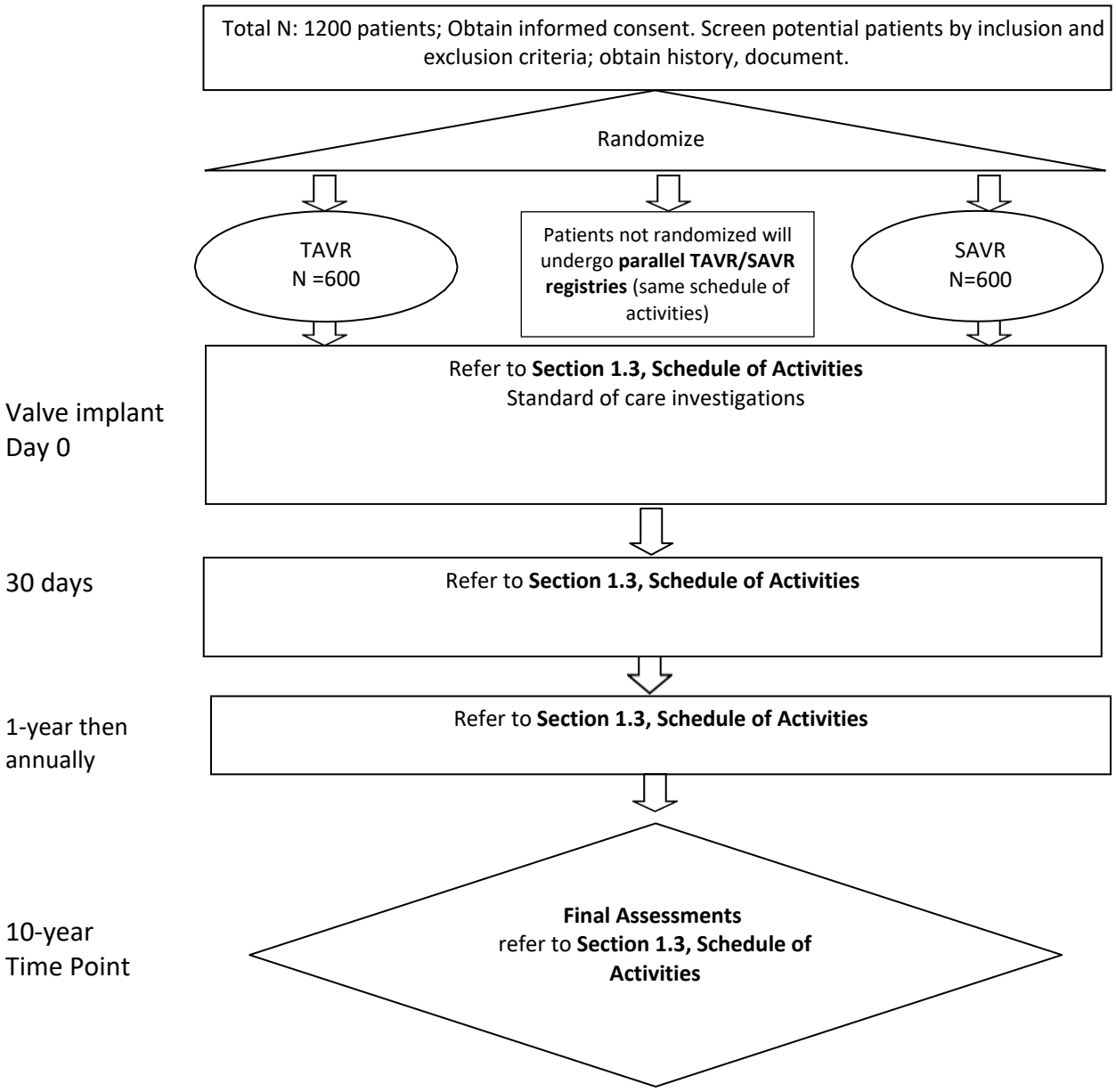
Secondary	Bioprosthetic valve failure (BVF); (time-to-first event)	Echo corelab determined	Event driven	Not powered
Secondary	Paravalvular leak severity (categorical)	Echo corelab determined	From baseline to discharge, 1, 12, 24, 36, 48, 60, 72, 84, 96, 108, 120 months	Not powered
Safety	Valve-related mortality (time-to-event)	CRF: clinical events assessed by direct follow-up	Event driven	Not powered
Safety	Myocardial infarction	CRF: clinical events assessed by direct follow-up	Event driven	Not powered
Safety	Coronary obstruction	CRF: clinical events assessed by direct follow-up	Event driven	Not powered
Safety	Major bleeding (VARC-3)	CRF: clinical events assessed by direct follow-up	Event driven	Not powered
Safety	Major vascular complication (VARC-3);	CRF: clinical events assessed by direct follow-up	Event driven	Not powered
Safety	Cardiac structural complication (major)	CRF: clinical events assessed by direct follow-up	Event driven	Not powered
Safety	Need for open heart surgery	CRF: clinical events assessed by direct follow-up	Event driven	Not powered
Safety	Atrial fibrillation/ atrial flutter	CRF: clinical events assessed by direct follow-up	Event driven	Not powered
Safety	Need for permanent pacemaker	CRF: clinical events assessed by direct follow-up	Event driven	Not powered
Safety	Device malpositioning (including embolization and migration)	CRF: clinical events assessed by direct follow-up	Event driven	Not powered
Safety	Acute Kidney Injury stage 3-4	CRF: clinical events assessed by direct follow-up	Event driven	Not powered
Safety	Endocarditis (valve-related)	CRF: clinical events assessed by direct follow-up	Event driven	Not powered
Safety	Clinically significant valve thrombosis (time-to-first event)	CRF: clinical events assessed by direct follow-up	Event driven	Not powered
Exploratory	Prosthesis-patient mismatch severity (categorical)	Echo corelab determined	From baseline to discharge, 1, 12, 24, 36, 48, 60, 72, 84, 96, 108, 120 months	Not powered
Exploratory	Subclinical valve thrombosis (time-to-first event)	CT corelab determined	Event driven	Not powered
Exploratory	Ascending aorta dimension > 50 mm (categorical)	CT corelab determined	From baseline to standard of care interval CTA	Not powered
Exploratory	Change in ascending aorta dimension from baseline to follow up as cm/y (continuous)	CT corelab determined	From baseline to standard of care interval CTA	Not powered

†valve or procedure related and including heart failure but excluding valve reintervention (CEC adjudicated)]
**<45 or a decrease of >10 from baseline as per VARC-3*
Unless otherwise specified, definitions are based on VARC-3 (see appendix B).

Figure 1: Heart team assessment of TAVR vs SAVR risk


Additional surgical Indications?
SAVR risk?
STS? %
"Surgical" CAD?
Co-existing valve disease?
Frailty
Aortopathy requiring surgery?
TAVR risk? (CT-based)
Likelihood of an optimal vs suboptimal early/late outcome
SAVR
TAVR

1.2 SCHEMA


Total N: 1200 patients; Obtain informed consent. Screen potential patients by inclusion and exclusion criteria; obtain history, document.
Randomize
TAVR
N =600
Patients not randomized will undergo **parallel TAVR/SAVR registries** (same schedule of activities)
SAVR
N=600
Refer to **Section 1.3, Schedule of Activities**
Standard of care investigations
Valve implant
Day 0
Refer to **Section 1.3, Schedule of Activities**
30 days
Refer to **Section 1.3, Schedule of Activities**
1-year then annually
Final Assessments
refer to **Section 1.3, Schedule of Activities**
10-year
Time Point

1.3 SCHEDULE OF ACTIVITIES

The majority of assessments and all laboratory and all non-invasive and invasive tests/interventions will follow the standard of care (SOC).

Visits	Screening and/or Baseline Day -90 to Day 0 (Before randomization)	procedure (valve implant – Day 0)	Post procedure (up to 72 hours post-procedure)	Discharge or 7 days post-procedure (whichever is c sooner)	30 days ±7 days	1 year ±30 days	Annual visits (2 to 10 year) ±45 days	Event Driven
Physical assessment								
Informed consent	X							
Demographics	X							
Medical history	X							
Physical exam (including height and weight)	X			X	X	X	X	
STS risk score	X							
EuroSCORE II	X							
SYNTAX score [1]	X							
Concomitant Medications	X			X	X	X	X	X[10]
Adverse event assessment		X	X	X	X	X	X	X
NIHSS [2]	X			X	X	X		X
mRS [2]	X				X	X		X
Index Procedure		X						
Additional Cardiac Interventions								X
Hospitalizations			X					X
Laboratory measurements								
WBC, Hgb, Platelet Count	X		X	X	X	X		
Serum chemistry [3]	X		X	X	X	X		
NT-ProBNP[4]	X				X	X		
Pregnancy test [5]	X							
Non-Invasive tests								
Vital signs	X		X	X	X	X	X	
12-Lead ECG/EKG	X		X	X	X	X	X[7]	
Echocardiogram (TTE) [6]	X		X		X	X	X	X
Pulmonary Function Test (PFT)[8]	X							
Functional Assessments								
NYHA classification	X			X	X	X	X	
CCS angina	X							
6 min walk test	X				X	X		
Frailty index	X							
Quality-of-Life Assessments								
KCCQ	X				X	X	X	
SF-12	X				X	X	X	
QOR-15 scale (Quality of recovery)	X[12]			X	X	X		
PHQ-9 scale (Depression score)	X				X	X	X	
Invasive tests								
3D Cardiac Contrast CT[9]	X					X[10]	X[10]	X[10]
Iliofemoral CT Angiography[9]	X							
Invasive or CT coronary Angiography[9]	X							
Supra-aortic angiogram or TEE (if performed)		X						
Final eligibility review								
Patient Selection Committee	X							
Randomization or assignment to registry	X							
Complete Case Report Forms (CRFs)	X	X	X	X	X	X	X	X

1. In the presence of coronary stenosis where coronary revascularization is deemed necessary.
2. NIHSS and mRS will be collected for all patients at screening/baseline as well as at the specified timepoints. In addition, during follow-up, NIHSS and mRS will be collected at the time of stroke and 30–90 days post-stroke only for patients who develop a new stroke during the trial.
3. Comprehensive metabolic panel (including but not limited to Albumin, total bilirubin, calcium, creatinine, glucose, potassium, AST, ALT, sodium, and eGFR).
4. If the site does not have the capability to collect an NT-proBNP lab, a BNP lab can be collected instead.
5. Serum pregnancy test (only for women of childbearing potential).
6. Echocardiography can be done at any time post procedure before discharge
7. A 12-Lead ECG at 2-10 year follow-up will only be collected if done per standard of care.
8. Only for patients with history of severe lung disease.
9. A 3D cardiac imaging or Coronary Angiogram done within 1 year of the patient selection committee date can be used for screening. If a TEE or a cardiac MRI are available per standard of care within 6 month of the patient selection committee date, the images will be collected for the study.
10. 3D Cardiac Contrast CT will be performed following SOC as per ACC/AHA guidelines.
11. Selected medications.
12. It will be conducted at time of pre-procedure evaluation.

2.0 INTRODUCTION

2.1 STUDY RATIONALE

Bicuspid aortic valve (BAV) is a congenital heart condition characterized by the presence of two, rather than the typical three, cusps in the aortic valve. This structural anomaly is the most common congenital heart defect, affecting approximately 1-2% of the population[2]. The condition can lead to various complications, including aortic stenosis (narrowing of the valve opening), aortic regurgitation (leaking of the valve), and an increased risk of aortic aneurysm. The most common associated pathology is aortic stenosis (AS), which if untreated leads to heart failure and death. Recently, there have been comparable clinical outcomes from randomized trials of transcatheter aortic valve replacement (TAVR) vs Surgical Aortic Valve Replacement (SAVR) in low-risk surgical cohorts with symptomatic AS [3].

However, despite TAVR devices being approved in both tricuspid aortic valves (TAV) and BAV anatomy, these trials have excluded patients with BAV anatomy. Small industry sponsored observational studies have included TAVR in BAV anatomy with favorable outcomes but have treated a carefully selected small minority of BAV patients[4,5] and excluded severely calcified anatomy, which is often seen in clinical practice. Propensity matched analyses of TAVR in BAV and TAV anatomy from national registries have shown a gross under-representation of BAV anatomy, indicating clear selection biases, with highly variable outcomes [6-8]. Importantly, BAV anatomy constitutes at least one third of the population presenting for surgery with AS and is more common in younger patients. Even experienced heart teams encounter enormous difficulties in deciding how to best treat BAV. Currently this decision is often arbitrary, and the lack of guidance for physicians has resulted in complications in some patients with **unfavorable anatomy who may inappropriately receive TAVR** and the **unnecessary dismissal of a potentially less invasive transcatheter approach** in others who are directed to SAVR with little or no discussion regarding therapeutic options. This is, in part, due to limited structured evidence available to inform decision making.

2.2 BACKGROUND

Transcatheter Aortic Valve Replacement (TAVR), also known as Transcatheter Aortic Valve Implantation (TAVI), is a minimally invasive transcatheter procedure used to treat aortic valve disease[9]. During a TAVR procedure, a collapsible artificial valve is typically delivered to the heart through a catheter, which is often inserted through a blood vessel in the leg (transfemoral approach) or, less commonly, through other access points. The new valve is then positioned within the diseased aortic valve and deployed, pushing aside the native valve leaflets and taking over its function.

Surgical Aortic Valve Replacement SAVR is a traditional and open-heart surgical procedure used to treat aortic valve disease[10]. SAVR involves a sternotomy (an incision through the breastbone) and the use of a heart-lung machine to temporarily take over the heart's pumping function. During SAVR, the surgeon removes the diseased or damaged aortic valve and replaces it with a prosthetic valve, which can be biological (made from animal or human tissues), or, if the patients are younger, mechanical (made of artificial materials)[11]. Due to a lack of anatomical information, with no direct comparison to SAVR outcomes, national registries have fallen short in providing the critical guidance desperately needed for physicians and their patients in directing the ideal therapy for specific BAV anatomies. Indeed, one expert commentator recently lamented: “in retrospect, an opportunity was missed when the FDA approved TAVR in patients with BAV without requiring prospective randomized data for TAVR versus SAVR”[12]. Indeed, in the **2020 ACC/AHA Guideline for the Management of Patients With Valvular Heart Disease,** while TAVR in TAV anatomy in patients >65 years old carried a class 1 (strong) recommendation, TAVR in BAV anatomy carried a **class 2b (weak) recommendation** (usefulness/effectiveness is unknown/unclear/uncertain or not well established), emphasizing the clear knowledge gap[13]. Moreover, there is a scarcity of research data available in BAV for women and ethnic minorities.

2.3 RISK/BENEFIT ASSESSMENT

2.3.1 *Known Potential Risks*

TAVR and SAVR are standard of care therapies that may be associated with serious complications including death and stroke. Although TAVR lacks definitive data in BAV, in suitably selected patients, this approach trial is not thought to confer added risk.

There are potential risks associated with TAVR or SAVR. The devices in this study are commercially approved devices and there are risks related to the overall procedures (complications associated with standard cardiac catheterization, balloon valvuloplasty, local and/or general anesthesia); a list of these, as well as specific potential risks associated with commercially approved TAVR or SAVR will be presented in the clinical informed consent as per each site's local policy. Based on prior low risk trials comparing TAVR and SAVR, these will be stated in the study's informed consent but not limited to the following post-procedural complications:

Death, stroke/TIA, device malpositioning (including embolization and migration), paravalvular leak, cardiovascular injury (including aortic root injury, aortic dissection, valvular or myocardial injury, ventricular perforation), coronary obstruction, myocardial infarction, acute kidney injury, bleeding, vascular complications, access site infection and arrhythmia including atrial fibrillation and need for permanent pacemaker.

When the two procedures' risks are compared, large clinical trials concluded that in TAVR relative to SAVR there is:
A reduced absolute frequency of major bleeding, atrial Fibrillation, acute kidney injury and procedural recovery time; an increased frequency of vascular complications and need for permanent pacemaker; a similar or lower frequency of death and stroke.

Later complications that can occur include clinical or subclinical valve thrombosis, bioprosthetic valve failure, valve reintervention, valve or heart-failure related hospitalization.

Data based on: Mack MJ, Leon MB, Thourani VH, et al. Transcatheter aortic-valve replacement with a balloon-expandable valve in low-risk patients. N Engl J Med 2019;380:1695-705. DOI: 10.1056/NEJMoa1814052;

2.3.2 *Known Potential Benefits*

Research patients will not have any direct benefits as a result of participation. The indirect benefit is knowledge gained about the comparative effectiveness of TAVR and SAVR in BAV. In addition, the study will provide more insight into quality of life, and for outcomes in women and ethnic minorities, for which there currently is scarce research data available.

2.3.3 *Assessment of Potential Risks and Benefits*

Efforts will be made to minimize risks through site/investigator selection and management. First, site and investigator selection criteria are established to ensure that the study personnel and their institutions are qualified to screen, perform and manage the study procedures as well as support the associated requirements for research. Second, the trial management structure is designed to provide disciplined oversight of the trial activities including close monitoring of site and personnel performance and also support opportunities for investigators and study personnel to share best practices through investigator meetings, ongoing education and case reviews.

3 OBJECTIVES AND ENDPOINTS

For purposes of registration and reporting to ClinicalTrials.gov, the terms Objectives and Endpoints as used in this template align with the terms Primary Purpose and Outcome Measures in ClinicalTrials.gov, respectively.

OBJECTIVES	ENDPOINTS	JUSTIFICATION FOR ENDPOINTS
Primary		
To compare the safety and effectiveness of TAVR vs SAVR for the treatment of severe AS in patients with BAV.	**A hierarchical composite (assessed by Win ratio at latest available follow-up) of:** **(1) death,** **(2) disabling stroke,** **(3) non-disabling stroke,** **(4) valve reintervention,** **(5) rehospitalization†,** **(6) unfavorable KCCQ (VARC-3*)** †valve or procedure related and including heart failure but excluding valve reintervention (CEC adjudicated)] *<45 or a decrease of >10 from baseline as per VARC-3).	The endpoint includes in decreasing hierarchical fashion of importance, key patient-centered endpoints.
Key Secondary		
To compare differences in change in quality of life over time for TAVR vs SAVR in surviving patients.	Death / time-averaged KCCQ	The time averaged KCCQ evaluates the totality of quality of life while patients are alive, providing a quantifiable metric of a “life well lived”.
Secondary		
To compare individual clinical components of hierarchical composite primary endpoint as well as other important clinical comparators for TAVR vs SAVR.	Time-to-first event (death, cardiovascular death, all stroke, disabling stroke, rehospitalization, death/stroke/rehospitalization), CV rehospitalization days, time to dissection and time to need for aortic surgery	Individual components of the composite hierarchical endpoint provide understanding of the contribution of them to the primary comparison.
To compare quality of life outcomes between TAVR and SAVR	Time-averaged KCCQ, KCCQ over time, SF-12, PHQ-9	These metrics provide further granularity for the quality-of-life outcomes.
To compare functional outcomes between TAVR and SAVR	NYHA, 6-min walk test, QOR-15 scale	These endpoints provide quantifiable metrics for functional status.

To compare clinically important imaging-related outcomes between TAVR and SAVR	Paravalvular leak severity, Bioprosthetic valve failure (BVF)	These endpoints provide important prognostically relevant metrics
Safety		
To compare additional safety related outcomes between TAVR and SAVR	Valve-related mortality, Myocardial infarction, Coronary obstruction, Major bleeding (VARC-3), Major vascular complication (VARC-3), Cardiac structural complication (major), Need for open heart surgery, Need for permanent pacemaker, Atrial fibrillation/ atrial flutter, Device malpositioning (including embolization and migration), Acute Kidney Injury stage 3-4, Endocarditis (valve-related), Clinically significant valve thrombosis	These endpoints provide additional comparisons of the frequency of adverse events for the respective procedures
Exploratory		
To compare other imaging outcomes between TAVR and SAVR	Prosthesis-patient mismatch, Ascending aorta dimension > 50 mm, change in ascending aorta dimension	These endpoints provide important metrics on device hemodynamic function, durability and disease progression.

Endpoint Definitions

General principles

Unless otherwise specified, clinical endpoints will be **adjudicated by a Clinical Events Committee (CEC)**. Imaging endpoints will be determined by the **CT Core Laboratory** (Cedars-Sinai Medical Center) and **Echocardiography Core Laboratory** (Cedars-Sinai Medical Center in collaboration with Université Laval in Québec) according to prespecified measurement procedures and charters. Endpoints and timepoints are summarized in Table 1.

Primary Endpoint Components (Hierarchical Composite)

1) All-cause death

Death from any cause occurring after randomization. Date of death will be determined from source documentation and/or vital status ascertainment processes.

2/3) Stroke (disabling and non-disabling)

Stroke is defined as an acute episode of focal or global neurological dysfunction caused by ischemic or hemorrhagic injury to the brain, spinal cord, or retina, with confirmation by at least one of: (a) neurology/neurosurgical specialist assessment; (b) neuroimaging (CT/MRI); or (c) clinical presentation alone when other causes are excluded.

Disabling stroke: mRS **≥2** at ~90 days (or last available evaluable visit if 90-day assessment is not available) **and** an increase of ≥1 mRS category from pre-stroke baseline.

Non-disabling stroke: mRS **<2** at ~90 days (or last available evaluable visit) **or** no increase of ≥1 mRS category from pre-stroke baseline.

Assessment timing: NIHSS and mRS will be collected for all patients at screening/baseline as well as at the specified timepoints (table 1). In addition, in the event of a stroke during follow-up, NIHSS and mRS will be collected at the time of stroke and 30–90 days post-stroke for patients who develop a new stroke during the trial. NIHSS and mRS reassessment should be performed by a neurologist or a certified assessor.

4) Valve reintervention

This is defined as any intervention that repairs, alters, or replaces the treated aortic valve after completion of the index valve-implant procedure, including: balloon aortic valvuloplasty, surgical AVR, valve-in-valve, and paravalvular leak closure (or other valve-directed reintervention).

5) Rehospitalization (valve-, procedure-, or HF-related; excludes valve reintervention)

This is defined as any **inpatient hospitalization** that is adjudicated as **valve-related, procedure-related, or heart failure–related**, **excluding** admissions where the primary qualifying event is **valve reintervention** (captured separately in the hierarchy). Heart failure rehospitalization is defined according to the VARC-3 definition: new or worsening heart failure be the predominant reason for a hospital stay ≥ 24 h on the basis of symptoms and signs of heart failure with confirmation by diagnostic tests and necessitating treatment using intravenous or mechanical heart failure therapies. Includes primary (cardiac related) and secondary (non-cardiac related.

6) Unfavorable KCCQ (VARC-3)

Unfavorable KCCQ is defined as **KCCQ <45** or a **decrease >10 points from baseline**, consistent with the protocol's VARC-3 definition.

Key Secondary Endpoint

Hierarchical composite of (1) death; (2) KCCQ score (time-averaged)

This endpoint is a hierarchical composite of **death and KCCQ score**. KCCQ will be assessed as a **time-averaged measure over follow-up** (time-weighted) as the area under the KCCQ-time curve using a step-function approximation, where each assessment represents the interval until the midpoint of the subsequent assessment. Therefore, the weighting factors (w) are as follows:

1-month assessment = weight of 6.5 (representing KCCQ between 0 and 6.5 months);
12-month assessment = weight of 11.5 (representing KCCQ between 6.5 and 18 months),
24-month assessment = weight of 12 (representing KCCQ between 18 months and 30 months),
36-month assessment = weight of 12 (representing KCCQ between 30 months and 42 months),
48-month assessment = weight of 12 (representing KCCQ between 42 months and 54 months),
60-month assessment = weight of 12 (representing KCCQ between 54 months and 66 months),
72-month assessment = weight of 12 (representing KCCQ between 66 months and 78 months),
84-month assessment = weight of 12 (representing KCCQ between 78 months and 90 months),
96-month assessment = weight of 12 (representing KCCQ between 90 months and 102 months),
108-month assessment = weight of 12 (representing KCCQ between 102 months and 114 months),
120-month assessment = weight of 12 (representing KCCQ between 114 months and 126 months)

Secondary Endpoints (Patient-centered and Clinical)

Patient-reported outcomes / functional outcomes

These are assessed as shown in Table 1 :

- **Time-averaged KCCQ**: time-weighted mean of KCCQ overall summary score across available follow-up timepoints.
- **KCCQ status (serial)**: KCCQ overall summary score at discharge and prespecified follow-up visits.
- **SF-12**: Physical and Mental Component Summary scores at prespecified visits.
- **NYHA class**: NYHA I–IV at prespecified visits.
- **6-minute walk test**: distance (meters) at prespecified visits.
- **PHQ-9**: depression score (0–27) at prespecified visits.

- **Time-to-return to baseline (QOR-15)**: time from index procedure to first follow-up at which QOR-15 returns to (or exceeds) the patient's pre-procedure baseline (operational rules and handling of missingness specified in SAP).

Additional clinical endpoints

- **Death (time-to-event)**, cardiovascular death (time-to-event)
- **All stroke**, **disabling stroke** (time-to-first event).
- **Rehospitalization** (time-to-first event), as defined above.
- **Composite of death/stroke/rehospitalization**: time to first occurrence of any of death, any stroke, or rehospitalization (time-to-first event), as defined above.
- **Aortic dissection (time-to-first-event)**: imaging-, operative-, or autopsy-confirmed aortic dissection after randomization.
- **Need for surgery of the aorta (time-to-first-event)**: any open or endovascular surgical procedure to repair/replace the ascending aorta/aortic root after randomization (including concomitant or follow-up procedures).
- **CV rehospitalization days**: cumulative number of inpatient hospital days for cardiovascular causes over follow-up (CEC adjudication rules and counting conventions will be specified in the SAP and CEC charter).

Secondary Imaging Endpoints

Echocardiography Core Lab (Cedars-Sinai Medical Center in collaboration with Université Laval in Québec)

- **Bioprosthetic valve failure (BVF)**: time-to-first BVF event, determined by Echo Core Lab using prespecified criteria in the Core Lab charter and SAP (aligned to contemporary consensus definitions).
- **Paravalvular leak (PVL) severity**: graded by Echo Core Lab per standardized criteria (none/trace, mild, moderate, severe) at prespecified visits.

Safety Endpoints

- Valve-related mortality (time-to-event)
- **Need for open heart surgery;** subsequent need for open heart surgery for any reason (following index procedure).
- **Myocardial infarction :** Using CK-MB preferred if normal baseline: peak CK-MB within 48h ≥10× ULN OR ≥5× ULN plus ≥1 supporting criterion (new pathologic Q-waves, new persistent LBBB, flow-limiting angiographic complication, or substantial new loss of viable myocardium on imaging). Alternative troponin thresholds provided if CK-MB not measured.
- **Coronary obstruction:** New partial/complete coronary ostial/epicardial obstruction by prosthesis/native leaflets/embolized material/external compression/instrumentation sequelae, during or after procedure, with objective ischemia or symptoms; classify under cardiac structural complications per severity.
- **Major or life-threatening bleeding (VARC-3);** Bleeding of type 2 or greater (appendix B).
- **Major vascular complication (VARC-3); (time-to-event):** Includes aortic dissection/rupture; vascular injury (arterial/venous) or compartment syndrome resulting in death, BARC/VARC bleeding ≥Type 2, limb/visceral ischemia, or irreversible neurologic impairment; distal embolization causing death/amputation/ischemia/irreversible damage; unplanned endovascular/surgical intervention with those consequences; or closure device failure with those consequences.
- **Cardiac structural complication (major):** Cardiac structure injury/perforation/compromise causing death, VARC bleeding ≥Type 2, hemodynamic compromise/tamponade, or requiring unplanned intervention; major pericardial effusion; coronary obstruction causing death/hemodynamic compromise/MI/unplanned coronary intervention; or coronary access difficulty for needed coronary procedure with major consequences.
- **New atrial fibrillation/ atrial flutter:** AF/flutter not present at baseline, with ECG characteristics and lasting long enough for a 12-lead ECG or ≥30s rhythm strip. Timing: periprocedural ≤30d vs late/spontaneous >30d.

- **Need for permanent pacemaker:** Report type, timing (days from index procedure), and indication (e.g., AV block, sick sinus syndrome). Exclude patients with pre-existing pacemaker from denominator for "new PPM" rate.
- **Device malpositioning (including ectopic valve deployment, embolization and migration); Ectopic valve deployment**: Irretrievable deployment of a valve prosthesis at a site other than the intended position because of valve embolization or inability to deliver the prosthesis to the desired location; Valve **embolization**: The valve prosthesis moves either upward or downward after final deployment such that it loses contact with the aortic annulus; Valve **migration**: After initial correct positioning, the valve prosthesis moves upward or downward, within the aortic annulus from its initial position, without valve embolization.
- **Acute Kidney Injury stage 3-4:** Creatinine increase >300% (>3.0×) within 7 days vs baseline OR creatinine ≥4.0 mg/dL with acute increase ≥0.5 mg/dL or new temporary or permanent renal replacement therapy (report separately; exclude chronic dialysis patients from denominator).
- **Endocarditis (valve-related):** Meets ≥1 Duke criteria; abscess/pus/vegetation confirmed at reoperation by histology/microbiology; or abscess/pus/vegetation confirmed on autopsy.
- **Clinically significant valve thrombosis**: Valve thrombosis associated with symptoms or clinical sequelae (e.g., thromboembolism or worsening valve function) and leaflet thrombosis findings, or (if asymptomatic) hemodynamic valve deterioration meeting Stage 2 or 3 criteria with confirmatory imaging evidence of leaflet thrombosis (site reported).

Exploratory Imaging Endpoints

Echo Core Lab (Cedars-Sinai Medical Center in collaboration with Université Laval in Québec)

- **Prosthesis-patient mismatch severity:** Aortic PPM is defined by indexed effective orifice area (iEOA) ≤0.85 cm^2/m^2; severe PPM is iEOA ≤0.65 cm^2/m^2. In obese patients (BMI ≥30 kg/m^2), use lower cutoffs: PPM iEOA ≤0.70 cm^2/m^2 and severe PPM iEOA ≤0.55 cm^2/m^2. (PPM is classified as nonstructural BVD/NSVD and generally is not staged as BVD Stage 1–3.)

CT Core Lab

- **Subclinical valve thrombosis (time-to-first event**): Imaging evidence of leaflet thrombosis (e.g., hypoattenuated leaflet thickening and/or reduced leaflet motion) with absent or mild hemodynamic changes and no symptoms or clinical sequelae.
- **Ascending aorta dimension >50 mm**: maximum ascending aorta diameter measured by CT Core Lab; endpoint met if >50 mm at any follow-up CT.
- **Change in ascending aorta dimension (cm/year)**: annualized change in maximum ascending aorta diameter from baseline to follow-up CT by CT Core Lab.

4 STUDY DESIGN

4.1 OVERALL DESIGN

- The study is a multicenter, randomized superiority trial of **standard of care** therapies for **severe aortic stenosis** (AS) in patients with a bicuspid aortic valve (BAV). Namely, the therapies to which patients will be randomized will be **transcatheter** aortic valve replacement (TAVR) or **surgical** aortic valve replacement (SAVR), in patients deemed clinically suitable for both **following patient selection committee review**.
- The null hypothesis is that there is **no difference between TAVR and SAVR** in relation to the hierarchical primary composite endpoint. The alternative hypothesis is that **TAVR differs from SAVR**. The test for superiority is two-sided, such that SAVR or TAVR superiority could be demonstrated.
- Patients deemed suitable for randomization at the individual level by a local heart team will be **affirmed by the patient selection committee**.
- For the patient to be suitable for randomization, there must be relative equipoise, defined as follows: the TAVR and SAVR risk strata, as adjudicated by the committee, must not deviate by more than one risk

stratum. For instance, a low SAVR risk patient cannot be randomized if the TAVR risk is deemed high, and vice versa. However, an intermediate SAVR risk patient could be randomized if the TAVR risk is low or high and vice versa.

- **Representativeness of Patient Population.** From the outset, we will require that at least 35% of enrolled patients are women and at least 20% are from racial or ethnic minority groups. We have chosen initial sites that already treat a high proportion of these patients, and we are partnering with Heart Valve Voice and Heart Valve Surgery (patient advocacy organizations) to provide culturally tailored outreach material, multilingual e-consent, and community-oriented communication materials that will facilitate targeted recruitment. Enrollment metrics for sex and race will be periodically reviewed. If any site drifts more than five percentage points below either target for 3 consecutive months, the study team will deploy additional recruitment tools (e.g., transportation vouchers) and, if necessary, activate "reserve" sites whose historical case-mix exceeds the diversity thresholds. These steps will ensure that all key demographic subgroups reach the numbers required for ≥ 80 percent power in the planned interaction tests. Many per protocol questionnaires such as KCCQ are available in multiple languages and which will be used in the patients native tongue as necessary; some patient centered questionnaires (such as QOR) have not been translated or validated for languages other than English, in which case an interpreter will be used, if available at the treating center.

- Patients will be randomized 1:1 to TAVR or SAVR using permuted block randomization with varying block size. We will require **≥35% to be female**. To **ensure a balance between treatment arms**, randomization will be **stratified by (1) sex** and (2) low or intermediate/high SAVR (clinical) risk, (3) planned TAVR type (in the event of randomization to TAVR). Randomization will be adaptive to maintain balance in study arm allocation within each site. This study is open-label; patients, treating clinicians, and site staff will not be blinded to treatment assignment.
- All randomized patients will be assessed peri- and post-procedure, at discharge, 30 days, 1 year, and then annually for up to 10 years post-procedure. The visits at 30 days and 1 yr are to be in-person at investigational site. Visits at years 2 -10 can be virtual or in-person at investigational site. Labs, ECG and Echo may be done locally.
- Patients deemed **unsuitable for randomization** but who **meet inclusion criteria** and ultimately undergo SAVR or TAVR are of interest and will be entered into the SAVR and TAVR registry cohorts. Operational details, follow-up procedures, and analytic plans for these parallel SAVR and TAVR registry cohorts are outside the scope of the present randomized trial protocol, as the registries will be supported through separate funding and described in separate registry-specific documents.

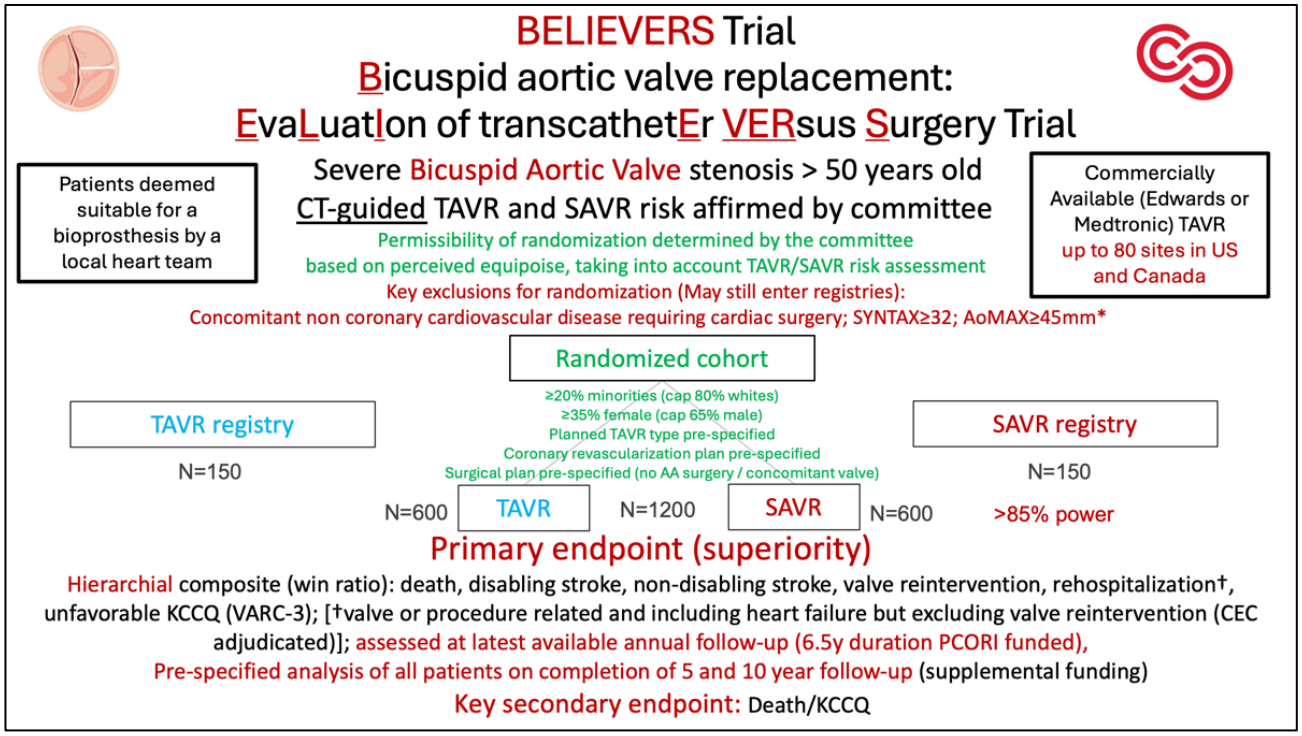
4.2 SCIENTIFIC RATIONALE FOR STUDY DESIGN

While TAVR has an extensive randomized evidence base in severe aortic stenosis, the pivotal trials that established its use across risk categories systematically excluded patients with bicuspid anatomy, leaving contemporary treatment decisions in BAV to be guided largely by observational data, selective registries, and an underpowered randomized trial, despite BAV being common and disproportionately affecting younger patients. In this setting, A pragmatic randomized comparison of two standard-of-care options (TAVR vs SAVR) is the best way to provide unbiased comparative effectiveness evidence. But BAV anatomy varies widely, and TAVR risk may differ from SAVR risk within the same "surgical risk" group. For this reason, the trial uses **imaging-guided selection** and prespecified risk strata to ensure clinical equipoise (TAVR and SAVR strata differ by no more than one level) and to avoid randomizing patients with clearly unfavorable anatomy for one approach. The primary endpoint uses a hierarchical win ratio because it incorporates both the timing and occurrence of events and uses all available follow-up rather than a single time point. This is especially important in younger BAV patients, where durability and later reintervention matter. The composite therefore includes valve reintervention and unfavorable KCCQ to capture both long-term outcomes and patient-centered health status.

4.3 END OF STUDY DEFINITION

A patient is considered to have completed participation in the study if he or she has completed all phases of the study including the last visit or the last scheduled procedure shown in the Schedule of Activities (SoA), Section 1.3, or has withdrawn from the study. The determination of loss to follow-up will not be made until the end of the study. The end of the study is defined as 10 years (+ or - 45 days) following the randomization of the 1200th patient.

5 STUDY POPULATION



The study population consists of patients with severe symptomatic AS presenting for TAVR or SAVR under standard of care treatment. Enrollment of patients in the randomized cohort of the study will be contingent on the Patient Selection Committee (PSC) review of the suitability for randomization, including an evaluation of operative (SAVR) risk presented by the treating site and an imaging-based evaluation of TAVR risk based on CT Corelab evaluation of uploaded CT data. For clarity, although the PCORI funding is only intended to support patients randomized in the study, all BELIEVERS trial consented patients who meet the broad inclusion criteria, including those deemed unsuitable for randomization but ultimately undergo SAVR or TAVR are of interest and will be entered into the SAVR and TAVR registry cohorts.

5.1 INCLUSION CRITERIA

In order to be eligible to participate in this study, an individual must meet all of the following criteria:

1. 50 years of age or older at time of consent;
2. Severe AS (see section 5.1.1) deemed suitable for a bioprosthesis by a local heart team (unsuitable or patient declined a mechanical valve or Ross procedure, following demonstration of **evidence-based shared decision making with a validated decision-aid(1)**;
3. Gated contrast CT available and suitable for core laboratory analysis;
4. BAV anatomy confirmed by CT core laboratory analysis;

5.1.1 Qualifying criteria for severe AS (site reported)

A. High-gradient severe AS (any one):

- Peak aortic jet velocity (Vmax) ≥ 4.0 m/s, or
- Mean transvalvular gradient ≥ 40 mmHg, or
- Aortic valve area (AVA) ≤ 1.0 cm^2 (or indexed AVA ≤ 0.6 cm^2/m^2), consistent with severe AS.

B. Low-flow, low-gradient severe AS (suspected)

If AVA ≤1.0 cm² but Vmax <4.0 m/s and mean gradient <40 mmHg, severe AS must be confirmed by at least one of the following, per site standard practice and documented in source records:

- Dobutamine stress echocardiography showing severe AS at peak stress (e.g., mean gradient ≥40 mmHg with AVA ≤1.0 cm²), or
- CT aortic valve calcium scoring supportive of severe AS (sex-specific thresholds per local standard), or
- Additional Heart Team-supported evidence consistent with true severe AS (e.g., consistent Doppler findings and clinical presentation).

C. Qualifying echo timing

The qualifying TTE should be performed within 90 days prior to randomization.

5.2 EXCLUSION CRITERIA

An individual who meets any of the following criteria will be excluded from randomization in this study. However, a Patient who fulfills the inclusion criteria but presents with any of the exclusion criteria would be enrolled in the registry (unfunded by PCORI).

1. Recent cardiovascular intervention within 30 days prior to randomization.
2. Presence of an existing TAVR or SAVR device
3. Pregnancy or lactation
4. Extreme or prohibitive TAVR or SAVR risk, adjudicated by the PSC review.
5. Active enrollment in another investigational study
6. Disproportionate TAVR vs SAVR risk, as adjudicated by the patient selection committee
7. Associated aortopathy (AA≥45mm by maximal cross-sectional dimension, as confirmed by CT core laboratory analysis, or AA<45mm but site plan for surgery of the aorta in the event of randomization to surgery)
8. Site plan for treatment of concomitant non-coronary cardiovascular disease in the event of randomization to surgery (for instance, concomitant valve surgery, septal defect or coarctation repair, aorta or root replacement or repair)
9. In the presence of coronary artery disease deemed necessary for revascularization in the event of randomization to SAVR or TAVR, Syntax score ≥ 32 or deemed unsuitable for PCI, or deemed unsuitable for coronary artery bypass grafting (CABG).
10. Plan to use any device other than commercially approved Edwards balloon expandable or Medtronic self-expanding TAVR.
11. Leukopenia (WBC < 3000 cells/µL), anemia (Hgb < 8 g/dL), Thrombocytopenia (Plt < 50,000 cells/µL) on latest available labs within 30 days prior to randomization.
12. Hemodynamic or respiratory instability requiring inotropic support, mechanical ventilation, or mechanical heart assistance within 30 days prior to randomization
13. LVEF < 25% within 90 days prior to randomization.
14. Stroke or transient ischemic attack (TIA) within 90 days prior to randomization
15. Renal insufficiency (eGFR < 30 ml/min per the Cockcroft-Gault formula)
16. Severe lung disease (FEV1 < 50% predicted), unresolved prior to randomization.
17. History of liver disease defined as MELD Score ≥ 10 or Child-Pugh Class B or C.
18. Unable to complete the KCCQ due cognitive impairment or other medical condition.

5.3 SCREEN FAILURES

Screen failures are defined as patients who consent to participate in the clinical trial but are not subsequently randomly assigned to the study intervention or are not included in the registry if not eligible to be randomized. A minimal set of screen failure information is required to ensure transparent reporting of screen failure patients, to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details (demographics, reasons for no enrollment including eligibility criteria) .

Individuals who do not meet the criteria for participation in this trial (screen failure) because of a modifiable exclusion criterion may be rescreened patient

5.4 STRATEGIES FOR RECRUITMENT AND RETENTION

The Clinical Coordinating Center (CCC) will review DCC-generated weekly data reports on screening and enrollment and actively reach out to sites on a regular basis, with emphasis on volume of enrollment but also sex-specific and racial/ethic minority targets for enrollment. A separate detailed recruitment and retention plan will be specified in the manual of procedures (MOP) and site-specific plans will be included in a site-specific standard operating procedure (SOP).

The Data Coordinating Center (DCC) will aid the process of screening and recruitment of eligible patients by issuing weekly data reports on the cadence of screening and enrollment, as well as patient retention. These reports will summarize the number of patients screened and the percent of patients randomized at each site and the reasons for screen failure. Demographic characteristics of screened and randomized patients will be reported to keep track of the cohort characteristics and to encourage enrollment of diverse populations. These reports will inform discussion of strategies to overcome enrollment obstacles unique to each site.

6.0 STUDY INTERVENTION

6.1 STUDY INTERVENTION(S) ADMINISTRATION

6.1.1 *Study Intervention Description*

The study intervention(s) (TAVR vs SAVR) are standard of care procedures performed with FDA-approved commercially available devices. Time between randomization and planned date of intervention should be 2 weeks or less.

6.2 MEASURES TO MINIMIZE BIAS: RANDOMIZATION

Patients will be randomized 1:1 to TAVR or SAVR using a centralized, secure web-based randomization system managed by the Data Coordinating Center, employing permuted blocks with varying block sizes and stratified by: (1) sex and (2) low or intermediate/high SAVR (clinical) risk and (3) planned TAVR type (in the event of randomization to TAVR). This is an open-label study; patients, treating clinicians, and site staff will not be blinded to treatment assignment. Randomization will be adaptive to maintain balance in study arm allocation within each site.

6.2.1 Risk Strata Definitions and Examples

6.2.1.1 Overview

To apply the trial equipoise requirement consistently, each patient will be assigned two independent strata by the **Patient Selection Committee**:

1. **SAVR Clinical Risk Stratum** (operative risk based on clinical factors and STS score), and

2. **TAVR Anatomic/Procedural Risk Stratum** (transcatheter risk based primarily on CT anatomy/access).

Strata are based on objective inputs (e.g., STS-PROM, CT measurements) plus committee judgment. Final classifications are documented in the committee review record.

6.2.1.2 SAVR Clinical Risk Strata

Low SAVR risk: STS-PROM typically **<3%** and no major modifiers expected to materially increase operative risk.

Intermediate SAVR risk: STS-PROM typically **3–8%**, or STS-PROM <3% with **one major modifier**.

High SAVR risk: STS-PROM typically **>8%**, or ≥2 major modifiers, or committee determination of substantially elevated operative risk.

Prohibitive/Extreme SAVR risk (not eligible): STS-PROM typically **≥15%** or SAVR deemed unreasonable/unsafe.

Major SAVR modifiers (examples): severe frailty/limited mobility, oxygen-dependent lung disease, severe pulmonary hypertension, dialysis/advanced CKD, advanced liver disease, hostile chest (redo sternotomy, radiation), porcelain aorta, prior CABG with high re-entry risk, other major organ dysfunction.

6.2.1.3 TAVR Anatomic/Procedural Risk Strata

Low TAVR risk: transfemoral access feasible with acceptable vascular features; anatomy within device ranges; no high-risk coronary/root features; bicuspid morphology/calcification pattern favorable.

Intermediate TAVR risk: feasible transfemoral access with borderline vascular features and/or borderline root/coronary features and/or moderate bicuspid risk features; may require routine mitigation strategies.

High TAVR risk: anatomy/access expected to materially increase major complication or technical failure risk (e.g., high coronary obstruction risk requiring protection strategy, severe bulky/asymmetric raphe/leaflet or LVOT calcification with underexpansion/PVL/annular injury concern, high-risk access).

Prohibitive/Extreme TAVR risk (not eligible): TAVR deemed unreasonable/unsafe due to access/anatomic constraints not amenable to mitigation.

6.2.1.4 Equipoise rule and examples

Patients are eligible for randomization only if **TAVR and SAVR strata differ by no more than one level** and neither approach is **prohibitive**.

- **Allowed:** Low vs Intermediate; Intermediate vs High
- **Not allowed:** Low vs High
- **Not allowed:** Any Prohibitive designation

Examples:

- Low SAVR + Intermediate TAVR → Eligible
- Low SAVR + High TAVR → Not eligible
- High SAVR + Intermediate TAVR → Eligible

- Prohibitive SAVR or Prohibitive TAVR → Not eligible

6.3 PATIENT SELECTION COMMITTEE: ELIGIBILITY ADJUDICATION AND EQUIPOISE DETERMINATION

A centralized PSC will confirm clinical equipoise and adjudicate final eligibility prior to randomization to ensure consistent application of inclusion/exclusion criteria and risk stratification across sites. Details will be specified in the PSC charter and MOP.

6.4 STUDY INTERVENTION COMPLIANCE

Site documentation will be kept and maintained and reviewed in line with the MOP.

7 STUDY INTERVENTION DISCONTINUATION AND PATIENT DISCONTINUATION/WITHDRAWAL

7.1 FAILURE OF PATIENT TO UNDERGO RANDOMIZED TREATMENT ASSIGNMENT

Failure for a patient to undergo the randomized treatment assignment does not mean discontinuation from the study, and remaining study procedures should be completed as indicated by the study protocol. If a clinically significant finding is identified (including but not limited to changes from baseline) after randomization, the investigator or qualified designee will determine if any change in patient management is needed. Any new clinically relevant finding will be reported as an adverse event (AE).

The data to be collected pertaining to this eventuality will include the following: Documentation for reasons for deviation from randomized intervention (including cross over or decision for no intervention).

7.2 PATIENT WITHDRAWAL FROM THE STUDY

Patients are free to withdraw from participation in the study at any time.

An investigator may discontinue or withdraw a patient from the study for the following reasons:

- Significant study intervention non-compliance
- If any clinical adverse event (AE), laboratory abnormality, or other medical condition or situation occurs such that continued participation in the study would not be in the best interest of the patient

The reason for patient discontinuation or withdrawal from the study will be recorded on the Case Report Form (CRF) specified in the MOP.

7.3 LOSS TO FOLLOW-UP

A patient will be considered lost to follow-up (LTF) will be ascertained at the time of the last study visit as per protocol, if the patient survival status cannot be determined and the patient is unable to be contacted by the study site staff.

The following actions must be taken if a patient fails to return to the clinic for a required study visit:

- The site will attempt to contact the patient and reschedule the missed visit within the manual of operations (MOP)- specified time frame and counsel the patient on the importance of maintaining the assigned visit schedule and ascertain if the patient wishes to and/or should continue in the study.
- Before a patient is deemed lost to follow-up, the investigator or designee will make every effort to regain contact with the patient (up to study completion). These contact attempts should be documented in the patient's medical record or study file.

7.4 PARTIAL WITHDRAWAL

To minimize loss of outcome information and preserve the integrity of long-term follow-up, the study team will make best efforts to ascertain vital status for all randomized patients through the end of study follow-up, even if a patient withdraws from in-person visits. Patients may choose to discontinue study visits and/or complete only remote follow-up; however, unless a patient explicitly withdraws consent for any further data collection, the study may continue to collect limited follow-up information including vital status (alive/deceased), date of death (if applicable), and location of care (in hospital or at home).

Vital status ascertainment may include review of the electronic health record and health system administrative data, contact with the patient or a designated proxy/emergency contact, communication with treating clinicians, and review of publicly available sources or applicable mortality databases, consistent with local regulations and IRB approvals. All attempts to contact the patient or proxy and all sources used for vital status determination will be documented. If a patient explicitly withdraws consent for all further data collection, no additional contact will be made and only data collected prior to withdrawal will be retained and analyzed as permitted by applicable regulations and IRB policy.

8 STUDY ASSESSMENTS AND PROCEDURES

8.1 SCREENING/BASELINE

The following screening and baseline assessments should be conducted within 90 days of index procedure, unless otherwise noted. All assessments marked with an asterisk (*) are required prior to the patient selection committee.

- Signed Informed Consent*
- Demographics and Medical History*
- Physical Exam and vital signs*
- STS risk score and EuroSCORE II*
- SYNTAX score only in the presence of coronary artery disease requiring intervention*
- Concomitant Cardiovascular Medications*
- NIH Stroke Scale (NIHSS) and Modified Rankin Scale (mRS)
- Laboratory Test (Complete Blood Count, Comprehensive Metabolic Panel, and NT-proBNP). Sites who do not have the capability to collect an NT-proBNP lab, a BNP lab will be accepted instead *
- Pregnancy test (only for women of childbearing potential)
- Pulmonary Function Test (PFT) only for patients with a history of severe lung disease
- 12-lead ECG*
- Transthoracic Echocardiogram (TTE)*
- NYHA classification and CCS angina*
- 6 min walk test
- Frailty index (ADLs, 5 Meter Walk Test, and Grip Strength)*
- Kansas City Cardiomyopathy Questionnaire (KCCQ)
- SF-12 Questionnaire
- QOR-15 scale (Quality of recovery)
- PHQ-9 scale (Depression score)
- 3D Cardiac contrast CT within 1 year of case review committee date. If a TEE or a cardiac MRI are available per standard of care within 6 months of the patient selection committee date, the images will be collected for the study. *
- Iliofemoral CT Angiography within 1 year of case review committee date*
- Invasive or CT coronary Angiography within 1 year of case review committee date*
- Patient Selection Committee will be scheduled after completion of all of the above assessments marked with an asterisk (*)

8.2 INDEX PROCEDURE (DAY 0)

The following assessments will be collected on the day of index procedure.

- Procedural data
- Adverse event assessment
- Supra-aortic angiogram or TEE (if performed per standard practice)

8.3 POST-PROCEDURE

The following assessments will be collected within 72 hours post index procedure

- Adverse event assessment
- Laboratory tests (Complete Blood Count and Comprehensive Metabolic Panel)
- Vital signs
- 12-Lead ECG
- Transthoracic Echocardiogram (TTE).

8.4 DISCHARGE or 7 DAYS POST-PROCEDURE (whichever is first)

The following assessments will be collected on the day of discharge (or 7 days post index procedure if the patient is not discharged by the 7th day). If the patient is discharged within 72 hours of index procedure, the post-procedure assessment should not be repeated.

- Physical Exam and vital signs
- Concomitant medications
- Adverse event assessment
- NIH Stroke Scale (NIHSS)
- Laboratory Test (Complete Blood Count and Comprehensive Metabolic Panel)
- 12-Lead ECG
- NYHA Classification
- QOR-15 scale (Quality of recovery)

8.5 30 DAY VISIT

The following assessments will be collected at 30 days (+ or – 7 days) from index-procedure.

- Physical Exam and vital signs
- Concomitant medications
- Adverse event assessment
- NIH Stroke Scale (NIHSS) and Modified Rankin Scale (mRS)
- Laboratory Test (Complete Blood Count, Comprehensive Metabolic Panel, and NT-proBNP)
- 12-Lead ECG
- Transthoracic Echocardiogram (TTE)
- NYHA Classification
- 6-Minute Walk Test
- Kansas City Cardiomyopathy Questionnaire (KCCQ)
- SF-12 Questionnaire
- QOR-15 scale (Quality of recovery)
- PHQ-9 scale (Depression score)

8.6 1 YEAR VISIT

The following assessments will be collected at 1 year (+ or – 30 days) from index-procedure.

- Physical Exam and vital signs
- Concomitant medications
- Adverse event assessment
- NIH Stroke Scale (NIHSS) and Modified Rankin Scale (mRS) (only for patients who develop a stroke post-index procedure)
- Laboratory Test (Complete Blood Count, Comprehensive Metabolic Panel, and NT-proBNP)
- 12-Lead ECG
- Transthoracic Echocardiogram (TTE)
- NYHA Classification
- 6-Minute Walk Test
- Kansas City Cardiomyopathy Questionnaire (KCCQ)
- SF-12 Questionnaire
- QOR-15 scale (Quality of recovery)
- PHQ-9 scale (Depression score)

8.7 ANNUAL (2 to 10 YEAR) VISITS

The following assessments will be collected at 2 to 10 years (annually) (+ or – 45 days) from index-procedure.

- Physical Exam and vital signs
- Concomitant medications
- Adverse event assessment, including assessment of re-interventions or re-hospitalizations
- 12-Lead ECG (If available per standard of care)
- Transthoracic Echocardiogram (TTE)
- NYHA Classification
- Kansas City Cardiomyopathy Questionnaire (KCCQ)
- SF-12 Questionnaire
- PHQ-9 scale (Depression score)

8.8 EFFECTIVENESS ASSESSMENTS

The specific timing of procedures/evaluations and timing at each study visit are captured in **Section 1.3, Schedule of Activities (SoA).**

- The majority of these procedures/evaluations will be completed during the study as part of regular standard of clinical care.
- This is except for specified functional and quality of life metrics which are supplemental and specified in section 1.3.

If an individual's medical chart or results of diagnostic tests performed as part of an individual's regular medical care are going to be used for screening or as a part of collection of trial data, Health Insurance Portability and Accountability Act (HIPAA) rules, other relevant federal or state laws, and local institutional requirements will be followed, as applicable. This includes corelab review of deidentified echocardiographic and CT data.

8.9 SAFETY AND OTHER ASSESSMENTS

These are as for the efficacy assessments, and specified in are captured in **Section 1.3, Schedule of Activities** (SoA).

8.10 ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

8.10.1 *Definition of Adverse Events and Reportable Adverse Events for the BELIEVERS trial*

An adverse event (AE) is any untoward medical occurrence associated with the use of an intervention, whether or not considered intervention related. Given this study is comparing commercially approved devices, reportable AEs for the BELIEVERS trial will be **restricted to those AEs (both serious and non-serious) corresponding to the study's primary, secondary and safety endpoints derived directly from site reporting** (table 1); those primary, secondary, safety and exploratory endpoints derived from echocardiography or CT corelabs will be reported directly to the DCC by the respective corelabs.

Other reportable AEs complications that can occur include clinical or subclinical valve thrombosis, bioprosthetic valve failure, valve reintervention, valve or heart-failure related hospitalization. Additional details on events that will require reporting will be specified in the MOP and specific guidance in this regard will be provided by the CCC to the sites on site initiation and to the CEC.

8.10.2 Definition of Serious Adverse Events (SAE)

An adverse event (AE) or suspected adverse reaction is considered serious if, in the view of either the investigator or sponsor, it results in any of the following outcomes:

- Leads to death;
- Leads to a serious deterioration in the health of the study patient that:
  - Results in life-threatening illness or injury;
  - Results in a permanent impairment of a body structure or a body function;
  - Requires inpatient hospitalization or prolongation of existing hospitalization;
  - Results in medical or surgical intervention to prevent permanent impairment to body structure or a body function;
- Led to fetal distress, fetal death or congenital abnormality or birth defect;
- Significant medical event.

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

8.10.3 Classification of an Adverse Event

8.10.3.1 Severity of Event

For adverse events (AEs) not included in the protocol-defined grading system (based on VARC-3), the following guidelines will be used to describe severity.

- **Mild** – Events require minimal or no treatment and do not interfere with the patient's daily activities.
- **Moderate** – Events result in a low level of inconvenience or concern with the therapeutic measures. Moderate events may cause some interference with functioning.
- **Severe** – Events interrupt a patient's usual daily activity and may require systemic drug

therapy or other treatment. Severe events are usually potentially life-threatening or incapacitating. Of note, the term "severe" does not necessarily equate to "serious".

8.10.3.2 Relationship To Study Intervention

All adverse events (AEs) must have their relationship to study intervention assessed by the clinician who examines and evaluates the patient based on temporal relationship and his/her clinical judgment. The level of causality/relatedness will be graded using the categories below, in line with the Academic Research Consortium Steering group followed by the majority of transcatheter device trials (2):

- **Not related:**
  Event is not a plausible consequence of use of the device;
  Temporal relationship is not consistent with device use;
  Event is attributable to another cause;
  No evidence of device deficiency or use error.

- **Possible:**
  Information to assess relationship is not available;
  Evidence is weak but relationship cannot be excluded;
  Alternative causes are also possible.

- **Probable:**
  Relationship with use of device seems relevant;
  Event cannot reasonably be explained by another cause.

- **Definite (causal):**
  Event is associated with a known side effect or complication of device;
  Temporal relationship to use of device;
  Event follows a known response pattern to use of the device;
  Other possible causes have been adequately excluded;
  Event is related to error in use.

8.10.3.3 Expectedness of adverse events

Reportable Adverse Events for the BELIEVERS trial are described in section 8.10.1 above and reiterated below.

Both the site treating the patient and the clinical events committee (CEC) specified in the MOP will be responsible for determining whether an adverse event (AE) is expected or unexpected. An AE will be considered unexpected if the nature, severity, or frequency of the event is not consistent with the risk information previously described for the study intervention. The site and CEC-determined expectedness will both be documented.

For clarity, in this study, the following events **will be** required to be reported to the CCC/CEC:

- Death
- Disabling stroke
- Non-disabling stroke
- Valve reintervention
- Rehospitalization (valve or procedure related and including heart failure but excluding valve

reintervention)
- Rehospitalization (*valve-, procedure-, or HF-related*)
- CV rehospitalization
- Myocardial infarction
- Coronary obstruction
- Cardiovascular Injury including aortic root injury, aortic dissection, valvular or myocardial injury, ventricular perforation
- Need for surgery of the aorta
- Major bleeding (VARC-3)
- Major vascular complication (VARC-3)
- Access Site Infection
- Cardiac structural complication (major)
- Need for open heart surgery
- Arrhythmia including atrial fibrillation/ atrial flutter
- Device malpositioning (including embolization and migration)
- Endocarditis (valve-related)
- Acute Kidney Injury stage 3-4
- Clinically significant valve thrombosis
- Need for permanent pacemaker
- Valve-related mortality.

8.10.4 Time Period and Frequency For Event Assessment And Follow-Up

The occurrence of an adverse event (AE) or serious adverse event (SAE) may come to the attention of study personnel during study visits and interviews of a study patient presenting for medical care, or upon review by a study monitor.

AEs including local and systemic reactions not meeting the criteria for SAEs will be captured on the appropriate case report form (CRF). Information to be collected includes event description, time of onset, clinician's assessment of severity, relationship to study product (assessed only by those with the training and authority to make a diagnosis), and time of resolution/stabilization of the event. All reported AEs occurring while on study must be documented appropriately regardless of relationship. All AEs will be followed to adequate resolution.

Any medical condition that is present at the time that the patient is screened will be considered as baseline and not reported as an AE. However, if the study patient's condition deteriorates at any time during the study, it will be recorded as an AE.

8.10.5 Adverse Event Reporting

All relevant AEs and SAEs (as defined in VARC-3) will be captured from the time of randomization until the study patient's participation has ended (i.e., completion of study or withdrawal of consent), time period as specified above.
Adverse events must be followed until resolution, stabilization, or study completion. The AE and/or SAE should be reported to the sponsor, and CRF Forms completed **as soon as possible but no later than 10 working days of awareness.**

This study uses standard-of-care procedures and FDA-approved, commercially available devices. Therefore, IRB reporting will follow institutional and local IRB requirements for AEs/SAEs, and endpoint clinical events will additionally be captured and adjudicated by the CEC throughout follow-up as specified in the protocol

and MOP.

8.11 STUDY PROCEDURES/ASSESSMENTS

8.11.1 Neurologic Event Identification and Stroke Assessment Pathway

Any suspected new neurologic deficit occurring after randomization (including peri-procedural events) will trigger the following standardized pathway to support consistent diagnosis, disability classification, and CEC adjudication.

1. **Recognition and initial response**
   - If a new focal neurologic deficit, altered mental status, seizure, or visual loss is observed or reported, site staff will initiate the institution's **stroke alert** process and notify the treating team immediately.
   - A focused neurologic exam will be performed as soon as feasible.
2. **Neurologic assessment (NIHSS)**
   - **NIHSS** will be performed at the time stroke is suspected/identified, preferably by a neurologist or a trained/certified assessor.
   - NIHSS timing and score will be documented in the source record.
3. **Neuroimaging and diagnostic work-up**
   - Brain imaging (non-contrast CT and/or MRI) and additional vascular imaging (CTA/MRA) will be obtained per local standard of care and documented.
   - If symptoms resolve rapidly, evaluation should still occur to support classification as stroke vs TIA.
4. **Event classification (Stroke vs TIA vs non-neurologic event)**
   - Events will be classified clinically using protocol endpoint definitions and available imaging.
   - **TIA** is considered when symptoms resolve and there is no imaging evidence of acute infarction, per endpoint definitions.
5. **Disability assessment (mRS)**
   - For confirmed stroke, **mRS** will be assessed at approximately **90 days** post-stroke (acceptable window **30–90 days** if needed), preferably by a neurologist or trained/certified assessor.
   - A pre-stroke baseline mRS (most recent pre-event functional status) will be documented to support disability change assessment.
6. **CEC adjudication packet**
   Sites will submit a standardized stroke packet to the CEC including:
   - admission/discharge summaries, neurology notes, procedure notes (if peri-procedural), NIHSS documentation, mRS assessment documentation, and neuroimaging reports (and images if required by the charter), plus relevant labs and ECG rhythm documentation.
7. **Clinical care**
   This pathway does not supersede clinical care. All diagnostic and treatment decisions remain the responsibility of the treating clinicians.

9 STATISTICAL CONSIDERATIONS

9.1 STATISTICAL HYPOTHESES

The null hypothesis is that there is **no difference between TAVR and SAVR** in relation to the hierarchical primary composite endpoint. The alternative hypothesis is that **TAVR differs from SAVR**. The test for superiority is two-sided, such that SAVR or TAVR superiority could be demonstrated.

Primary Efficacy Endpoint: **A hierarchical composite** of: (1) death, (2) disabling stroke, (3) non-disabling

stroke, (4) valve reintervention, (5) rehospitalization, (6) unfavorable KCCQ (VARC-3).

Secondary Efficacy Endpoint(s): Specified in section 1.1.

9.2 SAMPLE SIZE DETERMINATION

The study sample size has been calculated to achieve 85% power for the hierarchical composite outcome under the expected event rates given in Table 2 below. The expected SAVR event rate of 25.4% is based on 3-year SAVR rates from the PARTNER low risk study(3). This is a conservative approach since most patients will have more than 3 years follow-up and all patient data collected within the 6-year funded study period will be included. Comparisons in the win ratio are based on the most severe event experienced by each patient: we provide the assumed distribution of the most severe component of the primary outcome in the Table which is based on data from PARTNER-3. The assumed TAVR rates are then calculated assuming a relative risk of 0.75 comparing SAVR to TAVR.

Why we chose 25% surgical advantage (RR = 0.75) as a *reasonable estimate*:

- **Evidence spectrum:** randomized data (NOTION-2)(4) suggests a **~70 % benefit for surgery**, but this remains an inconclusive study given a very small sample size (n=100) designed for non-inferiority, but confidence intervals were very wide and spanned 1.0; the large Medicare dataset also suggesting survival advantage with SAVR though retrospective and claims-based. In addition, several administrative or meta-analytic datasets that show anywhere from **neutral to a small TAVR advantage**. Our assumption (25% benefit) sits **midway between clear surgical advantage to a possible slight TAVR edge**, acknowledging residual uncertainty.

- **Clinical plausibility:** Surgery, in removing the native leaflets, eliminates the impact of high TAVR risk anatomy (excessive valve and raphe calcium) yet TAVR, with less invasiveness offers significant putative advantages, reflected in early follow up data from the TAVR vs SAVR trials in tricuspid aortic valve. A **25% composite difference** balances these competing effects.

- **Bottom line:** Published 1-year results range widely from strong surgical benefit to slight TAVR benefit depending on data source and methodology. All involve predominantly older, higher-risk patients. Thus, in the presence of enormous uncertainty, using RR = 0.75 represents a *conservative midpoint* that:

- Reflects the full observed range,

- Incorporates known anatomic/mechanical advantages of SAVR in BAV, and

- Preserves statistical power without over-promising effect size.

Moreover, the use of a win ratio of 1.33 (corresponding to a RR of < 0.75) is consistent with recent uses of the win ratio in cardiovascular trials. Many cardiovascular trials in the last 2 years have used the win ratio and declared a significant benefit of intervention (summarized in a systematic review of trials by Gregson, Pocock and colleagues currently *in press* in the journal *Circulation*). Amongst these studies, in the majority the estimated win ratio was greater than 1.33 (corresponding to a RR of < 0.75)

Table 2: Assumed distribution of the primary outcome used for sample size calculations

Outcome	Assumed SAVR rate	Assumed TAVR rate
Death	5.3%	7.1%
Disabling stroke	1.1%	1.5%
Non-disabling stroke	3.0%	4.0%
Valve re-intervention	1.7%	2.3%
Re-hospitalization	9.3%	12.5%
Unfavorable KCCQ*	5.0%	6.7%
None of the above	74.6%	65.9%

9.3 POPULATIONS FOR ANALYSES

Intention-to-Treat (ITT) Analysis Dataset: All randomized patients analyzed according to their originally assigned treatment group, regardless of whether they actually received the assigned treatment, had treatment cross-over or protocol deviation, were lost to follow-up or partially withdrawn from the study.

As treated (AT) Analysis Dataset: All randomized patients analyzed according to the initial treatment actually received (TAVR or SAVR), irrespective of randomization assignment.

Safety Analysis Dataset: All randomized patients in whom the assigned valve-replacement procedure is initiated. Patients will be analyzed according to the procedure actually received.

9.4 STATISTICAL ANALYSES

9.4.1 General Approach

Under the stated assumptions, we used 10,000 simulated trials to determine that 1020 patients with complete 3-year data achieves 85.3% power for a two-sided Finkelstein-Schoenfeld at a 5% significance level. Simulations randomly generated time-to-event data for each clinical event using an exponential distribution, with the rates for each component tailored so that the distribution of the most severe outcome within each patient followed the distribution given in Table 2. KCCQ outcomes were randomly generated from a binomial distribution. To allow for a small number of crossovers, loss-to-follow up (estimated at around an eighth or 12.5% of patients, in line with PARTNER trials), we propose to recruit a total of **1,200 randomized patients, 600 in each arm**. This sample size yields >95% power for the analysis of the key secondary outcome (a hierarchical composite of death and time-averaged KCCQ score) if SAVR improves the average KCCQ score by 3 points under the assumption that the standard deviation of an individual KCCQ measurement is 20. **Our key secondary outcome** is similar to the primary endpoint of the PCORI-funded RECHARGE study, which will study a hierarchical composite of death and SF-12 quality of life assessment, using the win ratio(5). Such a magnitude of improvement in KCCQ is regarded as clinically meaningful and, in context, is similar to that seen in novel heart failure drugs that have impacted survival and quality of life(6).

9.4.2 Analysis of The Primary Efficacy Endpoint(S)

The primary endpoint is a hierarchical composite of: (1) death within a shared follow-up period by a pair of patients, (2) disabling stroke within a shared follow-up period by a pair of patients, (3) non-disabling stroke within a shared follow-up period by a pair of patients, (4) valve reintervention within a shared follow-up period by a pair of patients, (5) rehospitalization (valve- or procedure-related, including heart failure, excluding valve reintervention within a shared follow-up period by a pair of patients; CEC adjudicated), and (6) unfavorable last available shared by a pair of patients KCCQ (VARC-3 definition: KCCQ <45 or decrease >10 points from baseline). This will be analyzed at latest available annual follow-up.

The primary analysis will use the unadjusted win ratio comparing all possible pairs of patients across treatment arms (one TAVR vs one SAVR), using the Finkelstein–Schoenfeld approach to prioritize more clinically important outcomes. For clinical event components, the pairwise comparison will consider both occurrence and timing of events, using all follow-up time within the PCORI-funded follow-up period that is common to both patients in the pair.

For the KCCQ component (lowest tier), the comparison will be based on whether the latest available KCCQ measurement for both patients (and occurring at least 1-year post-randomization) meets the unfavorable KCCQ definition. The win ratio will be reported with its 95% confidence interval, the p-value from the Finkelstein–Schoenfeld test, and a breakdown of wins/ties/losses at each hierarchical level.

As secondary analysis, the adjusted win ratio by stratification covariates will be performed. Adjustment method will be discussed in more details in the SAP.

9.4.3 Analysis of The Secondary Endpoint(S)

Key secondary endpoint (hierarchical composite of death and time-averaged KCCQ)

The key secondary endpoint is a hierarchical composite of **(1) all-cause death** and **(2) time-averaged KCCQ overall summary score** within a shared follow-up period by a pair of patients, evaluated using the win ratio framework. Pairwise comparisons will prioritize death; among pairs tied on death status, the KCCQ component will be evaluated using the **time-averaged KCCQ overall summary score** over follow-up. Time-averaged KCCQ will be calculated using all available post-baseline KCCQ assessments and weighted by the time between assessments (i.e., a time-weighted average). The win ratio, 95% confidence interval, and p-value will be reported.

Additional secondary endpoints

Secondary endpoints include patient-reported outcomes, functional outcomes, clinical events, and imaging outcomes as prespecified in Table 1. These will be analyzed using methods appropriate to the endpoint type:

1. **Time-to-event endpoints** (e.g., all-cause death, cardiovascular death, any stroke, disabling stroke, rehospitalization, composite clinical endpoints, aortic dissection, need for surgery of the aorta, BVF/SVD): cumulative incidence functions will be plotted considering non-cardiac death as competing risk for cardiac death; all-cause death as competing risk for any stroke, disabling stroke, rehospitalization, recovery based on QOR-15, aortic dissection, need for surgery of the aorta, BVF/SVD, and need of surgery of aorta as competing risk for aortic dissection. Time-to-event models accounting for competing risk and stratification factors will be used. Results will be summarized as hazard ratios or cumulative incidences with 95% confidence intervals.
2. **Binary endpoints** (e.g., presence of moderate/severe PVL at prespecified timepoints, recovery based on QOR-15, ascending aorta dimension >50 mm, NYHA class): Logistic regression models for repeated measures will be fitted with time, as a categorical covariate, treatment and the interaction between treatment and time as fixed effects. Additionally, models will adjusted by the stratification factors. Results will be summarized as odds ratios between study arms with 95% confidence intervals.
3. **Continuous endpoints** (e.g., KCCQ at each follow-up timepoint, SF-12 component scores, 6-minute walk distance, PHQ-9, time-averaged KCCQ): For longitudinal continuous outcomes, linear mixed models will be fitted with baseline outcome value, time as a categorical covariate, study arm and the interaction between treatment and time as fixed effects. Additionally, models will adjusted by the stratification factors. A subject-specific random effect will be included to describe the correlation between measures over time. Estimates will be presented as mean differences between study arms with 95% confidence intervals at prespecified timepoints. For change in ascending aorta dimension, time will be considered as a continuous covariate to estimate mean difference in annualized change

between study arms with 95% confidence interval. For time-averaged KCCQ, linear regression will be fitted with treatment as main covariate adjusted by the stratification factors. Mean difference between study arms will be presented with 95% confidence interval.

4. **Rate/count endpoints** (e.g., cardiovascular rehospitalization days): Negative Binomial model will be fitted with study arm as main covariate adjusted by the stratification factors and offset by days alive and out of hospital. Incidence rate ratio between study arms will be estimated with 95% confidence interval.

9.4.4 Multiplicity and Control of Type I Error

Multiplicity and Control of Type I Error. To control the overall family-wise type I error rate at two-sided $\alpha = 0.05$, hypothesis testing will follow a prespecified gatekeeping (hierarchical) procedure. First, the primary endpoint will be tested at two-sided $\alpha = 0.05$. Only if the primary endpoint is statistically significant will the key secondary endpoint be tested at two-sided $\alpha = 0.05$. Only if both the primary and key secondary endpoints are statistically significant will confirmatory testing proceed to a prespecified family of additional secondary endpoints.

For this family of additional secondary endpoints, multiplicity will be controlled using the Holm step-down procedure at two-sided $\alpha = 0.05$.The set of endpoints included in the Holm family (and any prespecified rules for missing data and estimands) will be fully specified in the Statistical Analysis Plan.

9.4.5 Safety Analyses

AEs will be summarized as the number and percentage of participants experiencing at least one event, overall and by study arm. In addition, exposure-adjusted incidence rates (events per 100 patient-years) will be presented when appropriate to account for differences in exposure duration. For each AE the following will be recorded: seriousness, start date, stop date, severity, relationship, expectedness, and outcome. Adverse events leading to premature discontinuation from the study intervention and serious treatment-emergent AEs will be presented in a listing.

9.4.6 Sub-Group Analyses

We recognize that any overall treatment effect may not apply equally to all patients, so the use of subgroup analyses to explore such potential heterogeneity is of enormous value. Thus, we will pre-define key patient characteristics that will form the basis for subgroup analyses and their associated tests of heterogeneity. We have the relevant statistical expertise on this topic (e.g. Pocock et al, Statistical Controversies in Reporting of Clinical Trials, JACC 2015;66:2648-62(7)). While enquiries into heterogeneity of effects are useful, it is widely known that they have reduced statistical power. For instance, for the primary outcome we have 85% power under the assumption that the relative risk is 0.75. If such an effect truly splits into relative risks of 0.5 and 1.0 respectively in a subgroup analysis (an all-or-nothing interaction) this would be detectable with power slightly less than 60%. We will therefore also perform subgroup analyses of time-averaged KCCQ assuming a standard deviation of 14.5 for which we have adequate power to detect **heterogeneity of treatment effect.**

Sex: We will have 82% power to detect heterogeneity of the treatment effect between men and women (using a test of interaction with 5% significance) if the difference in the effect of time-averaged KCCQ between men and women is 5 units. This power is calculated for the mandated minimum 35% of women, and will be greater if the proportion of women actually recruited is higher.

Age: We will perform subgroup analyses according to age (<65 vs. ≥65 years). If the difference in the effect of TAVR vs. SAVR on time-averaged KCCQ between younger and older patients is 5 units, we will have 85% power to detect heterogeneity of treatment effect at a 5% significance level (alpha), assuming an approximately 50/50 split between age groups.

TAVR risk subgroup analysis: We will perform subgroup analyses according to TAVR risk strata (low vs. intermediate/high). If 25% of patients are considered intermediate/high TAVR risk and the difference in the effect of TAVR vs. SAVR between intermediate/high and low risk patients is 6 units, we will have 87% statistical

power.

SAVR risk subgroup analysis: We will perform subgroup analyses according to SAVR risk strata (low vs. intermediate/high). If 33% of patients are considered intermediate/high SAVR risk and the difference in the effect of TAVR vs. SAVR between intermediate/high and low risk patients is 6 units, we will have 92% statistical power.

The proposed plan was jointly devised with the input of Stuart Pocock's team from the London School of Hygiene & Tropical Medicine, who were responsible for the statistical planning and analysis of the PARTNER trials(8-10).

9.4.7 Exploratory Analyses

Other prespecified **exploratory** subgroups of interest will be **pre-specified planned TAVR type, pre-specified planned coronary revascularization**, presence of **aortopathy** (ascending aorta maximal dimension ≥40 mm). The win ratio comparing TAVR to SAVR will be calculated separately within each subgroup and formal tests of interaction subgroups will be used to ascertain whether the treatment effect differs between subgroups based on a Z-test calculated as the difference between stratified log win ratios. (11). For subgroup analyses using time-averaged KCCQ score, formal statistical tests of interaction will be used to compare whether the treatment effect on time-averaged KCCQ scores (estimated from linear models) varies according to patient characteristics.

9.4.8 Handling of missing data

The extent and pattern of missing data will be summarized by study arm and visit, including reasons for missingness when available.

For the Winratio analysis, participants without KCCQ at least 1-year post-randomization will have their KCCQ comparison considered as non-evaluable/tier, unless a higher-level component has already determined the winner.

For time-to-event endpoints, participants without an event will be right-censored at the last known contact date.

For longitudinal patient-reported and functional outcomes, models fitted by full maximum likelihood will be used, which provide valid inference under a missing-at-random (MAR) assumption conditional on included covariates and observed outcomes. As sensitivity analyses, departures from the MAR assumption will be assessed using delta-adjusted pattern-mixture models. Following multiple imputation under MAR, imputed outcome values occurring after permanent dropout will be systematically shifted by clinically meaningful offsets (δ) to reflect plausible worse (or better) unobserved outcomes. A range of δ values will be examined to evaluate robustness of conclusions.

For time-averaged KCCQ, missing KCCQ measurements will be imputed based on the the mean estimates from a linear mixed model with time as categorical covariate, study arm and the interaction between study arm and time as fixed effects and subject-specific random effects.

10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1 REGULATORY, ETHICAL, AND STUDY OVERSIGHT CONSIDERATIONS

10.1.1 Informed Consent Process

10.1.1.1 Consent/Assent And Other Informational Documents Provided To Patients

Consent forms describing in detail the study intervention, study procedures, and risks are given to the patient and written documentation of informed consent is required prior to starting study intervention. Our study will employ decision aids and clinician training modeled on proven strategies to ensure patients are meaningfully engaged in their care choices. Recognizing the importance of informed decision-making, the study will build upon a suite of educational tools in collaboration with our patient advocacy partners including HeartValveSurgery.com and Heart Valve Voice. These materials will include multilingual videos and infographics explaining TAVR and SAVR procedures, simplified decision aids presenting comparative information on the two interventions, and community outreach materials targeting underrepresented populations, such as rural and minority groups. To ensure accessibility and relevance, these materials will be pilot tested with diverse patient populations before full implementation.

The following consent materials are submitted with this protocol:

- BELIEVERS Trial ICF and HIPAA

10.1.1.2 Consent Procedures And Documentation

Informed consent is a process that is initiated prior to the individual's agreeing to participate in the study and continues throughout the individual's study participation. Consent forms will be Institutional Review Board (IRB)-approved and the patient will be asked to read and review the document. The investigator will explain the research study to the patient and answer any questions that may arise. A verbal explanation will be provided in terms suited to the patient's comprehension of the purposes, procedures, and potential risks of the study and of their rights as research patients.

Patients will have the opportunity to carefully review the written consent form and ask questions prior to signing. The patients should have the opportunity to discuss the study with their family or surrogates or think about it prior to agreeing to participate. The patient will sign the informed consent document prior to any procedures being done specifically for the study. Patients must be informed that participation is voluntary and that they may withdraw from the study at any time, without prejudice. A copy of the informed consent document will be given to the patients for their records. The informed consent process will be conducted and documented in the source document (including the date), and the form signed, before the patient undergoes any study-specific procedures. The rights and welfare of the patients will be protected by emphasizing to them that the quality of their medical care will not be adversely affected if they decline to participate in this study.

10.1.2 Study Discontinuation and Closure

This study may be temporarily suspended or prematurely terminated if there is sufficient reasonable cause. Written notification, documenting the reason for study suspension or termination, will be provided by the suspending or terminating party to study patients, investigator, funding agency and any other authorities specified in the MOP following commencement of the study. If the study is prematurely terminated or suspended, the Principal Investigator (PI) will promptly inform study patients, the Institutional Review Board (IRB), and sponsor and will provide the reason(s) for the termination or suspension. Study patients will be contacted, as applicable, and be informed of changes to study visit schedule.

Circumstances that may warrant termination or suspension include, but are not limited to:

- Determination of unexpected, significant, or unacceptable risk to patients
- Demonstration of efficacy that would warrant stopping
- Insufficient compliance to protocol requirements
- Data that are not sufficiently complete and/or evaluable

- Determination that the primary endpoint has been met
- Determination of futility

Study may resume once concerns about safety, protocol compliance, and data quality are addressed, and satisfy the sponsor, IRB and/or Food and Drug Administration (FDA).

10.1.3 Confidentiality and Privacy

Patient confidentiality and privacy is strictly held in trust by the participating investigators, their staff, and the sponsor(s) and their interventions. This confidentiality is extended to cover testing of biological samples and genetic tests in addition to the clinical information relating to patients. Therefore, the study protocol, documentation, data, and all other information generated will be held in strict confidence. No information concerning the study or the data will be released to any unauthorized third party without prior written approval of the sponsor.

All research activities will be conducted in as private a setting as possible.

The study monitor, other authorized representatives of the sponsor, representatives of the Institutional Review Board (IRB), regulatory agencies or pharmaceutical company supplying study product may inspect all documents and records required to be maintained by the investigator, including but not limited to, medical records (office, clinic, or hospital) and pharmacy records for the patients in this study. The clinical study site will permit access to such records.

The study patient's contact information will be securely stored at each clinical site for internal use during the study. At the end of the study, all records will continue to be kept in a secure location for as long a period as dictated by the reviewing IRB, Institutional policies, or sponsor requirements.

Study patient research data, which is for purposes of statistical analysis and scientific reporting, will be transmitted to and stored at the specified Data Coordinating Center at The Institute of Transformative Clinical Trials at Mount Sinai. This will not include the patient's contact or identifying information. Rather, individual patients and their research data will be identified by a unique study identification number. The study data entry and study management systems used by clinical sites and by the specified Data Coordinating Center research staff will be secured and password protected. At the end of the study, all study databases will be de-identified and archived at the specified Data Coordinating Center.

10.1.4 Future Use of Stored Specimens / Data

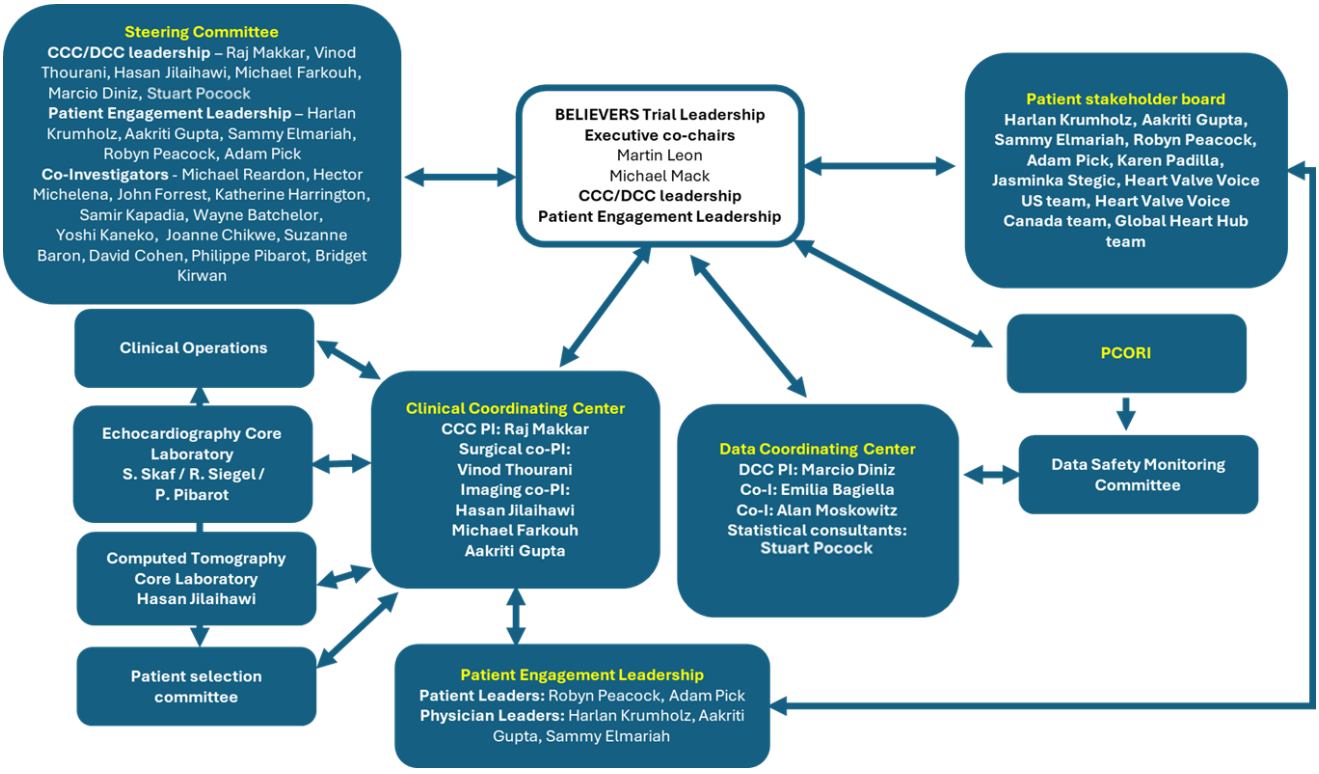
Data collected for this study will be analyzed and stored at the Data Coordinating Center (The Institute of Transformative Clinical Trials at Mount Sinai). After the study is completed, the de-identified, archived data will be transmitted to and stored at a specified Data Repository to be specified in the MOP on commencement of the study, for use by other researchers including those outside of the study. Permission to transmit data to the specified Data Repository will be included in the informed consent.

When the study is completed, access to study data and/or samples will be provided through the specified Repository.

10.1.5 Key Roles and Study Governance

Principal Investigator (CCC)	Principal Investigator (DCC)
Raj Makkar, MD	Marcio Diniz,
Cedars-Sinai Medical Center	Mount Sinai Institute for Transformative Clinical Trials
Los Angeles	New York
Email: raj.makkar@cshs.org	Email: marcio.diniz@mountsinai.org

CSMC is the sponsor for this trial. The organizational structure of trial is shown below:



10.1.6 Patient and Stakeholder Engagement Plan

10.1.6.1 Purpose and guiding principles

BELIEVERS is designed as a patient-centered comparative effectiveness trial of two standard-of-care treatment strategies for bicuspid aortic stenosis (TAVR vs SAVR). Patient and stakeholder engagement will be integrated into study governance and day-to-day trial operations to ensure that (1) the trial addresses outcomes and decisions that matter to patients and caregivers, (2) study materials and workflows are understandable and feasible for diverse patients, (3) recruitment and retention strategies are equitable and effective, and (4) interpretation and dissemination of results are meaningful and usable to end-users. Engagement will be conducted in alignment with PCORI Foundational Expectations, with explicit governance roles, bidirectional communication, ongoing assessment, and capacity-building supports.

10.1.6.2 Engagement governance and roles

A. Engagement Leadership Team (ELT)

The Engagement Leadership Team (ELT) will provide strategic oversight of engagement activities, ensure integration of patient perspectives into Steering Committee decisions, and maintain accountability to PCORI engagement expectations. The ELT will include:

- **Physician engagement co-leads:** Harlan Krumholz, MD; Aakriti Gupta, MD
- **Patient advocate co-leads:** Robyn Peacock; Adam Pick
  The ELT will serve on the trial Steering Committee and will participate in trial decision-making with equal voice in engagement-related deliberations (e.g., patient materials, recruitment/retention strategy, PRO burden, dissemination strategy).

B. Patient and Stakeholder Advisory Board (PASAB)
A standing Patient and Stakeholder Advisory Board (PASAB) will guide engagement activities across all trial phases. PASAB membership will include patients treated with TAVR and SAVR, caregivers, patient advocacy organization representatives, and clinician stakeholders with expertise in patient-centered outcomes and diverse recruitment. Initial PASAB membership includes (not limited to) leaders and advocates referenced in the research plan (e.g., Heart Valve Voice US, HeartValveSurgery.com, Global Heart Hub) and clinician-investigators with expertise in PROs, SDM, and disparities.

PASAB meeting cadence

- Feasibility/start-up phase: every 2 weeks
- Full trial execution: monthly
- Additional ad hoc working sessions as needed for time-sensitive deliverables (e.g., consent revisions, recruitment toolkits, results summaries).

PASAB scope
PASAB will advise and co-produce materials and decisions in the following domains:

1. Patient-facing materials (education, outreach, consent supports)
2. Recruitment/retention strategies, including equity-focused approaches
3. Minimization of patient burden (especially around PROs and long-term follow-up)
4. Patient experience monitoring (barriers, reasons for dropout, site-level issues)
5. Interpretation of interim descriptive study experience metrics (not unblinded outcomes)
6. Dissemination and return-of-results planning

PASAB operating procedures

- PASAB will have a written charter (in the Manual of Procedures) defining membership terms, quorum, decision-making approach (consensus-first; vote if needed), conflict management, and documentation requirements.
- Meetings will be facilitated to ensure equitable participation (e.g., structured agendas, pre-reads in plain language, explicit time for patient/caregiver perspectives, and documented action items).
- Meeting minutes and an “engagement decision log” will be maintained by the Patient Engagement Coordinator and shared with Steering Committee leadership.

C. Patient Engagement Coordinator (PEC)
A dedicated **Patient Engagement Coordinator (PEC)** will operationalize the engagement plan and serve as the primary connector among the ELT, PASAB, trial operations (CCC/DCC), and participating sites. Core responsibilities include:

- Scheduling and facilitating ELT and PASAB meetings; preparing agendas; maintaining minutes/action logs
- Managing the engagement workplan and deliverables calendar (patient materials, training modules, town halls, newsletters, pilot-testing)

- Coordinating translation/accessibility services (interpreters, captioning, multilingual materials)
- Supporting patient partners with onboarding, technology, and compensation processes
- Maintaining documentation of engagement feedback and resulting protocol/MOP adjustments for transparency and auditability

D. Engagement integration with trial governance
Engagement leadership is integrated into the trial's primary governance structures:

- **Steering Committee:** includes engagement leadership representation and receives routine engagement updates
- **Clinical Operations Team:** receives actionable engagement feedback (e.g., patient burden signals, retention barriers, communication gaps) and implements workflow improvements in coordination with the CCC/DCC.

10.1.6.3 Site-level engagement infrastructure: Peer Navigator Program

A. Overview
A Peer Navigator Program will be implemented as a core engagement and retention strategy. Each enrolling site will be given the option to pilot the program at their site. If a site selects to implement the program, at least two patient peer navigators and one caregiver peer navigator (when feasible) will be identified. These volunteers will be supported by the site PEC with additional support from the CCC PEC and overseen by the ELT (patient advocate lead: Robyn Peacock; clinician advocate lead: Aakriti Gupta).

B. Navigator selection
Each site will nominate navigators using the following minimum criteria:

- Lived experience as a patient with SAVR or TAVR for valve disease or a caregiver experience supporting valve replacement
- Ability to communicate empathetically and reliably (phone/video/email)
- Willingness to complete training and adhere to confidentiality and "no medical advice" boundaries
- Preference for navigators who can support diversity goals (language skills; representation of women and underrepresented racial/ethnic groups)

Navigators may be drawn from existing advocacy communities (e.g., Heart Valve Voice; HeartValveSurgery.com; Global Heart Hub) or local site networks.

C. Navigator training and boundaries
All navigators will complete standardized onboarding prior to patient contact:

- Study overview and patient journey (screening → randomization → procedure → follow-up)
- Confidentiality, privacy expectations, and documentation rules
- Communication skills (motivational interviewing basics, active listening, trauma-informed communication)
- Cultural humility and supporting diverse patients
- Clear boundaries: navigators do not provide clinical advice; they support understanding, logistics, and encouragement
- Escalation pathways: clinical questions → site study coordinator; urgent symptoms → clinical care pathways; psychosocial distress → site resources per local policy

Training will be delivered virtually, with refresher sessions quarterly and peer debriefs at least semiannually.

D. Navigator touchpoints (minimum standard)
Navigator contact will be standardized to reduce variability and support retention:

1. Pre-procedure (within 7 days of procedure date): logistics, recovery expectations, family/caregiver planning
2. Early recovery (7–14 days post-discharge): check-in on recovery experience; troubleshoot follow-up barriers
3. 30-day window: support for visit and PRO completion reminder
4. 1-year window: reinforcement of long-term follow-up value; address engagement fatigue
5. Annual years 2–10: brief annual touchpoint focused on retention, PRO completion reminder, and updated contact information

Sites may add touchpoints for patients with higher risk of attrition (e.g., long travel distance, limited support, language barriers).

10.1.6.4 Operationalizing shared decision-making (SDM) and consent support
Because patients with bicuspid AS face complex tradeoffs (invasiveness, recovery, stroke risk, long-term durability, future procedures), BELIEVERS will incorporate SDM supports into the consent workflow, building on the engagement work described in the research plan.

Core SDM operational components

- **Decision aids:** standardized decision tools addressing (a) prosthetic valve choice (bioprosthesis vs alternatives as applicable) and (b) TAVR vs SAVR in bicuspid AS, aligned with site workflow and IRB-approved materials.
- **Comprehension checks:** brief "teach-back" questions incorporated into consent to assess understanding of randomization and follow-up burden.

PASAB will review consent language and SDM materials for clarity, cultural sensitivity, and readability before finalization and will participate in pilot-testing with diverse patients during feasibility/start-up.

10.1.6.5 Communication workflows and deliverables
A. Routine engagement reporting
The CCC PEC will provide a standing engagement update to the Steering Committee at least quarterly (or more frequently during early launch), including:

- Patient-facing materials produced/updated and status (draft → pilot-tested → IRB-approved)
- Recruitment/retention experience themes from navigators and site teams (aggregate)
- Equity metrics and barriers identified (e.g., language, transportation, digital access)
- PRO completion rates and patient-reported burden signals
- Engagement evaluation findings and proposed adjustments

B. Engagement communication channels
To ensure bidirectional communication beyond meetings:

- Quarterly virtual town halls open to patients and caregivers (education + listening session)
- Regular stakeholder newsletters (trial progress updates, what we are learning operationally, reminders about follow-up importance)

- Rapid feedback loop: a dedicated email alias and structured web form (or portal-based messaging) for patients and navigators to report non-urgent barriers; triaged by CCC PEC and routed to the appropriate operational team

10.1.6.6 Equity-focused recruitment and retention support (operational details)
BELIEVERS will operationalize equity goals (≥35% women; ≥20% racial/ethnic minority participation) through engagement-led recruitment tools and monitoring:

- Community-facing materials co-created with PASAB and advocacy partners, including multilingual one-page explainers, short videos, and infographics describing the trial and the two procedures in plain language.
- Multilingual support: translation of key materials and access to interpreter services for consent and follow-up, prioritized based on enrolling site demographics.
- Barrier-reduction supports: where allowable, sites may deploy transportation vouchers, flexible scheduling, and remote follow-up options to reduce participation burden (details specified in MOP/site SOPs).
- Monitoring trigger: enrollment metrics will be reviewed periodically; if a site drifts below targets (or shows worsening trends) for consecutive reporting periods, the CCC/ELT will deploy targeted remediation (additional outreach tools, navigator reinforcement, or activation of additional sites with higher diversity case-mix), consistent with Section 4.1 representativeness language in the protocol.

10.1.6.7 Ongoing evaluation and continuous improvement of engagement
Engagement quality will be assessed and iteratively improved through a structured evaluation plan:

- Quarterly engagement evaluations: brief surveys and/or structured interviews with patient partners, navigators, and site staff assessing what is working, what is burdensome, and what to change.
- Biannual reflective workshops: PASAB-led sessions (facilitated by CCC PEC) to review feedback themes, prioritize actionable improvements, assign owners, and set timelines for changes.
- Real-time feedback mechanisms: town halls, newsletters, and listening sessions will be used to capture emerging issues quickly.
- Transparent adjustment process: all engagement-driven changes (materials, workflows, retention tactics) will be recorded in the engagement decision log and shared back to PASAB and the Steering Committee.

Engagement performance indicators (tracked by DCC/CCC PEC; reviewed by ELT/PASAB)

- PASAB attendance and participation metrics
- Time from identified barrier → implemented fix (cycle time)
- PRO completion rates by timepoint and subgroup (sex; race/ethnicity; language; age)
- Retention rates and reasons for missed visits/LTF (aggregate)
- Site-level navigator contact completion rates (planned vs completed touchpoints)

10.1.6.8 Minimizing patient burden and supporting PRO completion
Given long-term follow-up (annual through 10 years), the engagement plan will explicitly support feasible PRO collection and minimize dropout:

- Remote PRO options: PROs will be offered via the patient portal (preferred), telephone-assisted completion, or paper-based completion where needed.
- Reminder workflow: automated reminders (email/text/portal) will be sent ahead of windows for 30-day, 1-year, and annual assessments; navigators will reinforce completion during touchpoints.

- Accessibility: closed captioning for virtual interactions; interpreter services; technology support for portal access; flexible timing (including evenings/weekends where feasible).
- Escalation for distress: because PHQ-9 is collected, sites will follow local policies for responding to clinically concerning results (e.g., suicidality items), with clear instructions in the MOP and site SOPs.

PASAB will review the patient-facing schedule summary ("BELIEVERS Trial Patient Guide") to ensure it is understandable and realistic.

10.1.6.9 Patient-partner involvement in interpreting and disseminating findings
Patients and advocacy partners will be engaged in:

- Data interpretation sessions: after prespecified milestones (e.g., recruitment completion; early follow-up), patient partners will participate in structured interpretation meetings focused on patient-centered meaning of outcomes and experiences (without compromising blinding or DSMB processes).
- Co-authorship and co-presentation: patient partners will be invited to co-author primary and secondary manuscripts and co-present results at scientific and community meetings.
- Return of results: patient partners will co-create plain-language summaries, short videos, webinars, and FAQs for patients and the broader community via advocacy platforms and trial channels.

10.1.6.10 Documentation, confidentiality, and compensation

- Confidentiality: patient partners and navigators will sign confidentiality agreements and will receive training on handling sensitive information. They will not access protected health information unless specifically authorized under site policies and IRB approvals.
- Compensation: patient partners, navigators, and engagement leaders will be compensated for their time and contributions consistent with the grant budget and institutional policies, with clear processes for timely payment and reimbursement (travel, technology needs, caregiving needs when applicable).
- Documentation: the CCC PEC will maintain a centralized engagement binder (electronic) including charters, rosters, training logs, meeting minutes, decision logs, and engagement evaluation summaries.

10.1.7 Safety Oversight

Safety oversight will be under the direction of a Data and Safety Monitoring Board (DSMB) composed of individuals with the appropriate expertise. Members of the DSMB should be independent from the study conduct and free of conflict of interest, or measures should be in place to minimize perceived conflict of interest. The DSMB will meet at least semiannually to assess safety and efficacy data on each arm of the study. The DSMB will operate under the rules of an approved charter that will be written and reviewed at the organizational meeting of the DSMB. At this time, each data element that the DSMB needs to assess will be clearly defined. The DSMB will provide its input to the study sponsor.

10.1.8 Clinical Monitoring

Clinical site monitoring is conducted to ensure that the rights and well-being of trial patients are protected, that the reported trial data are accurate, complete, and verifiable, and that the conduct of the trial is in compliance with the currently approved protocol/amendment(s), with International Conference on Harmonisation Good Clinical Practice (ICH GCP), and with applicable regulatory requirement(s).

- Monitoring for this study will be performed by Cedars Sinai Office of Research Compliance and Integrity (ORCI).
- Details of clinical site monitoring are documented in a Clinical Monitoring Plan (CMP). The CMP describes in detail who will conduct the monitoring, at what frequency monitoring will be done, at what level of detail monitoring will be performed, and the distribution of monitoring reports.

10.1.9 Quality Assurance and Quality Control

Each clinical site will perform internal quality management of study conduct, data and biological specimen collection, documentation and completion. An individualized quality management plan will be developed to describe a site's quality management.

Quality control (QC) procedures will be implemented beginning with the data entry system and data QC checks that will be run on the database will be generated. Any missing data or data anomalies will be communicated to the site(s) for clarification/resolution.

Following written Standard Operating Procedures (SOPs), the monitors will verify that the clinical trial is conducted and data are generated, collected, documented (recorded), and reported in compliance with the protocol, International Conference on Harmonisation Good Clinical Practice (ICH GCP), and applicable regulatory requirements (e.g., Good Laboratory Practices (GLP), Good Manufacturing Practices (GMP)).

Each participating investigational site will provide direct access to all trial related sites, source data/documents, and reports for the purpose of monitoring and auditing by the sponsor, and inspection by local and regulatory authorities.

10.1.9.1 Data Collection and Management Responsibilities

The Data Coordinating Center (DCC) for this trial will be housed in The Institute for Transformative Clinical Trials at Mount Sinai, with Dr. Marcio Diniz as the lead investigator.

The DCC will provide the technical operational resources for the conduct of the trial, including the development of the trial's EDC system, a confidential document website for investigator communications and clinical site training, and a patient portal to facilitate the remote capture of patient-reported data. A few enhanced security features are available to address the privacy concerns of the patient population. These include multi-factor authentication for secure logins, user device registration, customized firewall rules, and the deployment of a physically isolated EDC system for the exclusive use of this trial. Standard DCC IT security includes Federal Information Processing Standard (FIPS)-certified encryption of all project data on disk and over the network, isolation of EDC servers on an internal network that is separate from the main campus network, periodic system vulnerability scanning, and a network intrusion detection system.

Data collection is the responsibility of the clinical trial staff at the site under the supervision of the site investigator. The investigator is responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported.

All source documents should be completed in a neat, legible manner to ensure accurate interpretation of data.

Hardcopies of the study visit worksheets will be provided for use as source document worksheets for recording data for each patient enrolled in the study. Data recorded in the electronic case report form (eCRF) derived from source documents should be consistent with the data recorded on the source documents.

Clinical data (including adverse events (AEs), concomitant medications, and expected adverse reactions data) and clinical laboratory data will be entered into the specified data capture system, a 21 CFR Part 11-compliant data capture system provided by the Data Coordinating Center. The data system includes password protection and internal quality checks, such as automatic range checks, to identify data that appear inconsistent, incomplete, or inaccurate. Clinical data will be entered directly from the source documents.

10.1.9.2 Study Records Retention

Study documents should be retained for a minimum of 2 years after the last approval of a marketing application in an International Conference on Harmonization (ICH) region and until there are no pending or contemplated marketing applications in an ICH region or until at least 2 years have elapsed since the formal discontinuation of clinical development of the study intervention. These documents should be retained for a longer period, however, if required by local regulations. No records will be destroyed without the written consent of the sponsor, if applicable. It is the responsibility of the sponsor to inform the investigator when these documents no longer need to be retained.

10.1.10 Protocol Deviations

A protocol deviation is any noncompliance with the clinical trial protocol, International Conference on Harmonisation Good Clinical Practice (ICH GCP), or Manual of Procedures (MOP) requirements. The noncompliance may be either on the part of the patient, the investigator, or the study site staff. As a result of deviations, corrective actions are to be developed by the site and implemented promptly.

These practices are consistent with ICH GCP:

- 4.5 Compliance with Protocol, sections 4.5.1, 4.5.2, and 4.5.3
- 5.1 Quality Assurance and Quality Control, section 5.1.1
- 5.20 Noncompliance, sections 5.20.1, and 5.20.2.

It is the responsibility of the site investigator to use continuous vigilance to identify and report deviations within 30 working days of identification of the protocol deviation, or within 30 working days of the scheduled protocol-required activity. Protocol deviations must be sent to the reviewing Institutional Review Board (IRB) per their policies. The site investigator is responsible for knowing and adhering to the reviewing IRB requirements. Further details about the handling of protocol deviations will be included in the MOP (available following commencement of the study).

10.1.11 Publication and Data Sharing Policy

An Executive Committee will be responsible for developing publication procedures and resolving authorship issues.

This study will comply with PCORI's Process for Peer-Review of Primary Research and Public Release of Research Findings, PCORI's Public Access to Journal Articles Presenting Findings from PCORI-Funded Research Policy and the Clinical Trials Registration and Results Information Submission rule. As such, this trial will be registered at ClinicalTrials.gov, and results information from this trial will be submitted to ClinicalTrials.gov.

10.1.12 Conflict of Interest Policy

The independence of this study from any actual or perceived influence, such as by the pharmaceutical

industry, is critical. Therefore, any actual conflict of interest of persons who have a role in the design, conduct, analysis, publication, or any aspect of this trial will be disclosed and managed. Furthermore, persons who have a perceived conflict of interest will be required to have such conflicts managed in a way that is appropriate to their participation in the design and conduct of this trial.

The study leadership has established policies and procedures for all study group members to disclose all conflicts of interest and will establish a mechanism for the management of all reported dualities of interest.

Appendix A. ABBREVIATIONS

AE	Adverse Event
ANCOVA	Analysis of Covariance
CFR	Code of Federal Regulations
CLIA	Clinical Laboratory Improvement Amendments
CMP	Clinical Monitoring Plan
COC	Certificate of Confidentiality
CONSORT	Consolidated Standards of Reporting Trials
CRF	Case Report Form
DCC	Data Coordinating Center
DHHS	Department of Health and Human Services
DSMB	Data Safety Monitoring Board
DRE	Disease-Related Event
EC	Ethics Committee
eCRF	Electronic Case Report Forms
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act of 2007
FFR	Federal Financial Report
GCP	Good Clinical Practice
GLP	Good Laboratory Practices
GMP	Good Manufacturing Practices
GWAS	Genome-Wide Association Studies
HIPAA	Health Insurance Portability and Accountability Act
IB	Investigator's Brochure
ICH	International Conference on Harmonisation
ICMJE	International Committee of Medical Journal Editors
IDE	Investigational Device Exemption
IND	Investigational New Drug Application
IRB	Institutional Review Board
ISM	Independent Safety Monitor
ISO	International Organization for Standardization
ITT	Intention-To-Treat
LSMEANS	Least-squares Means
MedDRA	Medical Dictionary for Regulatory Activities
MOP	Manual of Procedures
MSDS	Material Safety Data Sheet
NCT	National Clinical Trial
NIH	National Institutes of Health
NIH IC	NIH Institute or Center
OHRP	Office for Human Research Protections
PI	Principal Investigator
QA	Quality Assurance
QC	Quality Control
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SMC	Safety Monitoring Committee
SOA	Schedule of Activities

SOC	Standard of Care
SOP	Standard Operating Procedure
UP	Unanticipated Problem
US	United States

APPENDIX B.

Term	Definition	Reference / Justification
All-cause mortality	Any death from any cause. Report as time-to-event (Kaplan–Meier) when applicable.	VARC-3 Table 2
Cardiovascular mortality	Death related to heart failure/cardiogenic shock, bioprosthetic valve dysfunction, MI, stroke, thromboembolism, bleeding, tamponade, vascular complication, arrhythmia/conduction disturbance, cardiovascular infection (e.g., mediastinitis/endocarditis), other clear CV cause; includes intraprocedural death, sudden death, and death of unknown cause.	VARC-3 Table 2
Valve-related mortality	Death presumed related to bioprosthetic valve dysfunction (BVD).	VARC-3 Table 2 + Table 12
Non-cardiovascular mortality	Death clearly related to a non-cardiovascular cause (e.g., pneumonia not related to HF, renal/liver failure, non-CV infection, cancer, trauma, suicide).	VARC-3 Table 2
Periprocedural mortality	Death ≤30 days after index procedure OR >30 days but during index hospitalization (includes transfer for continuity of acute care; excludes chronic rehab/nursing home).	VARC-3 Table 2
Early mortality	Death >30 days but ≤1 year after index hospitalization.	VARC-3 Table 2
Late mortality	Death >1 year after index hospitalization.	VARC-3 Table 2
All stroke (overall)	Overt CNS injury (NeuroARC Type 1) including ischemic stroke, hemorrhagic stroke, or stroke not otherwise specified, per Table 3.	VARC-3 Table 3
Ischemic stroke	Acute focal neurologic signs/symptoms in a vascular territory with: symptoms ≥24h (or until death) with neuroimaging/pathology evidence of infarction, or symptoms <24h with imaging/pathology confirmation of infarction in corresponding territory.	VARC-3 Table 3
Haemorrhagic stroke	Acute neurologic signs/symptoms due to intracranial bleeding (intracerebral or subarachnoid) not due to trauma.	VARC-3 Table 3
Stroke, not otherwise specified	Acute neurologic signs/symptoms ≥24h (or until death) without sufficient imaging/pathology to classify as ischemic vs hemorrhagic.	VARC-3 Table 3
Transient ischemic attack (TIA)	Transient focal neurologic signs/symptoms <24h presumed ischemic, without evidence of acute infarction on imaging/pathology (or no imaging performed).	VARC-3 Table 3
Stroke severity (NIHSS)	Mild 0–5; Moderate 6–14; Severe ≥15 (assess at time of stroke diagnosis).	VARC-3 Table 3
Disabling stroke (stroke with disability)	mRS ≥2 at 90 days *and* increase ≥1 category from pre-stroke baseline. (mRS ideally at 90 days; 30–90 days acceptable.)	VARC-3 Table 3
Non-disabling stroke	mRS 0–1 at 90 days *or* no increase in mRS category from pre-stroke	VARC-3 Table 3

Term	Definition	Reference / Justification
(stroke without disability)	baseline.	
Hospitalization / rehospitalization (overall)	Any admission after index hospitalization/study enrolment to an inpatient unit/ward for ≥24 h, including an ED stay. Planned admissions for pre-existing conditions excluded unless worsening. ED/urgent care <24h may count only if substantive intensification of therapy occurs (e.g., IV diuretics, major med escalation, addition of new agents).	VARC-3 Table 4
Procedure-related or valve-related hospitalization	Includes hospitalization for new complications (e.g., stroke, bleeding, pericardial effusion, vascular/access complication, conduction disturbance/arrhythmia, AKI), deterioration of prior periprocedural complications, BVD (PVR, thrombosis, endocarditis, SVD/NSVD), or valve/procedure-related HF.	VARC-3 Table 4
Bleeding (VARC-3 "overt bleeding" framework)	"Overt bleeding" = clinically obvious source or source identified after appropriate evaluation; procedural blood loss counts as overt bleeding. Bleeding is graded as VARC Types 1–4.	VARC-3 Table 5
Bleeding Type 1	Overt bleeding requiring medical evaluation and leading to hospitalization/increased level of care OR transfusion of 1 unit RBC/whole blood.	VARC-3 Table 5
Bleeding Type 2	Overt bleeding requiring 2–4 units transfusion OR hemoglobin drop >3 g/dL but <5 g/dL.	VARC-3 Table 5
Bleeding Type 3	Overt bleeding in critical organ; or causing hypovolemic shock/severe hypotension requiring vasopressors/surgery; or requiring reoperation/re-intervention; or chest tube output ≥2 L/24h; or transfusion ≥5 units; or hemoglobin drop ≥5 g/dL.	VARC-3 Table 5
Bleeding Type 4	Overt bleeding leading to death.	VARC-3 Table 5
Vascular complications (major)	Includes aortic dissection/rupture; vascular injury (arterial/venous) or compartment syndrome resulting in death, VARC bleeding ≥Type 2, limb/visceral ischemia, or irreversible neurologic impairment; distal embolization causing death/amputation/ischemia/irreversible damage; unplanned endovascular/surgical intervention with those consequences; or closure device failure with those consequences.	VARC-3 Table 6
Vascular complications (minor)	Vascular injury/embolization/unplanned intervention/closure device failure not resulting in death, VARC bleeding ≥Type 2, limb/visceral ischemia, or irreversible neurologic impairment (as detailed in Table 6).	VARC-3 Table 6
Closure device failure	Failure to achieve successful hemostasis at access site leading to alternative treatment (not manual compression or planned adjunct balloon inflation).	VARC-3 text + Table 6
Access-related non-	Complications related to access but not directly vascular (e.g.,	VARC-3 Table 6

Term	Definition	Reference / Justification
vascular complications	pneumothorax, direct nerve injury, wound infection, mediastinitis, sternal instability/dehiscence, inability to close chest). Major/minor per Table 6.	
Cardiac structural complication (major)	Cardiac structure injury/perforation/compromise causing death, VARC bleeding ≥Type 2, hemodynamic compromise/tamponade, or requiring unplanned intervention; major pericardial effusion; coronary obstruction causing death/hemodynamic compromise/MI/unplanned coronary intervention; or coronary access difficulty for needed coronary procedure with major consequences.	VARC-3 Table 7
Cardiac structural complication (minor)	Similar mechanisms without death/VARC bleeding ≥Type 2/hemodynamic compromise/tamponade/unplanned intervention; coronary obstruction/access difficulty without major consequences.	VARC-3 Table 7
Coronary obstruction	New partial/complete coronary ostial/epicardial obstruction by prosthesis/native leaflets/embolized material/external compression/instrumentation sequelae, during or after procedure, with objective ischemia or symptoms; classify under cardiac structural complications per severity.	VARC-3 Table 7 footnote
Acute kidney injury (AKI) – general	Default classification uses serum creatinine criteria (urine output optional for dedicated AKI studies).	VARC-3 Table 10
AKI Stage 1	Creatinine increase 150–200% (1.5–2.0×) within 7 days vs baseline OR increase ≥0.3 mg/dL within 48h.	VARC-3 Table 10
AKI Stage 2	Creatinine increase >200–300% (>2.0–3.0×) within 7 days vs baseline.	VARC-3 Table 10
AKI Stage 3	Creatinine increase >300% (>3.0×) within 7 days vs baseline OR creatinine ≥4.0 mg/dL with acute increase ≥0.5 mg/dL.	VARC-3 Table 10
AKI Stage 4 (renal replacement therapy)	New temporary or permanent renal replacement therapy (report separately; exclude chronic dialysis patients from denominator).	VARC-3 Table 10
Myocardial infarction (MI) – periprocedural, Type 5 (≤48h)	Using CK-MB preferred if normal baseline: peak CK-MB within 48h ≥10× ULN OR ≥5× ULN plus ≥1 supporting criterion (new pathologic Q-waves, new persistent LBBB, flow-limiting angiographic complication, or substantial new loss of viable myocardium on imaging). Alternative troponin thresholds provided if CK-MB not measured.	VARC-3 Table 11
Conduction disturbances (reporting framework)	Report baseline and post-procedure conduction status; classify timing (procedural ≤24h vs delayed >24h), and duration (transient resolved by discharge/≤7d; persistent at discharge/>7d; permanent >30d).	VARC-3 Table 9
New permanent pacemaker	Report type, timing (days from index procedure), and indication (e.g., AV block, sick sinus syndrome). Exclude patients with pre-	VARC-3 Table 9

Term	Definition	Reference / Justification
implantation	existing pacemaker from denominator for "new PPM" rate.	
New-onset atrial fibrillation/flutter	AF/flutter not present at baseline, with ECG characteristics and lasting long enough for a 12-lead ECG or ≥30s rhythm strip. Timing: periprocedural ≤30d vs late/spontaneous >30d.	VARC-3 Table 9
Bioprosthetic valve dysfunction (BVD) – categories	SVD (intrinsic permanent valve changes), NSVD (non-intrinsic abnormalities causing dysfunction, e.g., PVR, malposition, PPM), thrombosis, endocarditis (per criteria below).	VARC-3 Table 12
Endocarditis (valve-related)	Meets ≥1: Duke criteria; abscess/pus/vegetation confirmed at reoperation by histology/microbiology; or abscess/pus/vegetation confirmed on autopsy.	VARC-3 Table 12
Bioprosthetic valve failure (BVF)	Stage 1: clinically expressive BVD (new/worse symptoms or LV remodeling/pulm HTN) or irreversible Stage 3 hemodynamic valve deterioration; Stage 2: aortic valve reoperation/re-intervention; Stage 3: valve-related death.	VARC-3 Table 12
Paravalvular regurgitation (PVR) grading	Grade using integrative echo assessment with either 3-class (none/trace, mild, moderate, severe) or 5-class scheme (none/trace, mild, mild-moderate, moderate, moderate-severe, severe) and Doppler criteria per Table 16.	VARC-3 Table 16
Unfavourable outcome (patient-reported, KCCQ-based)	At 1 year: not alive OR (alive and KCCQ-OS <45 and/or decline >10 points from baseline). For BELIEVERS, because death is a higher-tier endpoint, the "KCCQ tier" should use the alive portion (KCCQ-OS <45 or decline >10) when needed for pairwise comparisons.	VARC-3 Table 17 & 18
Hospitalization component for the primary endpoint	Use VARC-3 "procedure-related or valve-related hospitalization (including HF)" categories; exclude valve reintervention if reintervention is a separate tier.	VARC-3 Table 4
Prosthesis–patient mismatch (PPM)	Aortic PPM is defined by indexed effective orifice area (iEOA) ≤0.85 cm^2/m^2; severe PPM is iEOA ≤0.65 cm^2/m^2. In obese patients (BMI ≥30 kg/m^2), use lower cutoffs: PPM iEOA ≤0.70 cm^2/m^2 and severe PPM iEOA ≤0.55 cm^2/m^2. (PPM is classified as nonstructural BVD/NSVD and generally is not staged as BVD Stage 1–3.)	Pibarot et al. JACC 2022
Bioprosthetic valve dysfunction (BVD): Etiology categories	BVD should be classified by etiology into one of the following categories: (1) Structural valve deterioration (SVD/structural BVD): permanent intrinsic changes of the valve (leaflet/stent/sewing ring) causing dysfunction; (2) Nonstructural valve dysfunction (NSVD): any abnormality not intrinsic to the prosthesis causing dysfunction (e.g., prosthesis malposition, paravalvular regurgitation, prosthesis–patient mismatch, pannus/entrapment, sizing-related issues); (3) Valve thrombosis; and (4) Valve endocarditis. Hemodynamic valve deterioration may result from any of these etiologies and should be adjudicated accordingly.	Pibarot et al. JACC 2022
Nonstructural valve dysfunction (NSVD)	Any abnormality not intrinsic to the prosthetic valve that results in valve dysfunction. Examples include paravalvular regurgitation,	Pibarot et al. JACC 2022

	malposition/embolization, prosthesis–patient mismatch, and other extrinsic causes of dysfunction.	
Subclinical valve thrombosis	Imaging evidence of leaflet thrombosis (e.g., hypoattenuated leaflet thickening and/or reduced leaflet motion) with absent or mild hemodynamic changes and no symptoms or clinical sequelae.	Pibarot et al. JACC 2022
Clinically significant valve thrombosis	Valve thrombosis associated with symptoms or clinical sequelae (e.g., thromboembolism or worsening valve function) and leaflet thrombosis findings, or (if asymptomatic) hemodynamic valve deterioration meeting Stage 2 or 3 criteria with confirmatory imaging evidence of leaflet thrombosis.	Pibarot et al. JACC 2022
Bioprosthetic valve endocarditis	Meets at least one of: (1) Duke criteria for infective endocarditis; (2) abscess/pus/vegetation confirmed at reoperation with histological and/or microbiological evidence; or (3) abscess/pus/vegetation confirmed on autopsy.	Pibarot et al. JACC 2022
Baseline reference echocardiogram for hemodynamic deterioration (HVD) staging	For determination of Stage 2 or Stage 3 hemodynamic valve deterioration, follow-up echocardiographic parameters (mean gradient, AVA, DVI, transvalvular regurgitation) should be compared to an early post-procedure baseline study, preferably the echo performed ~1–3 months post-procedure (or discharge echo if a 1–3 month study is unavailable), per the Echo Core Lab charter.	Pibarot et al. JACC 2022
Measurement variability safeguard (echo comparisons)	Changes in valve hemodynamics over time should be interpreted with attention to inter-study measurement variability, and Doppler acquisition/interpretation should be standardized as specified in the Echo Core Lab charter to avoid misclassification of deterioration.	Pibarot et al. JACC 2022

APPENDIX C. PROTOCOL AMENDMENT HISTORY

The table below is intended to capture changes of IRB-approved versions of the protocol, including a description of the change and rationale. A Summary of Changes table for the current amendment is located in the Protocol Title Page.

Version	Date	Description of Change	Brief Rationale
1.1	24Dec2025	Initial Protocol	N/A

APPENDIX D. REFERENCES

1. Korteland NM, Ahmed Y, Koolbergen DR, Brouwer M, de Heer F, Kluin J, et al. Does the use of a decision aid improve decision making in prosthetic heart valve selection? A multicenter randomized trial. Circulation: Cardiovascular Quality and Outcomes. 2017;10(2):e003178.
2. Cutlip DE, Mehran R, Spitzer E, Morice MC, Krucoff MW. Device and Procedure Relatedness: Viewpoint From Members of the ARC Steering Group. JACC Cardiovasc Interv. 2022;15(7):783-8.
3. Mack MJ, Leon MB, Thourani VH, Pibarot P, Hahn RT, Genereux P, et al. Transcatheter Aortic-Valve Replacement in Low-Risk Patients at Five Years. N Engl J Med. 2023;389(21):1949-60.
4. Jorgensen TH, Thyregod HGH, Savontaus M, Willemen Y, Bleie O, Tang M, et al. Transcatheter Aortic Valve Implantation in Low-Risk Tricuspid or Bicuspid Aortic Stenosis: The NOTION-2 Trial. Eur Heart J. 2024.
5. Redfors B, Spertus JA, Yancy C, Masterson-Creber R, Stone GW, Gaudino MFL. Expanding revascularization trials to women and underserved minorities and shifting to patient-centered outcomes: RECHARGE trials program. Curr Opin Cardiol. 2024;39(6):478-84.
6. Kosiborod MN, Jhund PS, Docherty KF, Diez M, Petrie MC, Verma S, et al. Effects of Dapagliflozin on Symptoms, Function, and Quality of Life in Patients With Heart Failure and Reduced Ejection Fraction: Results From the DAPA-HF Trial. Circulation. 2020;141(2):90-9.
7. Pocock SJ, McMurray JJV, Collier TJ. Statistical Controversies in Reporting of Clinical Trials: Part 2 of a 4-Part Series on Statistics for Clinical Trials. J Am Coll Cardiol. 2015;66(23):2648-62.
8. Leon MB, Smith CR, Mack M, Miller DC, Moses JW, Svensson LG, et al. Transcatheter aortic-valve implantation for aortic stenosis in patients who cannot undergo surgery. N Engl J Med. 2010;363(17):1597-607.
9. Mack MJ, Leon MB, Thourani VH, Makkar R, Kodali SK, Russo M, et al. Transcatheter Aortic-Valve Replacement with a Balloon-Expandable Valve in Low-Risk Patients. N Engl J Med. 2019;380(18):1695-705.
10. Smith CR, Leon MB, Mack MJ, Miller DC, Moses JW, Svensson LG, et al. Transcatheter versus surgical aortic-valve replacement in high-risk patients. N Engl J Med. 2011;364(23):2187-98.
11. Pocock SJ, Gregson J, Collier TJ, Ferreira JP, Stone GW. The win ratio in cardiology trials: lessons learnt, new developments, and wise future use. Eur Heart J. 2024;45(44):4684-99.