Edwards

ALTERRA

Multicenter Study of Congenital Pulmonic Valve Dysfunction Studying the SAPIEN 3 Transcatheter Heart Valve with the Alterra Adaptive Prestent

NCT03130777

Dec 2021

ALTERRA

Multicenter Study of Congenital Pulmonic Valve Dysfunction Studying the SAPIEN 3 Transcatheter Heart Valve with the **Alterra** Adaptive Prestent

Clinical Protocol
Study Number: 2016-04

Version 7.0
December 16, 2021

Study Sponsor:
Edwards Lifesciences LLC
One Edwards Way
Irvine, CA 92614
USA

TABLE OF CONTENTS

LIST OF TABLES AND FIGURES

PROTOCOL SYNOPSIS

Title	**ALTERRA** Multicenter Study of Congenital Pulmonic Valve Dysfunction Studying the SAPIEN 3 Transcatheter Heart Valve with the **Alterra** Adaptive Prestent
Purpose	To demonstrate the safety and effectiveness of the Edwards Alterra Adaptive Prestent in conjunction with the Edwards SAPIEN 3 Transcatheter Heart Valve (THV) System in subjects with a dysfunctional right ventricular outflow tract/pulmonary valve (RVOT/PV) who are indicated for treatment of pulmonary regurgitation (PR)
Study Devices	• Edwards Alterra Adaptive Prestent and delivery system • Edwards SAPIEN 3 THV with the associated delivery systems
Study Design	Single arm, prospective, multicenter study. A separate registry will be conducted to evaluate the Pulmonic Delivery System (PDS) for delivery of the SAPIEN 3 THV.
Study Population	The study population will be comprised of subjects with a dysfunctional RVOT/PV, who are indicated for treatment of moderate to severe PR.
Sample Size	Up to 60 subjects will be enrolled in the main cohort. Subjects enrolled under earlier versions of the protocol (Early Feasibility Study versions 1.0 and 2.0) will count towards enrollment. Twenty-five additional subjects will be enrolled in the PDS Registry.
Study Sites	Up to 25 participating sites in the US and Canada
Assessment Schedule	Screening/baseline, discharge, 30 days, 6 months, 12 months and annually thereafter through 10 years
Primary Endpoint	**Main Cohort:** THV dysfunction at 6 months. THV dysfunction is defined as a non-hierarchical composite of: • RVOT/PV reintervention • Moderate or greater total PR via Transthoracic Echocardiography (TTE) • Mean RVOT/PV gradient ≥ 35 mmHg via TTE **PDS Registry:** Acute PDS Success, defined as a non-hierarchical composite of: • Single THV implanted in the desired location • Right ventricle to pulmonary artery (RV-PA) peak-to-peak gradient < 35 mmHg post-THV implantation • Less than moderate total PR by discharge TTE (or earliest evaluable TTE)

- Free of SAPIEN 3 / Alterra explant at 24 hours post-implantation

Secondary Endpoints

Main Cohort:

The following secondary endpoint will be evaluated for labeling purposes:

- Improvement in total PR from baseline to 30 days

Additional Safety and Effectiveness Outcomes

The following additional outcomes will be evaluated:

Main Cohort:

- Improvement in tricuspid regurgitation (TR) from baseline to 30 days and 6 months by TTE for subjects with TR of mild or greater at baseline
- Major vascular complications at 30 days and 6 months
- Life-threatening or disabling bleeding at 30 days and 6 months
- Alterra embolization at 30 days and 6 months
- THV embolization at 30 days and 6 months
- Alterra fracture that led to reintervention at 30 days and 6 months
- THV frame fracture that led to reintervention at 30 days and 6 months
- All-cause mortality at 30 days and 6 months
- Acute Device Success, defined as a non-hierarchical composite of:
  - Single Alterra deployed in the desired location
  - Single THV implanted in the desired location within Alterra (staged procedures allowed)
  - RV-PA peak-to-peak gradient < 35 mmHg post-THV implantation
  - Less than moderate total PR by discharge TTE (or earliest evaluable TTE)
  - Free of Alterra explant at 24 hours post-implantation

PDS Registry:

- Improvement in tricuspid regurgitation (TR) from baseline to 30 days by TTE for subjects with TR of mild or greater at baseline
- Major vascular complications at 30 days
- Life-threatening or disabling bleeding at 30 days
- Alterra embolization at 30 days
- THV embolization at 30 days

Inclusion Criteria

1. The candidate/candidate's legal guardian has been informed of the nature of the study, agrees to its provisions and has provided written informed consent
2. Weight is ≥ 20 kg (≥ 44 lbs)

3. RVOT/PV with moderate or greater PR by TTE
4. RVOT/PV proximal and distal landing zone diameter ≥ 27 mm and ≤ 38 mm, and minimum of 35 mm from contractile tissue to lowest pulmonary artery takeoff

Exclusion Criteria

1. Active infection requiring current antibiotic therapy (if temporary illness, patient may be a candidate 2 weeks after discontinuation of antibiotics)
2. History of or active endocarditis (active treatment with antibiotics) within the past 180 days
3. Leukopenia (WBC < 2000 cells/μL), anemia (Hgb < 7 g/dL), thrombocytopenia (platelets < 50,000 cells/μL) or any known blood clotting disorder
4. Inappropriate anatomy for introduction and delivery of Alterra or the SAPIEN 3 THV
5. Need for concomitant atrial septal defect or ventricular septal defect closure or other concomitant interventional procedures other than pulmonary artery or branch pulmonary artery stenting or angioplasty
6. Interventional/surgical procedures within 30 days prior to the Alterra or valve implant procedure
7. Any planned surgical, percutaneous coronary or peripheral procedure to be performed within the 30-day follow-up from the Alterra or valve implant procedure
8. History of or current intravenous drug use
9. Major or progressive non-cardiac disease resulting in a life expectancy of less than one year
10. Known hypersensitivity to aspirin or heparin and cannot be treated with other antiplatelet and/or antithrombotic medications
11. Known hypersensitivity to nitinol, cobalt-chromium, nickel or contrast media that cannot be adequately pre-medicated
12. Currently participating in an investigational drug or another device study [*Note: Trials requiring extended follow up for products that were investigational, but have since become commercially available, are not considered investigational devices.*]
13. Positive urine or serum pregnancy test in female patients of child-bearing potential
14. Renal insufficiency (creatinine > 3.0 mg/dL) and/or renal replacement therapy

Statistical Methods

Main Cohort:

For the primary endpoint of THV dysfunction at 6 months, an exact binomial 95% confidence interval (CI) for the percent of subjects with THV dysfunction will be calculated and compared to the performance goal of 25%. If the

upper bound of the CI is below 25% then the performance goal will be considered to be met.

PDS Registry:

Descriptive statistics will be provided; no formal hypothesis testing will be conducted.

Study Principal Investigator	Evan Zahn, MD, FACC, FSCAI Cedars-Sinai Heart Institute
Sponsor	Edwards Lifesciences One Edwards Way Irvine, CA 92614

INVESTIGATOR SIGNATURE PAGE

Protocol Title: ALTERRA: Multicenter Study of Congenital Pulmonic Valve Dysfunction Studying the SAPIEN 3 Transcatheter Heart Valve with the Alterra Adaptive Prestent

I have read this protocol and agree to adhere to its requirements. I will ensure that the study is conducted in compliance with the protocol, Good Clinical Practice, Declaration of Helsinki, and all applicable regulatory requirements.

_____

Investigative Site Name

_____

Site Principal Investigator Name (print)

_____ _____

Site Principal Investigator Signature Date

1 INTRODUCTION

1.1 Background

Congenital heart defects (CHD) can be complex, involving structures of either the right and/or left heart and are reported in approximately eight of every 1000 newborns. Right ventricular outflow tract (RVOT) defects such as pulmonary valve stenosis, Tetralogy of Fallot, and double outlet right ventricle are common in this population and may represent as many as 20% of those with CHD. Initial surgical correction of these lesions often involves relief of RVOT obstruction often using a combination of muscular resection, pulmonary valvotomy/valvectomy and a transannular patch. While surgical correction of these lesions has been performed safely for more than 50 years, many of these operations result in pulmonary insufficiency. For decades, it was believed that pulmonary insufficiency was a benign condition, as it is typically well tolerated throughout childhood and in many patients for several decades thereafter. Recently, however, it has been widely recognized that chronic pulmonary regurgitation (PR) in this patient population is associated with a number of pathologic conditions including: right ventricular dilation, diminished ventricular systolic function, arrhythmia, decreased functional capacity, right heart failure and death (1). Numerous surgical options exist for placing a competent valve in the pulmonic position (homografts, xenografts, bioprosthetic valves), however all of these options by definition require repeat open heart surgery and all of the attendant risks and morbidity associated with it (2). Furthermore, all currently available options for surgical pulmonary valve replacement are only temporizing in that essentially all of these valves will degenerate and need replacement (3, 4).

The durability of these prostheses is variable and time to reoperation often depends on the chosen conduit material and/or biological tissue and age of the patient at the time of the initial surgery. Thrombosis, recurrent stenosis and conduit tissue/valve leaflet calcification with concomitant PR are the most commonly reported reasons for additional surgical reinterventions. Patients receiving pulmonary xenografts are reported to have a mean time to reintervention of 10.3 years and for those implanted with a homograft 16 years. Multiple reoperations over a patient's lifetime are the current norm (3, 4).

Transcatheter replacement of the pulmonary valve, currently designed only to be used in the setting of a previously placed failed right ventricle-pulmonary artery (RV-PA) conduit, provides a less invasive alternative to surgical replacement, which requires open-heart surgery, re-sternotomy and cardiopulmonary bypass. Treatment of this patient population with a transcatheter heart valve (THV) may provide both short and long-term relief of their symptoms, improved hemodynamic function, and a gradual, consistent improvement of their cardiac function, which may delay the need for future repeat open-heart surgeries and provide improved quality of life (5) and might reduce the number of operations needed over the total lifetime of patients with RV-PA conduits (1, 2).

Currently there are two Food and Drug Administration (FDA) approved transcatheter pulmonic valves (TPV) for use as an adjunct to surgery in the management of patients with dysfunctional RVOT conduits. The Medtronic Melody Transcatheter Pulmonary Valve was approved on January 27, 2015 for use as an adjunct to surgery in the management of patients with

dysfunctional RVOT conduits. Due to its use of a bovine jugular vein, the Melody device can only be manufactured in sizes ≤ 22 mm for treatment of RVOT conduits ranging from 16-20 mm. The SAPIEN XT valve was approved in 2016 for use in the pulmonic position, also as an adjunct to surgery in patients with previously existing RV-PA conduits. The SAPIEN XT valve comes in diameters of 23, 26 and 29 mm. It is important to note that both of these devices are approved for use only in dysfunctional RV-PA conduits, not in patients who underwent other forms of RVOT surgery (e.g. pulmonary valvotomy, transannular patch repair). It is estimated that only 15% of congenital heart patients with RVOT dysfunction have had a previously placed surgical conduit resulting in the vast majority of these patients currently not being candidates for TPV implantation (TPVI) (6).

Currently there is no commercially-approved transcatheter valve available to treat patients with what is commonly referred to as a "native outflow tract", meaning they have had their RVOT surgically addressed as described above (muscle resection, valvotomy/valvectomy and patch) but have not undergone conduit or other form of surgical pulmonary valve replacement. This is a challenging anatomic substrate to design a TPV due to several factors including: large diameter of the RVOT, irregular shape of the RVOT, marked changes in RVOT dimensions during systole and diastole, compliant nature and unpredictable shape of the RVOT after transannular patch. Several novel approaches have been described utilizing existing technologies; however, the larger population remains untreatable. Existing evidence suggests that if a proper "landing zone" can be created in the RVOT, one that reduces RVOT volume and creates a circular semi-rigid area to place a TPV, this patient population can be successfully treated and avoid repeated open heart surgery. Phillips et al reported on 8 patients with native RVOT who underwent successful TPVI after using a novel hybrid approach to modify the RVOT (7).

The Edwards Alterra Adaptive Prestent (Alterra) is designed to provide a simple and safe way to reduce the diameter of these large irregular RVOTs and provide a circular, semi-rigid landing zone to place an Edwards SAPIEN 3 THV (8).

2 Study Objective

The objective of this study is to demonstrate the safety and effectiveness of the Edwards Alterra Adaptive Prestent in conjunction with the Edwards SAPIEN 3 THV System in subjects with a dysfunctional RVOT/pulmonary valve (PV) who are indicated for treatment of PR.

3 Study Design

This is a single arm, prospective, multicenter study. Up to 60 subjects will be enrolled in the main cohort at up to 25 sites in the US and Canada. Twenty-five additional subjects will be enrolled in a separate registry to evaluate the Pulmonic Delivery System (PDS) for delivery of the SAPIEN 3 THV. No site will be allowed to enroll more than 35% of subjects (21 subjects in main cohort; 8 subjects in PDS Registry). Subjects will be assessed at the following intervals: screening/baseline, discharge, 30 days, 6 months, 12 months and annually thereafter through 10 years.

Subjects enrolled under EFS protocol versions 1.0 and 2.0 will count towards enrollment in the main cohort.

4 STUDY DEVICES

The following devices will be used in this trial:

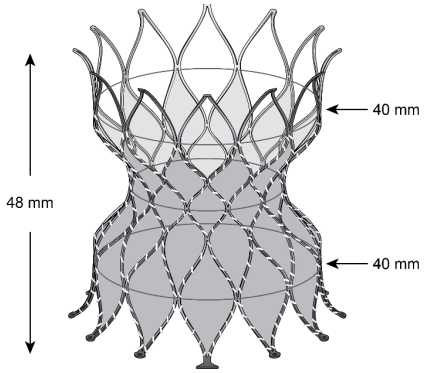
- Edwards Alterra Adaptive Prestent, model 29AP4045
- Edwards Alterra Adaptive Prestent delivery system
- Edwards SAPIEN 3 THV, model 9600TFX in a 29 mm size
- Edwards Commander Delivery System, model 9600LDS29
- Edwards SAPIEN 3 Pulmonic Delivery System, model 9630PL29
- Edwards Crimper, model 9600CR
- Edwards Expandable Introducer Sheath Set, model 916ES
- Edwards Balloon Catheter, model 9350BC25 (at physician's discretion)
- Inflation Devices

4.1 Investigational Device Descriptions

4.1.1 Edwards Alterra Adaptive Prestent

The prestent is used as a docking adaptor for the 29 mm SAPIEN 3 THV. It is comprised of a self-expanding, radiopaque, nitinol frame assembly and polyethylene terephthalate (PET) fabric covering. The prestent has designated inflow and outflow sides. The proximal inflow section is identifiable by the presence of two triangular tabs that are attached to the catheter of the delivery system. The distal outflow section is distinguished by the open cells for blood flow. The PET fabric is attached by sutures to the inside surface of the frame to create a sealing at the inflow section and opening for the outflow. Sutures are also used in the center to support the middle section when a SAPIEN 3 THV is implanted. Refer to **Table 1** for Alterra Device Sizing.

Figure 1: Edwards Alterra Adaptive Prestent



OD (Sealing)	Height
40 mm	48 mm

Table 1: Alterra Device Sizing

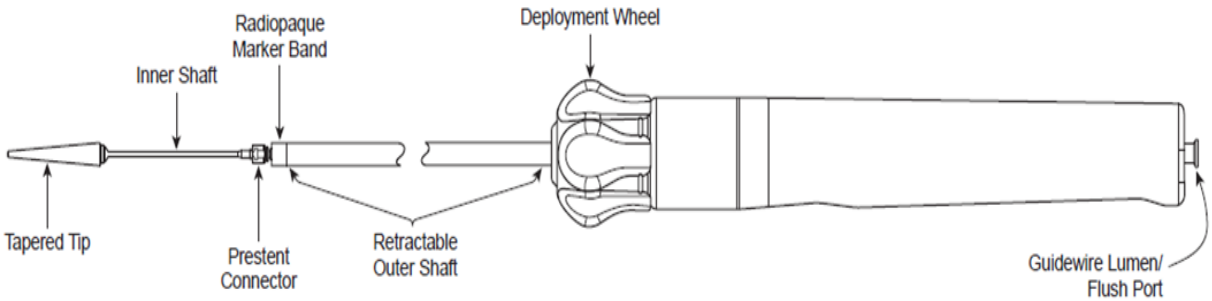
Perimeter	Perimeter Derived Diameter*	Prestent Size	THV Size
84.9 mm-119.3 mm	27-38 mm	40 mm x 48 mm	29 mm

* Diameter range throughout cardiac cycle

Edwards Alterra Delivery System

The delivery system includes a handle which consists of a wheel that allows for deployment, two primary shafts with a flush port to flush the delivery system, and a long compliant tapered tip at the distal end to facilitate tracking through the vasculature. The prestent is fully loaded in the delivery system. A stylet is included within the guidewire lumen.

Figure 2: Edwards Alterra Delivery System



4.1.2 Edwards SAPIEN 3 THV

The SAPIEN 3 THV is a catheter-delivered heart valve that combines a balloon expandable stent and bioprosthetic valve technology.

The SAPIEN 3 THV is comprised of a balloon-expandable, radiopaque, cobalt-chromium alloy frame, a tri-leaflet bovine pericardial tissue valve, a PET inner skirt, and a PET outer skirt. The valve tissue is treated according to the Edwards ThermaFix process, packaged and terminally liquid sterilized in a buffered glutaraldehyde solution.

The 29 mm SAPIEN 3 THV is intended to be implanted into the previously placed Alterra Adaptive Present within a dysfunctional RVOT.

4.1.3 Edwards Commander Delivery System

The Edwards Commander Delivery System includes:

- Edwards Commander Delivery System
- Loader
- Qualcrimp Crimping Accessory
- 2-piece Crimp Stopper

The Edwards Commander Delivery System consists of a balloon catheter for deployment of the THV and a Flex Catheter to aid in valve alignment to the balloon, tracking and positioning of the THV. The delivery system includes a tapered tip to facilitate crossing of the RVOT. The handle contains a Flex Wheel to control flexing of the Flex Catheter, and a Balloon Lock and Fine Adjustment Wheel to facilitate valve alignment and positioning of the valve within the RVOT. A stylet is included within the guidewire lumen of the delivery system. The Balloon Catheter has radiopaque Valve Alignment Markers defining the working length of the balloon. A radiopaque Center Marker in the balloon is provided to help with valve positioning. A radiopaque Triple Marker proximal to the balloon indicates the Flex Catheter position during deployment.

Loader

The loader is used to aid insertion of the delivery system into the sheath, and may be removed to utilize the full working length of the inserted device.

Qualcrimp Crimping Accessory

The Qualcrimp crimping accessory is a non-patient-contacting device that is designed to protect the SAPIEN 3 THV tissue leaflets during the crimping process. It is placed around the SAPIEN 3 THV during the crimping process to facilitate displacement of the valve tissue between the valve frame struts and to prevent potential tissue damage.

2-piece Crimp Stopper

This component is discussed in **Section 4.1.5**.

4.1.4 Edwards SAPIEN 3 Pulmonic Delivery System

The Edwards SAPIEN 3 Pulmonic Delivery System includes:

- Edwards SAPIEN 3 Pulmonic Delivery System
- 24F Dilator
- Qualcrimp Crimping Accessory
- 2-piece Crimp Stopper
- Lock Clip

The Edwards SAPIEN 3 Pulmonic Delivery System consists of an in-line sheath, balloon catheter for deployment of the Edwards SAPIEN 3 THV, and an outer shaft to cover the THV during insertion and tracking to the intended deployment location. The delivery system includes a tapered tip to facilitate crossing of right heart structures. A radiopaque Center Marker in the balloon is provided to help with valve positioning. A stylet is included within the guidewire lumen of the delivery system.

Dilator

The 24F Dilator (packaged with the delivery system) is used to predilate the vessel prior to insertion of the delivery system, if necessary.

Qualcrimp Crimping Accessory

The Qualcrimp crimping accessory (packaged with the delivery system) is used during crimping of the THV.

2-piece Crimp Stopper

This component is discussed in **Section 4.1.5**.

Lock Clip

The Lock Clip (packaged with the delivery system) is used to maintain the position of the outer shaft during delivery system insertion.

4.1.5 Edwards Crimper

The Crimper reduces the diameter of the SAPIEN 3 THV to mount it to the delivery system. The Crimper is comprised of a compression mechanism that is closed with a handle located on the housing. The Crimper is used with a 2-piece Crimp Stopper (packaged with the delivery system) to correctly crimp the THV to the appropriate size.

4.2 Intended Use

The Edwards Alterra Adaptive Prestent, used in conjunction with the 29 mm Edwards SAPIEN 3 THV, is intended for use in the treatment of moderate to severe PR in pediatric and adult patients with a dysfunctional RVOT/PV.

5 STUDY ENDPOINTS

5.1 Primary Endpoint

Main Cohort:

The primary endpoint is THV dysfunction at 6 months. THV dysfunction is defined as a non-hierarchical composite of:

- RVOT/PV reintervention
- Moderate or greater total PR via Transthoracic Echocardiography (TTE)
- Mean RVOT/PV gradient ≥ 35 mmHg via TTE

PDS Registry:

The primary endpoint is Acute PDS Success, defined as a non-hierarchical composite of:

- Single THV implanted in the desired location
- RV-PA peak-to-peak gradient < 35 mmHg post-THV implantation
- Less than moderate total PR by discharge TTE (or earliest evaluable TTE)
- Free of SAPIEN 3 / Alterra explant at 24 hours post-implantation

5.2 Secondary Endpoint

Main Cohort:

The following secondary endpoint will be evaluated for labeling purposes:

- Improvement in total PR from baseline to 30 days

5.3 Additional Safety and Effectiveness Outcomes

The following additional outcomes will be evaluated:

Main Cohort:

- Improvement in tricuspid regurgitation (TR) from baseline to 30 days and 6 months by TTE for subjects with TR of mild or greater at baseline
- Major vascular complications at 30 days and 6 months
- Life-threatening or disabling bleeding at 30 days and 6 months
- Alterra embolization at 30 days and 6 months
- THV embolization at 30 days and 6 months
- Alterra fracture that led to reintervention at 30 days and 6 months
- THV frame fracture that led to reintervention at 30 days and 6 months
- All-cause mortality at 30 days and 6 months
- Acute Device Success, defined as a non-hierarchical composite of:
- Single Alterra deployed in the desired location
- Single THV implanted in the desired location within Alterra (staged procedures allowed)
- RV-PA peak-to-peak gradient < 35 mmHg post-THV implantation
- Less than moderate total PR by discharge TTE (or earliest evaluable TTE)
- Free of Alterra explant at 24 hours post-implantation

PDS Registry:

- Improvement in tricuspid regurgitation (TR) from baseline to 30 days by TTE for subjects with TR of mild or greater at baseline
- Major vascular complications at 30 days
- Life-threatening or disabling bleeding at 30 days
- Alterra embolization at 30 days
- THV embolization at 30 days

6 STUDY POPULATION

The study population will be comprised of subjects with a dysfunctional RVOT/PV, who are indicated for treatment of moderate to severe PR.

6.1 Inclusion Criteria

Candidates for this study must meet **all** of the following inclusion criteria to be eligible:

1. The candidate/candidate's legal guardian has been informed of the nature of the study, agrees to its provisions and has provided written informed consent
2. Weight is ≥ 20 kg (≥ 44 lbs)
3. RVOT/PV with moderate or greater PR by TTE
4. RVOT/PV proximal and distal landing zone diameter ≥ 27 mm and ≤ 38 mm, and minimum of 35 mm from contractile tissue to lowest pulmonary artery takeoff

6.2 Exclusion Criteria

Candidates will be excluded from the study if **any** of the following conditions are present:

1. Active infection requiring current antibiotic therapy (if temporary illness, patient may be a candidate 2 weeks after discontinuation of antibiotics)
2. History of or active endocarditis (active treatment with antibiotics) within the past 180 days
3. Leukopenia (White Blood Cell (WBC) < 2000 cells/μL), anemia (Hemoglobin (Hgb) < 7 g/dL), thrombocytopenia (platelets < 50,000 cells/μL) or any known blood clotting disorder
4. Inappropriate anatomy for introduction and delivery of Alterra or the SAPIEN 3 THV
5. Need for concomitant atrial septal defect or ventricular septal defect closure or other concomitant interventional procedures other than pulmonary artery or branch pulmonary artery stenting or angioplasty
6. Interventional/surgical procedures within 30 days prior to the Alterra or valve implant procedure
7. Any planned surgical, percutaneous coronary or peripheral procedure to be performed within the 30-day follow-up from the Alterra or valve implant procedure
8. History of or current intravenous drug use
9. Major or progressive non-cardiac disease resulting in a life expectancy of less than one year
10. Known hypersensitivity to aspirin or heparin and cannot be treated with other antiplatelet and/or antithrombotic medications
11. Known hypersensitivity to nitinol, cobalt-chromium, nickel or contrast media that cannot be adequately pre-medicated
12. Currently participating in an investigational drug or another device study [*Note: Trials requiring extended follow up for products that were investigational, but have since become commercially available, are not considered investigational devices.]*
13. Positive urine or serum pregnancy test in female patients of child-bearing potential
14. Renal insufficiency (creatinine > 3.0 mg/dL) and/or renal replacement therapy

7 STUDY PROCEDURES

7.1 Informed Consent

The study investigator(s) and support staff will approach patients with a dysfunctional RVOT/PV who are indicated for treatment of PR. They will assess their interest in participating in the study by providing them an overview of the study including the background, risks, benefits and study procedures. If patients are interested in participating in the study, they must sign the Institutional Review Board (IRB) / Ethics Committee (EC)-approved informed consent form (ICF) and screening will commence. Informed consent must be obtained prior to performing screening procedures or baseline tests that are not standard of care.

For those subjects whose initial consent was obtained from the legal guardian, a new consent must be obtained once the subject reaches adult age (if study participation is on-going), as determined by state and/or local laws. If the subject refuses to sign a new ICF, they will be withdrawn from the study.

All candidates being considered for study inclusion should be entered into the electronic database; the reasons for screen failure will be documented.

7.2 Screening/Baseline Assessments

The following data will be collected for all subjects ≤ 30 days before the Alterra implant procedure, unless otherwise noted:

- Medical history
- Physical examination (blood pressure, heart rate, height, weight only)
- Medications – Antithrombotics (anticoagulants, antiplatelets, thrombolytics), antiarrhythmics, heart failure medications and antibiotics only
- New York Heart Association (NYHA) functional class
- Short form (SF)-36 health survey
- 12-lead electrocardiogram (ECG)
- TTE – Qualifying TTE must be performed within 90 days prior to the Alterra implant procedure.
- Gated computed tomography angiography (CTA) for general assessment of RVOT/PV, pulmonary artery and right heart anatomic parameters. CTA must be performed within 1 year prior to the Alterra implant procedure and meet the defined parameters within the applicable Core Lab Manual of Operations.
- Cardiac magnetic resonance imaging (cMRI) for general assessment of RVOT/PV and right heart function. cMRI must be performed within 1 year prior to the Alterra implant procedure and meet the defined parameters within the applicable Core Lab Manual of Operations.
- WBC, Hgb, hematocrit (Hct) and platelet count
- Serum creatinine

- Urine or serum pregnancy test for all females of childbearing potential
- International Normalized Ratio (INR), if subject is taking Warfarin (or other Coumadin derivative)

7.2.1 Case Review

All candidates being considered for participation must be approved by the Case Review Board. Before a case is submitted for review, the site will screen the candidate for initial enrollment criteria. Once fully screened and deemed an appropriate candidate, the site will submit the case for review and approval consideration by the Case Review Board.

Edwards will maintain a record of the case presentation and case review notes.

7.3 Procedure

7.3.1 Subject Enrollment

Subjects will be considered enrolled in the study after informed consent has been obtained and the Alterra procedure has begun (defined as the time of vascular access – incision or puncture). If these criteria are not met, the candidate will be considered a Screen Failure.

7.3.2 Recommended Concomitant Medical Therapy

Table 2 outlines the recommended concomitant medical therapy. It is expected that specific agents and dosing regimens may vary from site to site. It is strongly recommended that study subjects be treated prophylactically with antibiotics for endocarditis per the recommendation of the American Heart Association (9).

Table 2: Recommended Concomitant Medical Therapy

Pre-procedure	Aspirin:	At least 81 mg within 24 hours prior to procedure
Intra-procedure	Antibiotics:	1st dose prior to or at time of procedure
	Heparin:	To achieve/maintain activated clotting time (ACT) ≥ 250 sec
Post-procedure	Antibiotics:	2nd dose 8 hours after first dose 3rd dose 8 hours following the 2nd dose Prophylaxis for life
	Aspirin:	At least 81 mg once daily for life

7.3.3 Implant Procedure

It is strongly encouraged that the Alterra procedure be performed within 14 days of case review approval.

Alterra may be implanted during the same procedure as the THV or in a separate, staged procedure. If staged, the valve implant procedure should take place no more than 3 months after the Alterra procedure.

The Instructions for Use (IFU) will be included with each shipment of the investigational devices. Study devices and accessories will be used per the most current labeling at all times. Only physicians appropriately trained to the use of the device and identified on the Delegation of Authority (DoA) log on file with Edwards may perform the implant procedures in study subjects.

Pre-implantation, the following assessments should be performed:

- Angiogram to evaluate coronary artery patency and aortic root configuration
- Intracardiac echocardiography (ICE) to assess native valve function, regurgitation, and native leaflet location and length (if present)

Post-implantation, the following assessments should be performed:

- Angiogram:
  - Evaluate deployment and positioning of the Alterra
  - Evaluate THV function and position within Alterra
- Invasively measure RV-PA peak-to-peak gradient, pulmonary artery pressure (PAP) and right atrium pressure (RAP)
- ICE to assess THV function, regurgitation, and native leaflet location and length (if present)

7.4 Discharge

The following data will be collected for all subjects at discharge or within 48 hours prior to discharge, unless noted otherwise:

- Medications: Antithrombotics, antiarrhythmics, heart failure medications, antibiotics only
- 12-Lead ECG
- TTE
- Gated CTA: Must be performed after the valve implant procedure but prior to the end of the 30 days follow up period
- Chest X-Ray (CXR)
- Adverse events assessment

7.5 Follow-up

The day of the valve implant procedure will be considered Day 0 and will be used to schedule all subsequent visits and calculate visit windows. Six months is defined as 180 days; one year is defined as 365 days.

7.5.1 30 days

The following assessments will be conducted at 30 days post-procedure (+ 14 days):

- Medications: Antithrombotics, antiarrhythmics, heart failure medications and antibiotics only

- NYHA Functional Class
- SF-36 health survey
- 12-lead ECG
- TTE
- Gated CTA: Must be performed after the valve implant procedure but prior to the end of the 30 days follow up period
- CXR
- Adverse events assessment

7.5.2 6 months

The following assessments will be conducted at 6 months post-procedure (+ 14 days):

- Medications: Antithrombotics, antiarrhythmics, heart failure medications and antibiotics only
- NYHA Functional Class
- 12-lead ECG
- TTE
- Fluoroscopy
- Adverse events assessment

7.5.3 12 months

The following assessments will be conducted at 12 months post-procedure (+ 30 days):

- Medications: Antithrombotics, antiarrhythmics, heart failure medications and antibiotics only
- NYHA Functional Class
- SF-36 health survey
- TTE
- cMRI
- Fluoroscopy
- Adverse events assessment

7.5.4 Years 2 through 5, 7 and 10

The following assessments will be conducted at years 2 through 5, 7 and 10 (+ 45 days):

- Medications: Antithrombotics, antiarrhythmics, heart failure medications and antibiotics only
- NYHA Functional Class
- TTE

- CXR or fluoroscopy. For subjects with a previously identified device fracture, fluoroscopy must be performed.
- Gated CTA – at years 5 and 10 only
- Adverse events assessment

7.5.5 Years 6, 8 and 9

The following assessments will be conducted by telephone or office visit at years 6, 8 and 9 (+ 45 days):

- Medications: Antithrombotics, antiarrhythmics, heart failure medications and antibiotics only
- Adverse events assessment

7.6 Imaging Assessments

Imaging performed during the course of the study (TTE, CTA, cMRI, ICE, CXR, fluoroscopy) should follow the applicable Core Lab Manual of Operations.

If CXR reveals potential device fracture, fluoroscopy should be completed for confirmation. If another radiographic assessment (CT, fluoroscopy) has been performed by which fracture can be assessed, then CXR does not need to be performed.

7.7 Quality of Life Questionnaires

QoL will be measured through the following standard survey:

- The SF-36 is a generic health status instrument and rating scale that allows mapping of health status to population-level utility weights. This is an important metric for cost-effectiveness analysis.

Study sites will be provided with paper QoL questionnaires. Questionnaires will be IRB/EC-approved prior to use. Study site personnel will administer questionnaires to subjects at the required time points. Study sites should retain the completed questionnaire in the subjects' medical record.

An overview of study procedures is summarized in the Schedule of Events in **Table 3**.

Table 3: Schedule of Events

	Screening/ Baseline	Procedure	Discharge	Follow-up				
				30 Day (+ 14 days)	**6 Month** (+ 14 days)	**12 Month** (+ 30 days)	**2-5, 7, 10 Years** (+ 45 days)	**6, 8 and 9 Years** (+ 45 days) [11]
Informed Consent	X							
History & Physical	X							
Medications [1]	X	X	X	X	X	X	X	X
NYHA Functional Class	X			X	X	X	X	
SF-36 Health Survey	X			X		X		
12-lead ECG	X		X	X	X			
TTE	X [2]		X	X	X	X	X	
Gated CTA	X [3]		X [7]				X [9]	
cMRI	X [4]					X		
CXR [8]			X	X			X [10]	
Fluoroscopy					X	X	X [10]	
WBC, Hgb, Hct, Platelets	X							
Serum Creatinine	X							
Pregnancy test [5]	X							
INR, if taking Warfarin	X							
Case Review	X							
Alterra Procedure		X						
THV Implant Procedure [6]		X						
Pre- and Post-implantation Assessments		X						
Adverse Event Assessment		X	X	X	X	X	X	X

1. Antithrombotics, antiarrhythmics, heart failure medications and antibiotics only
2. Must be performed within 90 days prior to the Alterra implant procedure
3. General assessment of RVOT/PV, pulmonary artery and right heart anatomic parameters. Must be performed within 1 year prior to the Alterra implant procedure and meet the defined parameters within the applicable Core Lab Manual of Operations.
4. General assessment of RVOT/PV and right heart function. Must be performed within 1 year prior to the Alterra implant procedure and meet the defined parameters within the applicable Core Lab Manual of Operations.
5. If female of childbearing potential only (either urine or serum are acceptable)
6. This may be done in a two-stage approach
7. Must be performed after the valve implant procedure but prior to the end of the 30 days follow up period
8. If CXR reveals potential device fracture, fluoroscopy should be completed for confirmation. If another radiographic assessment (CT, fluoroscopy) has been performed by which fracture can be assessed, then CXR does not need to be performed.
9. At years 5 and 10 only
10. CXR or fluoroscopy. For subjects with a previously identified device fracture, fluoroscopy must be performed.
11. Telephone or office visit

7.8 Missed Visits / Subject Discontinuation

7.8.1 Missed Visits

Site personnel should make all reasonable efforts to locate and communicate with the subject at each visit time point. For each missed visit, multiple attempts to contact the subject should be made and details recorded in source documentation

7.8.2 Subject Discontinuation

Every subject should remain in the study until completion of the required follow-up period; however, a subject's participation may be discontinued. Should this occur, the reason for discontinuation should be documented in the subject's medical record. Potential reasons for discontinuation may include, but are not limited to the following:

- Subject Withdrawal: Subject participation in a clinical trial is voluntary and the subject may discontinue participation (refuse all subsequent testing/follow-up) at any time without loss of benefits or penalty.
- Investigator Termination: The investigator may terminate the subject's participation without regard to the subject's consent if the investigator believes it is medically necessary
- Investigational Device Never Implanted: Subjects considered enrolled but the Alterra Adaptive Prestent was never implanted will be followed for 30 days or until resolution of any adverse events related to the study implant procedure, whichever is later, and then exited from the study.
- Investigational Device Explanted: Subjects who have the study valve explanted (e.g., valve replaced due to endocarditis or subject growth requiring larger valve) will be followed for 30 days post-explant or until resolution of any adverse events related to the procedure, whichever is later, and then exited from the study.
- Lost-to-Follow-up: A subject is not considered lost-to-follow up until the full 10 years of follow-up have elapsed.

Subjects that have valvuloplasty or valve-in-valve procedure will continue to be followed for the duration of the study.

Subjects who discontinue prematurely will be included in the analysis of results and will not be replaced.

For subjects that are lost-to-follow-up or withdraw early, Edwards may request the site to search the Social Security Death Index and/or other death registries and may request the site to obtain the death certificate, if applicable.

8 ADVERSE EVENTS

8.1 Adverse Event Definitions

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

AEs may be volunteered by subjects, elicited by the Investigator or designee, the Clinical Events Committee (CEC), safety team, monitoring team, or collected via observation by the Investigator. In addition, subjects should be instructed to contact the investigator, and/or study coordinator if any significant AEs occur between study visits.

All AEs will be assessed by the Investigator who will determine whether or not the event is related to the device and/or implant procedure and if it meets serious criteria. If it is determined that an AE has occurred, the investigator should obtain all the information required to complete the AE electronic Case Report Form (eCRF).

A Serious Adverse Event (SAE) is any AE that:

- led to death
- led to a serious deterioration in the health of the subject, that either resulted in:
  - a life-threatening illness or injury
  - a permanent impairment of a body structure or a body function
  - in-patient or prolonged hospitalization, or
  - medical or surgical intervention to prevent life threatening illness or injury or permanent impairment to a body structure or a body function
- led to fetal distress, fetal death or a congenital abnormality or birth defect
- Important medical event: Important medical events that do not meet the above criteria may still be considered an SAE if they seriously jeopardize the subject and require immediate medical or surgical intervention to prevent one of the aforementioned outcomes.

An Unanticipated Adverse Device Effect (UADE) is any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan or application (including a supplementary plan or application), or any other unanticipated serious problem associated with a device that relates to the rights, safety or welfare of subjects.

Pre-existing medical conditions or symptoms reported prior to subject enrollment will not be recorded as an AE. In the event there is a worsening in the pre-existing medical condition due to the device or study related procedure, then an AE must be recorded.

Death should not be recorded as an AE, but should only be reflected as an outcome to another specific AE.

8.2 AE Reporting Requirements

All AEs will be captured from the time of enrollment until subject participation has ended (i.e. completion of study or subject discontinuation). AEs must be followed until resolution, stabilization or study completion. Expected, non-clinically significant events such as non-significant lab variances are not required to be reported.

AE information must be entered into the EDC. When EDC system is not available/accessible, AE information must be reported directly via email to THV_Safety@edwards.com, copying the Safety Officer of the study.

At the time of initial notification, the following minimal information must be provided:

- Study site
- Subject ID
- AE description
- Causal relationship to device and implant procedure
- Aware date

The site Principal Investigator is responsible for informing the IRB/EC of SAEs, UADE and/or AEs, as required. A copy of this report should be provided to Edwards Lifesciences (or designee).

Enrolling sites must provide to the Sponsor at a minimum an index hospitalization admission history and physical, implant procedure report, discharge summary, and relevant echocardiographic reports for all enrolled subjects. This will be done irrespective of subject having any AE/SAE.

The site will provide a copy of supporting documentation (example: admission H&P, index procedure reports, anesthesia records, discharge summary, echocardiogram and ECG reports, laboratory results, etc.) for all endpoint-related events, device and procedure-related events, and UADEs to Edwards Lifesciences (or designee). Source documentation may be requested by the Edwards Safety Officer for other AEs that may meet potential complaint reporting criteria or in order to verify that events are being assessed appropriately.

All AEs must be reported to Edwards Lifesciences **within 10 working days of the site becoming aware of the event**.

Edwards Lifesciences will notify FDA, all participating investigators and participating IRBs/ECs of all UADEs that occur during this study within 10 working days of the Sponsor becoming aware of the event. Investigators are responsible for reviewing information received about UADEs.

8.3 Investigator Assessment

For each AE, the investigator will determine whether the event is related to the device and/or the procedure, and whether the event meets the definition of a SAE or UADE as outlined in **Section 8.1**.

The causal relationship of the event to the device and the procedure will be categorized as follows:

- **None:** The event is not associated with the device or procedure. There is no relation between the event and the device or procedure.
- **Possibly Related:** The temporal sequence between the device or procedure and the event is such that the relationship is not unlikely or there is no contradicting evidence that can reasonably explain the study subject's condition. There is a possibility of any relation between the event and the device or procedure.
- **Definitely Related:** The temporal sequence is relevant or the event abates upon device application completion/removal or the event cannot be reasonably explained by the subject's condition or comorbidities. The event is related or most likely associated with the device or procedure.

8.4 Sponsor Assessment

All AEs will be reviewed by the Edwards Safety Officer. Each AE will be assessed as to its relationship to the study device and/or procedure, whether it was anticipated or not anticipated, based on the list of anticipated events provided in **Section 9.2**, and whether it qualifies as an SAE and/or UADE.

8.5 Device Malfunctions

A device malfunction is defined as the failure of a device to meet its performance specifications or otherwise perform as intended. Performance specifications include all claims made in the labeling for the device. The intended performance of a device refers to the intended use for which the device is labeled or marketed. Device malfunctions may or may not be associated with an AE.

Any clinical events or sequelae resulting from fractures of either the SAPIEN 3 THV or Alterra Adaptive Prestent will be recorded as an AE.

Device malfunctions should be reported to Edwards Lifesciences **within 10 working days of the site becoming aware of the event**.

9 RISK / BENEFIT ANALYSIS

9.1 Benefits

There are no guaranteed benefits from participation in this study. Information gained from this study may be of benefit to other people with the same medical condition in the future. The long-term results of using the Alterra Adaptive Prestent and SAPIEN 3 THV are not known at the present time. Alternative treatments include palliative medical therapy, commercially available percutaneous pulmonic valve implantation and surgical pulmonic valve replacement.

9.2 Risks

The potential risks associated with this study can be grouped into two categories. There are the potential risks associated with anesthesia and interventional procedures used to deliver and deploy the devices. There are the additional potential risks uniquely associated with the use of the Alterra Adaptive Prestent, SAPIEN 3 THV and the delivery systems.

Potential risks associated with the overall procedure including access, cardiac catheterization, balloon-sizing, local and/or general anesthesia include but are not limited to:

- Allergic reaction to anesthesia, contrast media, antithrombotic therapy, device materials
- Anemia
- Angina
- Arrhythmia
- Arteriovenous fistula
- Atelectasis
- Blood loss requiring transfusion
- Cardiac failure
- Cardiovascular or vascular injury, such as perforation or damage (dissection) of vessels, myocardium, or valvular structures including rupture of the pulmonary RVOT that may require intervention
- Conduction system injury
- Death
- Deep vein thrombosis
- Dislodgement of previously implanted devices (i.e. pacing lead)
- Electrolyte imbalance
- Embolic event: air, calcific material, thrombus
- Exercise intolerance or weakness
- Fever
- Hematoma or ecchymosis
- Hypertension or hypotension
- Infection including incisional site infection, septicemia and endocarditis

- Inflammation
- Myocardial infarction
- Pain
- Pericardial effusion/cardiac tamponade
- Pleural effusion
- Pneumothorax
- Pulmonary edema
- Radiation Injury
- Renal insufficiency or renal failure
- Respiratory insufficiency or respiratory failure
- Stroke/transient ischemic attack
- Syncope
- Systemic or peripheral ischemia
- Systemic or peripheral nerve injury

In addition to the risks listed above, additional potential risks associated with the use of Alterra, SAPIEN 3 THV, the delivery systems and/or accessories include, but may not be limited to, the following:

- Aortic root distortion
- Cardiac arrest
- Cardiogenic shock
- Chest pain/discomfort
- Coronary flow obstruction/transvalvular flow disturbance
- Device dysfunction (regurgitation and/or stenosis)
- Device embolization
- Device fracture
- Device migration or malposition
- Device thrombosis
- Dyspnea
- Embolic event: device fragments
- Emergent and non-emergent reintervention
- Endocarditis
- Hemolysis/hemolytic anemia
- Injury to tricuspid valve/chordae resulting in tricuspid regurgitation
- Mechanical failure of the delivery system and/or accessories

9.2.1 Risk Minimization

Product handling and procedure guidance are provided in the IFU and training manual, which will be used for device training to minimize risks associated with device use.

Additionally, 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.

A complete regimen of testing has been conducted on the Alterra Adaptive Prestent model 29AP4045, delivery system, and accessories to verify the performance of the devices and to demonstrate adequate safety and effectiveness for their use in the trial. Testing was performed in accordance with applicable international standards, relevant FDA guidance documents, and specifications based on clinical relevance.

The SAPIEN 3 THV represents a third generation THV for Edwards Lifesciences and was developed with the experience from the first and second generation SAPIEN THVs. The SAPIEN 3 System has undergone extensive clinical testing in the aortic position and is commercially available for transcatheter aortic valve replacement in the US and countries that honor the CE mark.

10 STATISTICAL CONSIDERATIONS

10.1 Sample Size Calculations

The primary safety and effectiveness endpoint for the main cohort is THV dysfunction at 6 months. THV dysfunction is defined as a non-hierarchical composite of the following events:

- RVOT/PV reintervention
- Moderate or greater total PR via TTE
- Mean RVOT/PV gradient ≥ 35 mmHg via TTE

The observed percentage of subjects with THV dysfunction at 6 months and a two-sided exact binomial 95% confidence interval (CI) will be calculated.

If the true rate of THV dysfunction is 7.4% or less and the performance goal is set to 25%, then a sample of 38 subjects will yield at least 85% power to detect this difference at a one-sided significance level of 0.025 (i.e. the upper limit of the two-sided 95% CI is less than the performance goal, 25%). The total enrolled sample size will be up to 60 subjects to account for trial contingencies.

Power	Enrolled Sample Size	Observable Sample Size	Performance Goal	True Rate	Target Alpha	Alpha	Beta
0.8531	60	38	0.2500	0.0740	0.0250	0.0235	0.1469

Sample size calculations were performed using PASS 13's power analysis of one proportion using an exact test and a one-sided alternative (11).

10.2 Analysis Populations

The All Treated (AT) population is defined to include all enrolled subjects. Subjects will be considered enrolled in the study after informed consent has been obtained and the Alterra procedure has begun (defined as the time of vascular access – incision or puncture).

The Attempted Implant (AI) population is defined as all AT subjects who had an attempted implant of the Alterra. Subjects will be considered to have an attempted implant at the time in which the introducer sheath for vascular delivery of the Alterra is inserted.

The Valve Implant (VI) population will consist of all AI subjects who received and retained the SAPIEN 3 THV upon leaving the catheterization laboratory/hybrid suite.

10.3 Primary Endpoint Analysis

Main Cohort:

The primary endpoint is THV dysfunction at 6 months. THV dysfunction is defined as a non-hierarchical composite of:

- RVOT/PV reintervention
- Moderate or greater total PR via TTE (as assessed by Echo Core Lab)
- Mean RVOT/PV gradient ≥ 35 mmHg via TTE

The observed proportion with THV dysfunction and a two-tailed exact binomial 95% CI will be calculated for the composite endpoint as well as each of the individual components.

A performance goal of 25% was pre-specified for the 6-month rate. The hypothesis for the primary endpoint is as follows:

$$H_0: \pi_{Alterra} \geq 25\%$$
$$H_A: \pi_{Alterra} < 25\%$$

Where $\pi_{Alterra}$ represents the proportion of subjects with THV dysfunction at 6 months. If the upper 95% confidence limit for the composite event is less than 25%, the performance goal will have been met.

The primary endpoint will be evaluated on the VI population.

PDS Registry:

The primary endpoint is Acute PDS Success, defined as a non-hierarchical composite of:

- Single THV implanted in the desired location
- RV-PA peak-to-peak gradient < 35 mmHg post-THV implantation
- Less than moderate total PR by discharge TTE (or earliest evaluable TTE)
- Free of SAPIEN 3 / Alterra explant at 24 hours post-implantation

No formal hypothesis testing will be conducted. Data will be analyzed by descriptive summary tables only.

10.4 Center Poolability

The center effect and center-poolability will be evaluated using a Fisher's exact test on the contingency table of main cohort primary endpoint by center at alpha level of 0.15. Once confirmed that there is no qualitative center effect, data from all centers will be combined for analysis.

10.5 Endpoints for Labeling

A hierarchical gatekeeping approach will be used to control the overall type I error between the primary endpoint and the secondary endpoint analyses. If the null hypothesis for the primary endpoint is rejected, testing of the endpoint for labeling will proceed using a one-sided α=0.025. If the primary endpoint's null hypothesis is not rejected, testing the endpoint for labeling will not occur.

10.5.1 Improvement in Total PR from Baseline to 30 Days

Total PR at baseline and 30 days will be presented. The change in total PR from baseline to 30-days will be tested using a Wilcoxon Signed Rank Test using the following hypothesis:

$$H_0: D_{PR} \geq 0$$
$$H_A: D_{PR} < 0$$

Where D_{PR} represents the difference in total PR from baseline to 30 days. In order to calculate the difference, a numerical value will be assigned to each level.

0 = None
1 = Trace
2 = Mild
3 = Moderate
4 = Severe

For each subject, the difference between the value at baseline and 30 days will be calculated (30-days - baseline). Evaluation of the null hypothesis will be done using a Wilcoxon signed rank test on the VI population and the p-value will be presented.

10.6 Additional Safety and Effectiveness Outcomes

All clinically relevant baseline and follow-up variables will be tabulated. Descriptive statistics will be used for continuous variables (e.g., mean, standard deviation, sample size, minimum, and maximum) and frequency tables or proportions for discrete variables. Kaplan-Meier (KM) estimates will be performed at the pre-specified follow-up times to project the estimates for time-related safety endpoints.

11 STUDY ADMINISTRATION

11.1 General Study Organization

Edwards Lifesciences is the Study Sponsor and has the overall responsibility for the conduct of the study, including assurance that the study meets the appropriate regulatory requirements.

Edwards Lifesciences will be responsible for obtaining Investigational Device Exemption (IDE) approval for the study, selecting investigators, ensuring that sites have IRB/EC approval prior to investigational device shipment, and conducting clinical site monitoring to ensure that subjects are being properly consented and the study is being conducted according to the protocol. Edwards will notify investigative sites of enrollment closure.

As appropriate, Edwards Lifesciences will submit changes in the Investigational Plan to the FDA and investigators to obtain FDA/IRB/EC re-approval.

Edwards Lifesciences will maintain copies of correspondence, data, shipment of devices, adverse device effects and other records related to the clinical trial as appropriate.

Edwards Lifesciences will submit all reports required by the FDA as identified in 21 Code of Federal Regulations (CFR) 812.150(B). This includes UADEs, withdrawal of IRB/EC approval, current investigator list, annual progress reports, recall information, final reports and protocol violations.

11.2 Steering Committee

A Steering Committee will be selected to provide oversight and medical expertise to the study.

11.3 Case Review Board

The Case Review Board will be comprised of a subset of Investigators who are participating in the study. The role of the Case Review Board is to review submitted cases to determine if the subject is an appropriate candidate for the study, with a focus on confirming appropriate anatomy for device size and vascular access, and any relevant clinical factors impacting enrollment eligibility.

11.4 Data Safety Monitoring Board

An independent Data Safety Monitoring Board (DSMB) will review study data, evaluate trends in reported AEs and any potential changes in risk assessment, and make recommendations to Edwards regarding safety issues and risks to research subjects as well as the continuing validity and scientific merit of the study. DSMB oversight will occur minimally through enrollment completion. DSMB activities are defined in the DSMB Charter.

11.5 Clinical Events Committee

An independent CEC will adjudicate endpoint events and device- and procedure-related AEs as determined by site and/or Edwards Safety Officer. The CEC will include cardiologists and cardiothoracic surgeons with experience in the field of CHD pulmonary homografts who are not

involved in the study and have no significant conflict of interest. CEC activities will be defined in the CEC Charter.

11.6 Study Procedures

11.6.1 Investigational Site Selection

Edwards Lifesciences will select investigators based on training and experience. Up to 25 investigational sites in the US and Canada will enroll subjects.

11.6.2 Training

Training by Edwards or its designee is required for study site personnel in accordance with the roles outlined in the DoA log. Training may include review of the device IFU, study protocol, case review process, identification of eligible subjects, instructions on data collection, standardized image acquisition, methods for soliciting data from alternative sources and regulatory requirements.

Documentation of site personnel qualification and training should be maintained in the site's clinical trial files with copies sent to Edwards.

Training may be provided in one of the following formats: in-person training sessions, teleconference, online meeting applications, or read and review. Retraining may be performed for sites who have demonstrated protocol or implant procedure compliance issues.

11.6.3 Echocardiography

An independent echocardiographic core lab will review and analyze echocardiographic images. A standardized protocol for acquiring images and training will be provided to the clinical sites prior to enrollment start.

11.6.4 Radiographic Imaging

A central lab will independently review and analyze CTA, cMRI, CXR and fluoroscopic images. Analysis will include an assessment of RVOT/PA anatomy, ventricular function, PR, possible fracture of either the SAPIEN 3 valve or the Alterra Adaptive Prestent. Standardized protocols for acquiring images and training will be provided to the clinical sites prior to enrollment start.

11.6.5 Image Management

A image transfer vendor will receive, maintain, and provide echocardiographic and radiographic images to the core labs for analysis.

Instructions for image uploads will be provided to investigative staff prior to enrollment start. Study site personnel should make every reasonable effort to upload all images to the image transfer vendor within 5 business days of image acquisition. Any unscheduled imaging performed related to the safety or performance of the device should also be uploaded.

11.6.6 Histopathology

Histopathology will be performed on all explanted valves. Explants will be prepared, preserved and shipped to the Histopathology Core Lab per instructions provided by Edwards.

11.7 Device Management

11.7.1 Study Devices

All products will be supplied by Edwards. Each Alterra Adaptive Prestent and SAPIEN 3 THV will have a unique identifier, which should be recorded in the subject's medical file.

11.7.2 Device Storage

All components should be stored in a secure location where only study personnel can access the device for use.

11.7.3 Device Accountability

The study site will maintain detailed records of the receipt and disposition of all investigational devices. Device disposition will be verified by the clinical monitor periodically throughout the study. The Investigator will return unused devices to the Sponsor at completion of enrollment. Use of the investigational devices and accessories provided for use in the study is prohibited outside of this protocol.

11.8 Data Management

This study will use a secure, password protected EDC system accessible via the Internet. A unique Subject ID will be assigned for each subject enrolled in the study. All pertinent data will be entered by the study site and core lab personnel into the eCRFs.

Every reasonable effort should be made to complete data entry within one week of data collection. Data review by Edwards Lifesciences personnel will occur remotely as well as during on-site monitoring. Data discrepancies will be queried and resolved through the EDC system.

The site Principal Investigator must ensure the accuracy and completeness of the recorded data and then provide his/her electronic signature on the appropriate eCRFs at regular intervals during the study, as requested by Edwards. If changes are made to data previously signed-off, a new electronic signature will be required to acknowledge/approve the changes.

11.9 Monitoring Procedures

All sites will be monitored periodically by Edwards Lifesciences or designee to ensure compliance with the protocol and the Investigator's Agreement, and that all study subjects have been properly consented. The monitor will ensure that the completed eCRFs match the medical records and work with the site to resolve differences through queries or formal action items.

11.10 Site Discontinuation

Edwards has the right to discontinue an Investigator or study site for the following reasons:

- Failure of the Investigator to enroll patients into the study at an acceptable rate
- Failure of the Investigator to comply with pertinent regulations of appropriate regulatory authorities
- Insufficient adherence to protocol requirements
- Submission of knowingly false information from the research facility to the Sponsor, Study Monitor, or appropriate regulatory authority.

If a study site is discontinued, subjects enrolled prior to discontinuation will continue to be followed per the protocol.

11.11 Auditing

The study may be subject to a quality assurance audit by Edwards Lifesciences or a designee, as well as inspection by regulatory authorities. It is important that the investigator and relevant study personnel are available during any audits and that sufficient time is devoted to the process. In the event of an audit by regulatory authorities, the investigator should contact Edwards Lifesciences as soon as possible.

11.12 Publication Policy

Publication or presentation of the overall clinical study results and/or site-specific results requires prior written approval of Edwards. If Edwards approves the publication or presentation of the overall clinical study results and/or site-specific results, then Institutions and Investigators will comply with the Publications and Public Disclosure Section of the Clinical Trial Agreement. Edwards will provide statistical support for the publication process.

12 ETHICAL AND REGULATORY CONSIDERATIONS

12.1 Applicable Principles and Regulations

The study will be performed in accordance with the ethical principles that have their origin in the Declaration of Helsinki (as updated in Fortaleza Brazil in 2013) and in compliance with Title 21 Code of Federal Regulations (CFR) Parts 11, 50, 54, 56, 812 and Good Clinical Practices.

12.2 Institutional Review Board/Ethics Committee

This protocol, the proposed ICF, other written subject information and any proposed advertising material must be submitted to the IRB/EC for written approval. A copy of the written IRB/EC approval of the protocol and ICF must be received by Edwards Lifesciences before recruitment of subjects into the study and shipment of investigational product.

The investigator must submit and, where necessary, obtain approval from the IRB for all subsequent protocol amendments and changes to the ICF.

The investigator is responsible for obtaining annual IRB/EC approval and renewal throughout the duration of the study. Copies of the investigator's reports and the IRB/EC continuance of approval must be sent to Edwards Lifesciences.

12.3 Subject Informed Consent

Edwards Lifesciences will provide a sample ICF to the investigator to prepare for use at his/her site. The site-specific ICF must be in agreement with Title 21 CFR Part 50 and current GCP guidelines. Edwards Lifesciences must approve the site-specific ICF prior to submission to the IRB/EC; the reviewing IRB/EC must approve the ICF before use at that site. The ICF documents should be translated into the languages understandable to potential subject populations.

Before participating in the clinical trial, each subject/ subject's legal guardian must give written Informed Consent after the context of the study has been fully explained in a language that is easily understood by the subject/ subject's legal guardian. The subject/ subject's legal guardian must also be given the opportunity to ask questions and have those questions answered to his/her satisfaction.

A copy of each subject's signed consent form must be maintained by each investigator. A signed copy of the consent form must be given to each subject/ subject's legal guardian. The consent process must be documented in the subject's medical chart; at minimum, the documentation should include that consent was obtained prior to participation in the study, date consent was obtained, and confirmation that a copy of the consent was given to the subject.

Any modifications to the site-specific ICF must be approved by Edwards Lifesciences and the IRB/EC.

Once the subject reaches 18 years of age (or adult age as defined by state or local laws), a new ICF must be obtained (if study participation is on-going). If the subject refuses to sign a new ICF, they will be withdrawn from the study.

12.4 Confidentiality

All data used in the analysis and reporting of this evaluation will be without identifiable reference to the subject. Authorized personnel assigned by Edwards Lifesciences will have access to the confidential files and will have the right to inspect and copy all records pertinent to this trial.

12.5 Investigator Records

Records to be maintained by the investigator include, but are not limited to, the following:

- Clinical trial protocol and all amendments
- Signed Clinical Trial Agreement and any amendments
- IRB/EC approval letters, including continuing reviews and all amendments/changes
- IRB/EC-approved informed consent documents

- All correspondence with another Investigator, IRB/EC, Edwards, monitor or FDA, including required reports
- Records of receipt, use or disposition of a device

The following records must be maintained for each subject enrolled in the trial:

- Signed ICF
- All relevant source documentation for study visits and study-related procedures
- Supporting documentation of any AEs

All enrolling sites will maintain the study records for a period of two years after the latter of the following two dates: The date on which the investigation is terminated or completed, or the date that the records are no longer required for purposes of supporting a premarket approval application.

12.6 Investigator Reports

AE reporting requirements are discussed in **Section 8.2**.

Withdrawal of IRB/EC approval. Within 5 working days, the Principal Investigator will report to Edwards Lifesciences a withdrawal of approval by the reviewing IRB/EC of the investigator's part of an investigation.

Informed consent. If an investigator uses a device without obtaining informed consent, the investigator shall report such use to Edwards Lifesciences and the reviewing IRB/EC within 5 working days after the issue is identified.

Progress Reports. The Principal Investigator will submit progress reports on the investigation to Edwards Lifesciences and the IRB/EC at least yearly.

Final report. Upon completion or termination of this Trial, the Principal Investigator must submit a final written report to Edwards Lifesciences and the IRB/EC as required by the regulations. The report must be submitted within 3 months of completion or termination of the trial.

12.7 Protocol Amendments

The protocol can be altered only by written amendments made by Edwards. The amended protocol will be submitted to the required regulatory agencies, as applicable, before being distributed to sites. Each site must obtain IRB/EC approval and complete required training (if any, and as required by DoA role).

12.8 Protocol Deviations

An investigator must not make any changes or deviate from this protocol, except to protect the life and physical well-being of a subject in an emergency. Emergency changes do not require

prior approval but must be reported to Edwards Lifesciences and the reviewing IRB/EC within 5 days of the incident.

Each deviation from the protocol must be documented with the date and reason for the deviation and reported to Edwards Lifesciences as soon as possible, and to the IRB/EC per local guidelines and government regulations.

APPENDIX A: Abbreviations

Abbreviation	Full Term
ACT	Activated Clotting Time
AE	Adverse Event
AI	Attempted Implant
AT	All Treated
CEC	Clinical Events Committee
CFR	Code of Federal Regulations
CHD	Congenital Heart Defects
CI	Confidence Interval
cMRI	Cardiac Magnetic Resonance Imaging
CTA	Computed Tomography Angiography
CXR	Chest X-Ray
DoA	Delegation of Authority
DSMB	Data Safety Monitoring Board
EC	Ethics Committee
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
Echo	Echocardiogram
FDA	Food and Drug Administration
Hct	Hematocrit
Hgb	Hemoglobin
ICE	Intracardiac Echocardiogram
ICF	Informed Consent Form
IDE	Investigational Device Exemption
IFU	Instructions for Use
INR	International Normalized Ratio
IRB	Institutional Review Board
KM	Kaplan-Meier
NYHA	New York Heart Association
PA	Pulmonary Artery
PAP	Pulmonary Artery Pressure
PDS	Pulmonic Delivery System
PET	Polyethylene Terephthalate
PR	Pulmonary Regurgitation
PV	Pulmonary Valve
RAP	Right Atrium Pressure
RV	Right Ventricle
RVOT	Right Ventricular Outflow Tract

Abbreviation	Full Term
SAE	Serious Adverse Event
SF	Short Form
THV	Transcatheter Heart Valve
TIA	Transient Ischemic Attack
TPV	Transcatheter Pulmonic Valve
TPVI	Transcatheter Pulmonic Valve Implantation
TR	Tricuspid Regurgitation
TTE	Transthoracic Echocardiogram
UADE	Unanticipated Adverse Device Effect
VARC	Valve Academic Research Consortium
VI	Valve Implant
WBC	White Blood Cell

APPENDIX B: Definitions

Term	Definition	Reference
Acute Kidney Injury	Increase in serum creatinine to 150-199% (1.5-1.99 × increase compared with baseline) OR increase of ≥ 0.3 mg/dL (≥ 26.4 mmol/L) compared with baseline, within 48 days of the index procedure	VARC-2 (12)
Access Site	Any location (arterial or venous) traversed by a guidewire, a catheter or a sheath	VARC-1 (13)
Access site related complication	Any adverse clinical consequence possibly associated with any of the access sites used during the procedure	VARC-1
Anemia	A condition in which the blood is deficient in red blood cells, in hemoglobin, or in total volume, without clear evidence of overt bleeding, that is actionable (e.g. requires medications, transfusion etc.)	Sponsor
Aortic Root Compression	Aortic Root Compression (ARC) can occur during balloon sizing of the RVOT or during coronary compression testing (BS/CCT) prior to TPVI, causing aortic valve dysfunction and/or root distortion with or without coronary compression.	(14)
Arrhythmia / Conduction System Injury (Defect)	Arrhythmia: an irregular heart rate or abnormal rhythm resulting in symptoms or requiring medical intervention. Conduction system defect: an impairment of the electrical pathways and specialized muscular fibers that conduct impulses through the heart (ex. bundle branch block, heart block, etc.)	Sponsor
Bleeding Event	Bleeding, including, but not limited to fatal bleed, bleeding associated with transfusion, drop in Hgb or visible sign of blood loss	Sponsor
Coagulopathy	A pathologic condition that affects the ability of the blood to coagulate. Examples include hemophilia, drug-induced clotting disorder, thrombocytopenia and Von Willebrand's disease	Sponsor
Cardiopulmonary bypass (CPB)	Bypass of the function of the heart and lungs as in open heart surgery	Sponsor
Conversion to open surgery	Any conversion to complete TPVI procedure secondary to any procedure-related complications	Sponsor
Coronary artery compression	Angiographic or echocardiographic evidence of a new, partial or complete, compression of a coronary artery, associated with the TPVI procedure	Sponsor

<table>
<tr><th>Term</th><th>Definition</th><th>Reference</th></tr>
<tr><td>Device Fracture</td><td>
<table>
<tr><td>Type I</td><td>Wire fracture(s) without loss of frame integrity[1] or hemodynamic dysfunction[2]</td></tr>
<tr><td>Type IIa</td><td>Wire fracture(s) resulting in loss of frame integrity[1] without hemodynamic dysfunction[2] or embolization</td></tr>
<tr><td>Type IIb</td><td>Wire fracture(s) resulting in loss of frame integrity[1] resulting in hemodynamic dysfunction[2] without embolization</td></tr>
<tr><td>Type IIIa</td><td>Wire fracture(s) with fragment separation resulting in embolization without hemodynamic dysfunction[2]</td></tr>
<tr><td>Type IIIb</td><td>Wire fracture(s) with fragment separation resulting in embolization and hemodynamic dysfunction[2]</td></tr>
</table>
[1] Significant deformation (e.g., partial collapse, in-folding, fragmentation, etc.) or instability of a stent segment resulting in an increased risk of future hemodynamic dysfunction and/or embolization (Type IIa) or hemodynamic dysfunction (Type IIb)
[2] Increase in mean gradient ≥10 mmHg resulting in mean gradient ≥35 mmHg, or new occurrence or increase of ≥1 grade of total pulmonary regurgitation resulting in ≥ moderate pulmonary regurgitation as compared to most recent echocardiographic assessment prior to stent fracture
</td><td>Sponsor</td></tr>
<tr><td>Device Success</td><td>Device Success is defined as a composite of:
Single Alterra deployed into the desired location and
Single THV implanted in the desired location within the Alterra (staged procedures allowed) and
Right ventricle to pulmonary artery (RV-PA) peak-to-peak gradient < 35 mmHg post-THV implantation and
Less than moderate total PR by discharge TTE (or earliest evaluable TTE) and
Free of explant at 24 hours post-implantation</td><td>Sponsor</td></tr>
<tr><td>Device (Valve) thrombosis</td><td>Any thrombus attached to or near an implanted valve that occludes part of the blood flow path, interferes with valve function, or is sufficiently large to warrant treatment. Note that valve-associated thrombus identified at autopsy in a patient whose cause of death was not valve-related should not be reported as valve thrombosis</td><td>VARC-2</td></tr>
<tr><td>Embolism</td><td>Embolism is defined as a free-flowing blood clot or lesion material that is located in the systemic or pulmonary circulation that occurs in the absence of infection after immediate perioperative period.
Pulmonary embolic event is an operative, autopsy or clinically documented embolus that produces symptoms from complete or partial obstruction of a pulmonary or bronchial artery</td><td>STS alignment</td></tr>
<tr><td>Explant</td><td>Removal of the Alterra for any reason</td><td>Sponsor</td></tr>
<tr><td>Index Procedure</td><td>Placement of Alterra Adaptive present study device and/or additional procedures (ex. placement of Sapien 3 valve) occurring in the catheter lab and/or operating room which are completed prior to subject transfer to a post-procedure recovery unit (e.g. Recovery Room, ICU/CCU, etc.)</td><td>Sponsor</td></tr>
</table>

Term	Definition	Reference
Mortality	Cardiovascular mortality Any of the following criteria: • Death due to proximate cardiac cause (e.g. myocardial infarction, cardiac tamponade, worsening heart failure) • Death caused by non-coronary vascular conditions such as Neurological events, pulmonary embolism, ruptured aortic aneurysm, dissecting aneurysm or other vascular disease • All procedure-related deaths, including those related to a complication of the procedure or treatment for a complication of the procedure • All valve-related deaths including structural or nonstructural valve dysfunction or other valve-related adverse events • Sudden or unwitnessed death • Death of unknown cause	VARC-2
	Non-cardiovascular mortality Any death in which the primary cause of death is clearly related to another condition (e.g. trauma, cancer, suicide)	
Myocardial Infarction	An acute ischemic event that is associated with documented and clinically significant myocardial necrosis.	STS
New York Heart Association Classification (NYHA)	Class I: Patients with cardiac disease but resulting in no limitation of physical activity Class II: Patients with cardiac disease resulting in slight limitation of physical activity. They are comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnea or anginal pain Class III: Patients with cardiac disease resulting in marked limitation of physical activity. They are comfortable at rest. Less than ordinary physical activity causes fatigue, palpitation, dyspnea, or anginal pain Class IV: Patients with cardiac disease resulting in inability to carry on any physical activity without discomfort. Symptoms of heart failure or the anginal syndrome may be present even at rest. If any physical activity is undertaken, discomfort increases	NYHA
Other TPVI-Related Complications	Conversion to open surgery Conversion to open sternotomy during the TPVI procedure secondary to any procedure-related complications	VARC-2 alignment
	Unplanned use of cardiopulmonary bypass (CPB) Unplanned use of CPB for hemodynamic support at any time during the TPVI procedure.	VARC-2

<table>
<tr><th>Term</th><th>Definition</th><th>Reference</th></tr>
<tr><td></td><td><u>Coronary artery compression</u>
Angiographic or echocardiographic evidence of a new, partial or complete, compression of a coronary artery, associated with the TPVI procedure
Aligned from VARC-2 definition for Coronary Obstruction</td><td>VARC-2 alignment</td></tr>
<tr><td></td><td><u>Ventricular septal perforation</u>
Angiographic or echocardiographic evidence of a new septal perforation during or after the TPVI procedure</td><td>VARC-2 alignment</td></tr>
<tr><td></td><td><u>Tricuspid valve apparatus damage or dysfunction</u>
Angiographic or echocardiographic evidence of new damage (chordae papillary muscle, or to the leaflet) to the tricuspid valve apparatus or dysfunction (e.g. restrictions due to the THV) of the tricuspid valve during or after the TPVI procedure</td><td>VARC-2 alignment</td></tr>
<tr><td></td><td><u>Cardiac tamponade</u>
Evidence of a new pericardial effusion associated with hemodynamic instability and clearly related to the TPVI procedure</td><td>VARC-2 alignment</td></tr>
<tr><td></td><td><u>Endocarditis</u>
Any one of the following:
Fulfillment of the Duke endocarditis criteria (15)
Evidence of abscess, paravalvular leak, pus, or vegetation confirmed as secondary to infection by histological or bacteriological studies during a re-operation
Findings of abscess, pus, or vegetation involving a repaired or replaced valve during an autopsy</td><td>VARC-2</td></tr>
<tr><td>Pulmonary Hypertension</td><td>Resting mean PA pressure of greater than 25 mmHg and greater than 30 mmHg during exercise or when the pulmonary vascular resistance is greater than 4 woods units.</td><td>(16)</td></tr>
<tr><td></td><td>Severe: Primary or secondary pulmonary hypertension with PA systolic pressures greater than 2/3 of systemic pressure</td><td>VARC-2</td></tr>
<tr><td>Pulmonary Regurgitation</td><td>Regurgitation of blood through (transvalvular) and/or around (paravalvular) the pulmonary valve</td><td>ASE (17)</td></tr>
<tr><td></td><td>Criteria for Defining Pulmonary Regurgitation by TTE<table><tr><th>Grade</th><th>Jet Width at its Origin
(Diameter of Pulmonary Annulus)</th></tr><tr><td>None/Trace</td><td>Not quantifiable or within the error of the methods</td></tr><tr><td>Mild</td><td>5-30 %</td></tr><tr><td>Moderate</td><td>30-64 %</td></tr><tr><td>Severe</td><td>≥ 65 %</td></tr></table></td><td>Echo Core Lab</td></tr>
</table>

<table>
<tr><th>Term</th><th>Definition</th><th>Reference</th></tr>
<tr><td>Reintervention</td><td>Any intervention that repairs, alters or replaces a previously implanted or operated valve, which occurs after the completion of the valve implant procedure and the transfer to the procedure room. These interventions include:
Balloon pulmonary valvuloplasty
Transcatheter pulmonic valve implantation
Surgical pulmonary valve replacement
Valve in valve
Paravalvular leak closure</td><td>Sponsor</td></tr>
<tr><td>RVOT Stenosis/ Obstruction</td><td>Narrowing of the pulmonary artery and/or valve leading to diminished blood flow. Pulmonary stenosis is rated on the severity of the stenosis based on the following criteria:
RVOT obstruction is defined as a peak gradient > 45 mmHg and/or right ventricle pressure to systemic pressure ratio of more than 70%:
Criteria for Defining Pulmonary Stenosis<table><tr><th>Severity</th><th>Peak Gradient (mmHg)</th></tr><tr><td>Mild</td><td>≤ 30</td></tr><tr><td>Moderate</td><td>31-45</td></tr><tr><td>Severe</td><td>> 45</td></tr></table></td><td>ACC/AHA Congenital , (18)</td></tr>
</table>

Term	Definition	Reference
Stroke/ Transient Ischemic Attack (TIA)	Diagnostic criteria • Acute episode of a focal or global neurological deficit with at least one of the following: change in level of consciousness, hemiplegia, hemiparesis, numbness or sensory loss affecting one side of the body, dysphasia or aphasia, hemianopia, amaurosis fugax, or other neurological signs or symptoms consistent with stroke • Stroke – Duration of a focal or global neurological deficit ≥24 h; OR <24 h if available neuroimaging documents a new hemorrhage or infarct; OR the neurological deficit results in death • TIA – Duration of a focal or global neurological deficit <24 h, any variable neuroimaging does not demonstrate a new hemorrhage or infarct • No other readily identifiable non-stroke cause for the clinical presentation (e.g. brain tumor, trauma, infection, hypoglycemia, peripheral lesion, pharmacological influences), to be determined by or in conjunction with designated neurologist* • Confirmation of the diagnosis by at least one of the following: o Neurologist or neurosurgical specialist o Neuroimaging procedure (CT scan or brain MRI), but stroke may be diagnosed on clinical grounds alone	VARC-2
	Stroke Classification: • Ischemic – An acute episode of focal cerebral, spinal, or retinal dysfunction caused by infarction of central nervous system tissue • Hemorrhagic – An acute episode of focal or global cerebral or spinal dysfunction caused by intraparenchymal, intraventricular or subarachnoid hemorrhage • A stroke may be classified as undetermined if there is insufficient information to allow categorization as ischemic or hemorrhagic	
	* Patients with non-focal global encephalopathy will not be reported as a stroke without unequivocal evidence of cerebral infarction-based upon neuroimaging studies (CT scan or Brain MRI).	

Term	Definition	Reference
Syncope	A temporary loss of consciousness due to generalized cerebral ischemia	
Vascular injury	Injury that may be caused by a guidewire, vascular sheath, delivery catheter, or any balloon used for pulmonic valve predilatation and can include arterial dissection, perforation, arteriovenous fistula, pseudoaneurysm formation, retroperitoneal hemorrhage, or incomplete arteriotomy closure Venous injuries can include perforation, tears and thromboembolism Cardiac vascular injury can include perforation or tearing of the major cardiac structures that require repair	Sponsor
Valve/Stent malpositioning	**Valve/Stent migration** • After initial correct positioning, the valve or stent prosthesis moves upward or downward >4 mm within the landing zone from its initial position, with or without consequences **Valve/Stent embolization** • The valve or stent prosthesis moves during or after deployment such that it loses contact with the landing zone **Ectopic valve/stent deployment** • Permanent deployment of the valve or stent prosthesis in a location other than the intended location in the pulmonary artery	Sponsor/ VARC-2

APPENDIX C: References

1. Lurz P, Coats L, Khambadkone S, Nordmeyer J, Boudjemline Y, Schievano S, et al. Percutaneous pulmonary valve implantation: impact of evolving technology and learning curve on clinical outcome. Circulation. 2008;117(15):1964-72.
2. Bonhoeffer P, Boudjemline Y, Qureshi SA, Le Bidois J, Iserin L, Acar P, et al. Percutaneous insertion of the pulmonary valve. Journal of the American College of Cardiology. 2002;39(10):1664-9.
3. Tweddell JS, Pelech AN, Frommelt PC, Mussatto KA, Wyman JD, Fedderly RT, et al. Factors affecting longevity of homograft valves used in right ventricular outflow tract reconstruction for congenital heart disease. Circulation. 2000;102(suppl 3):Iii-130.
4. Homann M, Haehnel JC, Mendler N, Paek SU, Holper K, Meisner H, et al. Reconstruction of the RVOT with valved biological conduits: 25 years experience with allografts and xenografts. European journal of cardio-thoracic surgery. 2000;17(6):624-30.
5. Cribier A, Eltchaninoff H, Bash A, Borenstein N, Tron C, Bauer F, et al. Percutaneous transcatheter implantation of an aortic valve prosthesis for calcific aortic stenosis: first human case description. Circulation. 2002;106(24):3006-8.
6. Capelli C, Taylor AM, Migliavacca F, Bonhoeffer P, Schievano S. Patient-specific reconstructed anatomies and computer simulations are fundamental for selecting medical device treatment: application to a new percutaneous pulmonary valve. Philosophical Transactions of the Royal Society A: Mathematical, Physical and Engineering Sciences. 2010;368(1921):3027.
7. Phillips AB, Nevin P, Shah A, Olshove V, Garg R, Zahn EM. Development of a novel hybrid strategy for transcatheter pulmonary valve placement in patients following transannular patch repair of tetralogy of fallot. Catheterization and cardiovascular interventions : official journal of the Society for Cardiac Angiography & Interventions. 2016;87(3):403-10.
8. Zahn EM, Chang JC, Armer D, Garg R. First human implant of the Alterra Adaptive Prestent(TM) : A new self-expanding device designed to remodel the right ventricular outflow tract. Catheterization and cardiovascular interventions : official journal of the Society for Cardiac Angiography & Interventions. 2018;91(6):1125-9.
9. Dajani AS, Taubert KA, Wilson W, Bolger AF, Bayer A, Ferrieri P, et al. Prevention of bacterial endocarditis: recommendations by the American Heart Association. Circulation. 1997;96(1):358-66.
10. Food and Drug Administration. Melody Transcatheter Pulmonary Valve Summary of Safety and Effectiveness 2017 [Available from: https://www.accessdata.fda.gov/cdrh_docs/pdf14/p140017s005b.pdf.
11. Hintze J. PASS 13. www.ncss.com ed. Kaysville, Utah, USA: NCSS, LLC; 2014.
12. Kappetein AP, Head SJ, Genereux P, Piazza N, van Mieghem NM, Blackstone EH, et al. Updated standardized endpoint definitions for transcatheter aortic valve implantation: the Valve Academic Research Consortium-2 consensus document (VARC-2). European journal of cardio-thoracic surgery : official journal of the European Association for Cardio-thoracic Surgery. 2012;42(5):S45-60.
13. Leon MB, Piazza N, Nikolsky E, Blackstone EH, Cutlip DE, Kappetein AP, et al. Standardized endpoint definitions for Transcatheter Aortic Valve Implantation clinical trials:

a consensus report from the Valve Academic Research Consortium. J Am Coll Cardiol. 2011;57(3):253-69.

14. Lindsay I, Aboulhosn J, Salem M, Levi D. Aortic root compression during transcatheter pulmonary valve replacement. Catheterization and cardiovascular interventions : official journal of the Society for Cardiac Angiography & Interventions. 2016;88(5):814-21.
15. Durack DT, Lukes AS, Bright DK. New criteria for diagnosis of infective endocarditis: utilization of specific echocardiographic findings. Duke Endocarditis Service. The American journal of medicine. 1994;96(3):200-9.
16. Nihill MR. Clinical management of patients with pulmonary hypertension. Moss and Adams heart disease in infants, children, and adolescents Baltimore: Williams & Wilkins. 1995:1695-711.
17. Rudski LG, Lai WW, Afilalo J, Hua L, Handschumacher MD, Chandrasekaran K, et al. Guidelines for the echocardiographic assessment of the right heart in adults: a report from the American Society of Echocardiography: endorsed by the European Association of Echocardiography, a registered branch of the European Society of Cardiology, and the Canadian Society of Echocardiography. Journal of the American Society of Echocardiography. 2010;23(7):685-713.
18. Allen HD, Beekman RH, Garson A, Hijazi ZM, Mullins C, O'Laughlin MP, et al. Pediatric therapeutic cardiac catheterization: a statement for healthcare professionals from the Council on Cardiovascular Disease in the Young, American Heart Association. Circulation. 1998;97(6):609-25.
19. Nordmeyer J, Khambadkone S, Coats L, Schievano S, Lurz P, Parenzan G, et al. Risk stratification, systematic classification, and anticipatory management strategies for stent fracture after percutaneous pulmonary valve implantation. Circulation. 2007;115(11):1392-7.