7.01.131	Transcatheter Pulmonary Valve Implantation		
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Section:	7.0 Surgery	**Page:**	Page 1 of 26

Policy Statement

I. Transcatheter pulmonary valve implantation (TPVI), with a Food and Drug Administration-approved valve may be considered **medically necessary** for individuals with congenital heart disease and current right ventricular outflow tract obstruction (RVOT) or regurgitation including **one or more** of the following indications:
   A. Individuals with right ventricle-to-pulmonary artery conduit with or without bioprosthetic valve with at least moderate pulmonic regurgitation
   B. Individuals with native or patched RVOT with at least moderate pulmonic regurgitation
   C. Individuals with right ventricle-to-pulmonary artery conduit with or without bioprosthetic valve with pulmonic stenosis (mean RVOT gradient at least 35 mm Hg)
   D. Individuals with native or patched RVOT with pulmonic stenosis (mean RVOT gradient at least 35 mm Hg)

II. Transcatheter pulmonary valve implantation is considered **investigational** for all other indications.

NOTE: Refer to Appendix A to see the policy statement changes (if any) from the previous version.

Policy Guidelines

Coding

The following category I CPT code is for this procedure:

- **33477**: Transcatheter pulmonary valve implantation, percutaneous approach, including pre-stenting of the valve delivery site, when performed

Description

Transcatheter pulmonary valve implantation (TPVI) is a less invasive alternative to open surgical pulmonary valve replacement or reconstruction for right ventricular outflow tract (RVOT) obstruction. Percutaneous pulmonary valve replacement may be indicated for congenital pulmonary stenosis. Pulmonary stenosis or regurgitation in a patient with congenital heart disease who has previously undergone RVOT surgery are additional indications. Patients with prior congenital heart disease repair are at risk of needing repeated reconstruction procedures.

Related Policies

- Transcatheter Aortic-Valve Implantation for Aortic Stenosis

Benefit Application

Benefit determinations should be based in all cases on the applicable contract language. To the extent there are any conflicts between these guidelines and the contract language, the contract language will control. Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.

Some state or federal mandates (e.g., Federal Employee Program [FEP]) prohibits plans from denying Food and Drug Administration (FDA)-approved technologies as investigational. In these instances, plans may have to consider the coverage eligibility of FDA-approved technologies on the basis of medical necessity alone.

Regulatory Status

Devices for transcatheter pulmonary valve implantation were initially cleared from marketing by the U.S. Food and Drug Administration (FDA) through the humanitarian device exemption (HDE) process or used off-label until approved by FDA through the premarket approval (PMA) (see Table 1).

Table 1. Regulatory Status of Transcatheter Pulmonary Valve Implantation Devices

Device	Manufacturer	Date Approved	PMA No.	Indications
Melody® Transcatheter Pulmonary Valve (TPV)	Medtronic	Jan 2010	H080002 (HDE)	Pulmonary valve replacement for pediatric and adult patients with a dysfunctional, noncompliant RVOT conduit
Melody® TPV	Medtronic	Jan 2015	P140017	Pulmonary valve replacement for pediatric and adult patients with a dysfunctional, noncompliant RVOT conduit
Melody® TPV	Medtronic	Feb 2017	P140017/S005	Valve-in-valve for patients with a dysfunctional surgical bioprosthetic pulmonary valve
SAPIEN XT™ Transcatheter Heart Valve (pulmonic)	Edwards Lifesciences	Feb 2016	P130009/S037	Pulmonary valve replacement for pediatric and adult patients with a dysfunctional, noncompliant RVOT conduit
Harmony™ TPV	Medtronic	Mar 2021	P200046	Pulmonary valve for pediatric and adult patients with severe pulmonary regurgitation

HDE: humanitarian device exemption; PMA: premarket approval; RVOT: right ventricular outflow tract.

In January 2010, the Melody® TPV and the Ensemble® Transcatheter Valve Delivery System (Medtronic) were approved by FDA under the HDE program for use as an adjunct to surgery in the management of pediatric and adult patients with the following clinical conditions:

- Existence of a full (circumferential) RVOT conduit that is 16 mm or greater in diameter when originally implanted, and
- Dysfunctional RVOT conduits with clinical indication for intervention, and either:
    - regurgitation: moderate-to-severe regurgitation, or
    - stenosis: mean RVOT gradient ≥35 mm Hg.

On January 27, 2015, approval of the Melody system was amended to a PMA because FDA determined that the device represented a breakthrough technology. The PMA was based, in part, on 2 prospective clinical studies, the Melody TPV Long-term Follow-up Post Approval Study and the Melody TPV New Enrollment Post Approval Study.

On February 24, 2017, approval of the Melody system was expanded to include patients with a dysfunctional surgical bioprosthetic valve (valve-in-valve).

The Edwards SAPIEN XT™ Transcatheter Heart Valve (Pulmonic) (Edwards Lifesciences) was approved by FDA in 2016 "for use in pediatric and adult patients with a dysfunctional, noncompliant Right Ventricular Outflow Tract (RVOT) conduit with a clinical indication for intervention and:

- pulmonary regurgitation ≥ moderate and/or
- mean RVOT gradient ≥ 35 mmHg."

The approval for the pulmonic valve indication is a supplement to the 2014 PMA for use of the Edwards SAPIEN XT Transcatheter Heart Valve System for relief of aortic stenosis in patients with symptomatic heart disease due to severe native calcific aortic stenosis and who are judged by a heart team, including a cardiac surgeon, to be at high or greater risk for open surgical therapy (i.e., Society of Thoracic Surgeons operative risk score ≥8% or at a ≥15% risk of mortality at 30 days).

The Harmony™ Transcatheter Pulmonary Valve (Medtronic) received breakthrough technology status in 2019 and PMA in 2021. This device is indicated "for use in pediatric and adult patients with severe pulmonary regurgitation (determined by echocardiography and/or pulmonary regurgitant fraction ≥ 30% by cardiac magnetic resonance imaging) who have a native or surgically-repaired right ventricular outflow tract and are clinically indicated for surgical pulmonary valve replacement."

FDA product code: NPV

Rationale

Background

Congenital Heart Disease

Congenital heart disease, including tetralogy of Fallot, pulmonary atresia, and transposition of the great arteries, is generally treated by surgical repair at an early age. This involves reconstruction of the right ventricular outflow tract (RVOT) and pulmonary valve using a surgical homograft or a bovine-derived valve conduit. These repairs are prone to development of pulmonary stenosis or regurgitation over long periods of follow-up. Individuals living with congenital heart disease also face disparities in social determinants of health and the inability to obtain quality lifelong care for their condition which can contribute to inequities in morbidity and mortality. [1,]

Because individuals with surgically corrected congenital heart disease repair are living into adulthood, RVOT dysfunction following initial repair has become more common. Calcification of the RVOT conduit can lead to pulmonary stenosis, while aneurysmal dilatation can result in pulmonary regurgitation. RVOT dysfunction can lead to decreased exercise tolerance, potentially fatal arrhythmias, and/or irreversible right ventricular dysfunction.[2,]

Treatment

Treatment options for pulmonary stenosis are open surgery with valve replacement, balloon dilatation, or percutaneous stenting.[2,]The established interventions for pulmonary regurgitation are primarily surgical, either reconstruction of the RVOT conduit or replacement of the pulmonary valve. The optimal timing of these interventions is not well understood.[3,]

Literature Review

Evidence reviews assess the clinical evidence to determine whether the use of a technology improves the net health outcome. Broadly defined, health outcomes are length of life, quality of life, and ability to function-including benefits and harms. Every clinical condition has specific outcomes that are important to patients and to managing the course of that condition. Validated outcome measures are necessary to ascertain whether a condition improves or worsens; and whether the magnitude of that change is clinically significant. The net health outcome is a balance of benefits and harms.

To assess whether the evidence is sufficient to draw conclusions about the net health outcome of a technology, 2 domains are examined: the relevance and the quality and credibility. To be relevant, studies must represent one or more intended clinical use of the technology in the intended population and compare an effective and appropriate alternative at a comparable intensity. For some conditions, the alternative will be supportive care or surveillance. The quality and credibility of the evidence depend on study design and conduct, minimizing bias and confounding that can generate incorrect findings. The randomized controlled trial (RCT) is preferred to assess efficacy; however, in some circumstances, nonrandomized studies may be adequate. Randomized controlled trials are rarely large enough or long enough to capture less common adverse events and long-term effects. Other types of studies can be used for these purposes and to assess generalizability to broader clinical populations and settings of clinical practice.

Transcatheter Pulmonary Valve Implantation

Clinical Context and Therapy Purpose

The purpose of transcatheter pulmonary valve implantation (TPVI) is to provide a treatment option that is an alternative to or an improvement on surgical pulmonary valve implantation (SPVI) for patients with congenital heart disease.

Interventions for right ventricular outflow tract (RVOT) dysfunction in patients with congenital heart disease often require numerous repeat open heart procedures for patients who live into adulthood. Transcatheter pulmonary valve replacement offers a less invasive treatment option for patients with congenital heart disease and RVOT dysfunction. It is possible that a less invasive valve replacement technique could spare patients from multiple repeat open heart procedures over long periods of follow-up.

The question addressed in this evidence review is: Does the use of TPVI improve the net health outcome in patients with congenital heart disease and moderate pulmonary stenosis or regurgitation?

The following PICO was used to select literature to inform this review.

Populations

The relevant population of interest is individuals with congenital heart disease and moderate pulmonary stenosis or regurgitation with dysfunctional RVOT or RVOT conduit.

Enrollment in the COngenital Multicenter trial of Pulmonic vAlve regurgitation Studying the SAPIEN InterventIONal THV (COMPASSION) study was limited to patients who met the following inclusion criteria:

- Weight ≥35 kg.
- In situ conduit size of 20 to 26 mm in diameter.
- Moderate or severe pulmonary regurgitation defined as ≥3+ pulmonary regurgitation by transthoracic echocardiogram (TTE) or
- RVOT conduit obstruction with a mean gradient of ≥35 mm Hg by TTE.
- Symptomatic as evidenced by cardiopulmonary exercise testing.
- Catheterization was determined to be feasible by the treating physician.

Interventions

The therapy being considered is TPVI. U.S. Food and Drug Administration (FDA)-Approved Devices are described below.

The Melody Transcatheter Pulmonary Valve (TPV) and the Ensemble Transcatheter Valve Delivery System are used together for percutaneous replacement of a dysfunctional pulmonary valve. The Melody valve consists of a section of bovine jugular vein with an intact native venous valve. The valve and surrounding tissue are sutured within a platinum-iridium stent scaffolding. The transcatheter delivery system consists of a balloon-in-balloon catheter with a retractable sheath and distal cup into which the valve is placed. The procedure is performed on a beating heart without the use of cardiopulmonary bypass. The Melody valve is first crimped to fit into the delivery system. It is introduced through the femoral vein and advanced into the right side of the heart and put into place at the site of the pulmonary valve. The inner balloon is inflated to open the artificial valve, and then the outer balloon is inflated to position the valve into place.

The FDA, under the humanitarian device exemption (HDE) program, cleared these devices for marketing for use as an adjunct to surgery in the management of pediatric and adult patients with the following clinical conditions:

- Existence of a full (circumferential) RVOT conduit that is 16 mm or greater in diameter when originally implanted, and
- Dysfunctional RVOT conduits with clinical indication for intervention, and either:
  - o regurgitation: moderate-to-severe regurgitation, or
  - o stenosis: mean RVOT gradient ≥35 mm Hg.

In 2017, approval of the Melody system was expanded to include patients with a dysfunctional surgical bioprosthetic valve (valve-in-valve).

The Edwards SAPIEN XT Transcatheter Heart Valve (Pulmonic) (Edwards Lifesciences) is composed of a stainless steel frame with bovine pericardial tissue leaflets and available in 23- and 26-mm sizes. It includes a delivery accessories system. It is indicated "for use in pediatric and adult patients with a dysfunctional, noncompliant Right Ventricular Outflow Tract (RVOT) conduit with a clinical indication for intervention and:

- pulmonary regurgitation ≥ moderate and/or
- mean RVOT gradient ≥ 35 mmHg."

The Harmony TPV is composed of self-expanding Nitinol wire struts, a knitted polyester fabric graft, and a porcine pericardial tissue valve. It includes a delivery accessories system, and is indicated for "use in the management of pediatric and adult patients with severe pulmonary regurgitation (i.e., severe pulmonary regurgitation as determined by echocardiography and/or pulmonary regurgitant fraction ≥ 30% as determined by cardiac magnetic resonance imaging) who have a native or surgically-repaired right ventricular outflow tract and are clinically indicated for surgical pulmonary valve replacement."

Comparators

The following practice is currently being used to treat this indication: Open surgical pulmonary valve implantation or reconstruction.

Outcomes

The outcomes of interest are

- Overall survival
- Symptoms: a surrogate for recurrence of symptoms would be needed for reintervention
- Functional outcomes: functional improvement in New York Heart Association NYHA functional class
- Quality of life
- Hospitalizations: length of stay after the procedure
- Treatment-related mortality: periprocedural mortality
- Treatment-related morbidity: periprocedural complications and infective endocarditis

Follow-up at short-term (perioperative), mid-term (3-7 years), and long-term (>7 years) are of interest to monitor outcomes and reintervention rates.

Study Selection Criteria

Methodologically credible studies were selected using the following principles:

- To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs;
- In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies.
- To assess long-term outcomes and adverse events, single-arm studies that capture longer periods of follow-up and/or larger populations were sought.
- Studies with duplicative or overlapping populations were excluded.

Review of Evidence
Food and Drug Administration-Approved Devices and Indications

Systematic Reviews
Systematic Review of Transcatheter Versus Surgical Pulmonary Vein Replacement
Systematic review characteristics and results are described in Tables 2 and 3.

Ribeiro et al (2020) performed a systematic review and meta-analysis of 18 nonrandomized comparative studies of surgical pulmonary valve replacement (SPVR) and transcutaneous pulmonary valve replacement (TPVR).[4,] No RCTs were identified. There were no significant differences in age or gender between the groups, but there were significant differences in anatomic and functional characteristics. Patients undergoing TPVR were more likely to have pulmonary stenosis (29% vs. 12%), while those undergoing SPVR were more likely to have pulmonary regurgitation (57% vs. 22%). There were large numerical differences in the presence of a native ventricle outflow tract/transannular patch (TPVR: 16%, SPVR: 60%; odds ratio [OR]: 0.20, 95% confidence interval [CI]: 0.03 to 1.31), but this difference did not achieve statistical significance. Meta-analysis suggested a reduction in peri-procedural complications (16.5% vs. 41.3%, p=.01) and length of hospital stay (-4.32 days) with the percutaneous approach, with an increased risk of infective endocarditis (5.8% vs. 2.7%, p<.001). There were no significant differences in early mortality, late mortality and need for reintervention. Interpretation is limited by the differences in baseline characteristics between the 2 groups and the possibility of selection bias.
The authors noted that a number of patients underwent SPVR because they were not candidates for TPVR due to RVOT anatomy and/or other cardiac defects.

Table 2. Systematic Review Characteristics

Study	Dates	Trials	Participants	Studies (range)	Design	Duration
Ribeiro et al (2020)[4,]	to 2019	29	Patients undergoing TPVR or SPVR	18 (6-11)	Non-randomized comparative studies of any design.	

SPVR: surgical pulmonary valve replacement; TPVR: transcatheter pulmonary valve replacement

Table 3. Systematic Review Results

Study	Early Mortality	Periprocedural Complications	Length of Hospital Stay	Mid-term Mortality	Infective Endocarditis	Need for Reintervention
Studies	11	7	10	6	10	9
Total N	6071	2284	5174	1503	2338	4692
TPVR	0.2%	16.5%		1.5%	5.8%	2.5%
SPVR	1.2%	41.3%		2.7%	2.7%	5.3%
Diff or (95% CI)	0.56 (0.19 to 1.59)	0.38 (0.18 to 0.82)	-4.32 days (-5.33 to -3.31)	0.78 (0.30 to 2.00)	3.09 (1.89 to 5.06)	0.51 (0.17 to 1.55)
p	.27	.01	<.001	.60	<.001	.24
I^2	0%	73%	100%	0%	0%	71%

CI: confidence interval; OR: odds ratio; SPVR: surgical pulmonary valve replacement; TPVR: transcatheter pulmonary valve replacement.

Nonrandomized Studies
Melody Transcatheter Pulmonary Valve

Pivotal and Post-Approval Studies
The multicenter US Melody transcatheter pulmonary valve (TPV) trial was a prospective uncontrolled trial designed to assess the safety, procedural success, and short-term effectiveness of the Melody TPV. The Summary of Safety and Probable Benefit to support the approval of a HDE to market the Melody TPV was based on clinical data from 99 subjects who were catheterized for potential implantation with the TPV from January 2007 through December 2008,

with expected follow-up and adverse event data on these subjects current through March 2009.[5] Approved indications included RVOT dysfunction, defined as pulmonic regurgitation (moderate or greater) or pulmonic stenosis (mean gradient, ≥35 mm Hg). Also, a circumferential RVOT conduit should exist that is 16 mm or greater in diameter when originally implanted.

The investigators planned to follow 150 patients over 5 years. Eligibility criteria included a dysfunctional RVOT conduit or a dysfunctional bioprosthetic pulmonary valve, plus evidence of heart failure. For patients with NYHA class I heart failure, a Doppler mean gradient of 40 mm Hg or greater or severe pulmonary regurgitation was required; for patients with NYHA class II to IV heart failure, a mean gradient of 35 mm Hg or greater or moderate pulmonary regurgitation was required. These inclusion criteria generally are indications for pulmonary valve replacement. The primary outcomes were defined as procedural success, adverse events from the procedure, and effectiveness, as measured by the proportion of patients with acceptable valve function at 6 months.

Trial results have been published in several reports.[3,6,7] Short- and medium-term outcomes for 136 patients who underwent attempted TPVI were reported by McElhinney et al (2010).[3] A total of 124 (91.2%) of 136 patients had successful implantation. In 12 patients, implantation was not possible due to anatomic or other intraprocedural findings. One (0.7%) death occurred as a result of the procedure, and serious adverse events occurred in 8 (6%) of 136 patients. Adverse events included coronary artery dissection, conduit rupture/tear, wide complex tachycardia, respiratory failure, femoral vein thrombosis, and perforation of the pulmonary artery.

Ninety-four patients with successful implantation had reached the 6-month follow-up at the time of publication. Acceptable valve function, defined as mild pulmonary regurgitation or less on echocardiography, was present in more than 90% of patients. Right ventricular (RV) pressure and RVOT gradient improved following the procedure, and 71 (75.5%) of 94 were in NYHA class I heart failure at 6 months. During follow-up, stent fractures were diagnosed in 25 (20.2%) of 124 patients, and 9 (7.3%) of 124 required implantation of a second valve.

Cheatham et al (2015) reported on outcomes up to 7 years following TPVI for the 148 patients who received and were discharged with a TPV in the US Melody TPV trial (of 171 patients enrolled).[7] Of the 171 patients enrolled, 167 underwent catheterization, 150 had a Melody valve implanted, and 148 of those survived to discharge with the Melody valve in place. On echocardiogram at discharge, pulmonary regurgitation was absent/trivial or mild in 140 patients and 5 patients, respectively, which represented a significant improvement from baseline. Over a median follow-up of 4.5 years (range, 0.4 to 7.0 years), 4 deaths occurred. During the follow-up period, 32 patients required a reintervention on RVOT, 25 of which were TPV reinterventions. A total of 11 patients required Melody valve explantation. Among the 113 patients who were alive and free from reintervention at a median of 4.5 years postimplantation, the most recent RVOT gradient was unchanged from early after valve implantation. Functional outcomes generally improved during the study: before TPVI, 14% of patients were in NYHA class I and 17% were in class III or IV. At every postimplantation annual evaluation, at least 74% of patients were in class I and no more than 1% to 2% were in class III or IV.

A secondary publication (2012) from the US Melody TPV trial focused on the change in exercise function following TPVI.[8] Patients completed a standardized cardiopulmonary regimen 2 months before and 6 months after TPVI. Results of pre- and postexercise parameters were available for 94 to 114 patients, depending on the specific outcome. Numerous physiologic outcome measures were reported, with some showing a statistically significant change between the 2 time points, and others not. For example, there was a significant increase in the percent predicted maximal workload from 65.0% at baseline to 68.3% at follow-up ($p<.001$) and a significant decrease in the ratio of minute ventilation to CO_2 production from 30.8 at baseline to 29.1 at follow-up ($p<.001$). In contrast, there were no significant changes in peak oxygen consumption or spirometric measures of pulmonary function. This trial reported modest benefits in exercise parameters for patients treated with TPVI. The results were limited by the lack of a control group and by a large number of patients who did not have completed exercise results available (approximately one-third of total).

The 2015 premarket approval (PMA) of the Melody TPV was based on the interim analysis and a retrospective pooling analysis of the 2 postapproval studies conditioned by the prior humanitarian device exemption. An additional supplemental dataset from the Melody TPV European and Canadian Post-Market Surveillance Study (PMSS) was included in the PMA.[9,]

Armstrong et al (2014) published 1-year follow-up results of the Melody TPV Long-term Follow-up Post Approval Study (PAS), a prospective study designed to evaluate the short-term hemodynamic changes following device implantation.[10,] The study used historical controls from the Melody pivotal investigational device exemption (IDE) trial described above to investigate whether the short-term effectiveness of the device was noninferior to results shown in the IDE trial. PAS enrolled 120 subjects, 101 of whom underwent attempted TPVI. Patient selection was based on the criteria used in the IDE trial but did not include the age (³5 years of age) and weight (≥30 kg) limitations. Procedure-related significant adverse events occurred in 16 patients (13.3% of total cohort; 15.8% of those who had an attempted TPVI), the most common of which was a confined conduit tear. Procedural success occurred in 99 subjects (98% of those with an attempted TPVI). At 1-year follow-up, the proportion of patients in NYHA class I heart failure increased from 35% at baseline to 89%. Of the 99 patients implanted for at least 24 hours, 87 had acceptable TPV hemodynamic function confirmed at 6 months (96.7% of those with evaluable echocardiographic data, 87.9% of entire cohort) and 82 had acceptable TPV hemodynamic function at 1 year (94.3% of those with evaluable echocardiographic data, 82.8% of the entire cohort). Following the procedural period, serious device-related adverse events occurred in 8%, most commonly endocarditis (n=3 patients).

Gillespie et al (2015) evaluated results of TPVI after a Ross procedure in a retrospective review of pooled findings from the US Melody TPV trial and PAS and an additional European registry, the manufacturer-sponsored Melody TPV PMSS conducted in Canada and Europe (NCT00688571).[11,] In the pooled sample (N=358 patients), 67 (19%) had a prior Ross procedure. A Melody valve was successfully implanted in 56 (84%) of 67 Ross patients who underwent catheterization with intent for TPVI. Six (9%) patients had symptomatic coronary artery compression after TPVI or did not undergo implantation due to the risk of compression. RV hemodynamics generally improved after TPVI, but RVOT reinterventions were required in 12 of 55 patients discharged from the implant hospitalization with the Melody valve in place.

The Melody TPV New Enrollment Study was intended to roll in the new patient enrollment study specified as a condition of approval for the Melody TPV HDE on January 25, 2010.[12,] This study used the protocol dated September 24, 2013, Version 2, included in H080002/S015. The study is a prospective, nonrandomized, multicenter, historically controlled clinical trial, designed to assess the postmarket performance of the Melody TPV in a representative population of providers and patients, with 5-year follow-up. The primary endpoint is freedom from TPV dysfunction, with a performance goal of 75% or greater at 6 months. Secondary end points include procedural success, serious procedural- and device-related adverse events, stent fracture, reintervention on the TPV, surgical replacement of the RVOT conduit, death (all-cause, procedure-related, and device-related), and NYHA classification.

The February 2017 approval of the Melody system expanded to include patients with a dysfunctional surgical bioprosthetic valve (valve-in-valve) is based on data pooled from 3 sources[13,]:

- Melody TPV Long-term Follow-up PAS: 8 patients
- Melody TPV New Enrollment PAS: 17 patients
- Real-World Data: 100 patients.

Of 125 patients pooled from the 3 studies listed above, 56.8% (71) patients were available for analysis at study completion, the 1-year postimplant visit. Baseline pooled subject median age was 22.0 years (range, 5.0-79 years), with 45.6% female and 54.4% male. Tetralogy of Fallot was the most common congenital heart disease diagnosis recorded in 72.8% of subjects, 66.4% of whom had pulmonary stenosis or atresia. There was no mortality for any cause, major stent fracture, occurrence of endocarditis, RVOT reoperation, or catheter reintervention among available patients at 1 year. Procedural failure as defined by more than trivial pulmonary regurgitation by angiography postimplant occurred in 10.1% (12/119) subjects. There were no device explants within 24 hours of implantation. The mean RVOT gradient was reduced from 29.5 mm Hg at baseline to 14.3 mm Hg at 1 year postimplantation. In this PMA, existing clinical data were not leveraged to support approval of a pediatric patient population. This submission included pediatric data to support the pediatric indication and no extrapolation was necessary.

Jones et al (2021) reported on 10-year outcomes of the Melody IDE trial.[14,] There were 171 patients enrolled in the Melody IDE trial, and 58 of those patients completed the 10-year follow-up assessment. The primary outcome assessed was freedom from TPV dysfunction; additional outcomes were time-dependent (i.e., time to catheter reintervention, surgical RVOT reoperation, stent fracture, and death). The estimated freedom at 10 years from TPV dysfunction was 53% (95% CI, 40% to 65%) and was significantly shorter in children than in adults. The estimated freedom from mortality at 10 years was 90% (95% CI, 79% to 96%) and did not differ significantly between age groups. The estimated freedom from any TPV reintervention and freedom from RVOT reoperation were 60% (95% CI, 47% to 71%) and 79% (95% CI, 67% to 87%), respectively.

Comparative Observational Studies

Georgieve et al (2020) interrogated a database of all patients who had undergone TPVI (n=241) with the Melody valve or SPVR (n=211) between 2006 and 2018 at a European heart center.[15,] If technically possible, TPVI was preferred. Patients with inappropriate anatomy of the coronary arteries or with large RVOTs were treated with SPVR. The median follow-up time was 5.4 years (3 months to 12.5 years). Estimated survival after 10 years was 94% in the Melody group and 92% in the SPVR group. Infective endocarditis tended to be higher with the percutaneous approach, but there was no difference in survival of the implanted pulmonary valve (TPVI: 80% vs. SPVR: 73%, p=.46). There were a number of significant differences in patient characteristics and follow-up, limiting interpretation of these results.

Edwards Sapien XT Transcatheter Heart Valve (Pulmonic)

Pivotal Study

Edwards Lifesciences, manufacturer of the SAPIEN transcatheter heart valve (THV), performed a clinical study to establish the safety and efficacy of its pulmonic implantation in patients with dysfunctional RVOT conduits in the United States under IDE G060242 (COMPASSION trial). Data from this clinical study were the basis for the PMA decision for the pulmonary valve implantation indication. Patients were treated between April 2008 and November 2014. The database supplement reflects data collected through March 2015 and includes 81 patients. There were 7 investigational sites.

This prospective, nonrandomized, multicenter clinical study assessed the safety and effectiveness of pulmonic implantation of the SAPIEN THV in patients with dysfunctional RVOT conduits requiring treatment for moderate or severe pulmonary regurgitation by TTE and/or RVOT conduit obstruction with a mean gradient of 35 mm Hg or higher by TTE. The SAPIEN THV, the first-generation valve of the SAPIEN device line, is no longer available for distribution. The valve sizes used in the COMPASSION trial included the 23- and 26-mm sizes, which were the only sizes available for the SAPIEN THV. The 29-mm valve size was not evaluated in the COMPASSION trial. Most data derived from patients who received the 23-mm THV size. Aortic experience with the 29-mm SAPIEN XT THV showed no significant difference in the long-term performance compared with the 23- and 26-mm sizes. Furthermore, no observed results suggested that the 29-mm valve size would perform worse than other available sizes in the pulmonic location.

All patients were scheduled to return for follow-ups at day 1 postprocedure, discharge, 30 days, 6 months, 12 months, and annually after that for 5 years postoperatively. Baseline evaluation included TTE, x-ray, magnetic resonance imaging, or computed tomography, angiogram, and electroencephalograph. Assessment of NYHA class, magnetic resonance imaging or computed tomography, and angiogram were part of the 6-month evaluation.

The primary end point was freedom from the device- or procedure-related death and/or reintervention at 1 year. The secondary end points were:

- Freedom from major adverse cardiac and cerebrovascular events at 6 months. Major adverse cardiac and cerebrovascular events was defined as all-cause mortality, myocardial infarction, reintervention, vascular injury resulting in the need for an unplanned vascular intervention, stroke, and pulmonary embolism.
- Functional improvement at 6 months as defined by:
    - Improved valve hemodynamics as demonstrated via TTE:
        - Decrease in pulmonary regurgitation to mild or less for regurgitant lesions
        - Decrease in the mean pulmonary gradient to less than 30 mm Hg for stenotic lesions
        - Improvement in both pulmonary regurgitation and gradient (above) for mixed lesions.
    - Improvement of 1 or more NYHA functional classes from baseline for patients in NYHA functional classes ≥2 at baseline.
    - Freedom from recurrent pulmonary stenosis.

Of 81 patients enrolled in the PMA study, 2 patients were screening failures, 9 patients did not receive the valve, another received the valve in a nontarget location. Therefore, 69 patients were available for analysis in the valve implant population at study completion.

The median duration of follow-up for the safety population was 3.04 years (range, 0 to 5.31 years). Males were 65.8% of the population, and 63.3% were at least 22 years of age. The primary indications for valve implantation were pulmonary stenosis (8.9%), pulmonary regurgitation (12.7%), and both stenosis and regurgitation (78.5%). The primary etiology requiring reconstruction of the RVOT and placement of a pulmonary conduit for the safety population was tetralogy of Fallot (42%).

The prespecified performance goal for the primary end point was 75%. The primary outcome was met by 100% of patients; there were 3 reintervention events. At 5 years, the primary outcome using a Kaplan-Meier estimate was 77.1%. Because there was no device- or procedure-related patient deaths at 5 years, the incidence of reinterventions solely contributed to the estimate.
Freedom from reintervention to 5 years for the valve implant population using a Kaplan-Meier estimate was reported by type of reintervention: (a) freedom from surgical pulmonic valve repair was 98.3% at 1 year and 91.8% at 5 years; (b) freedom from TPVI was 97.1% at 1 year and 85.8% at 5 years; (c) freedom from balloon valvuloplasty was 100% at 1 year and 93.7% at 5 years; and (d) freedom from other types of reintervention was 100% at 1 year and 97.9% at 5 years.

For secondary outcomes, freedom from major adverse cardiac and cerebrovascular events at 6 months in the valve implant population was 94.1%. Because 2 (2.5%) of 79 patients experienced a device migration early in the trial, the instructions for use were modified. No other device migrations subsequently occurred in the trial. Serious adverse events for RVOT conduit ruptures occurred in 5 (6.3%) of 79 patients. These 5 ruptures were related to balloon valvuloplasty or placement of a present; no ruptures occurred during placement of the SAPIEN THV. There was 1 neurologic event (not stroke), 1 thromboembolism, and 4 endocarditis events at the 1-year follow-up.

Adjunctive analyses of safety and effectiveness stratified by patients ages 21 years or younger at baseline versus patients ages 22 years or older at baseline were conducted. The COMPASSION study was not designed to investigate the differences in outcomes between age groups and, therefore, no statistical inferences can be made.

The analysis of functional improvement outcomes by age group is summarized in Table 4.

Table 4. Edwards Sapien XT Transcatheter Heart Valve (Pulmonic) PMA Approval Study: Overall Functional Improvement by Age Group for Valve Implanted Population

End Points	Age 21 or Younger (n=27)		Age 22 or Older (n=42)	
	Outcome Rate, n/N (%)		Outcome Rate, n/N (%)	
	1 Year	5 Year	1 Year	5 Year
Overall functional improvement	18/22 (85.7)	3/7 (42.9)	29/33 (87.9)	5/8 (62.5)
Improved valve function	19/19 (100.0)	5/5 (100.0)	28/30 (93.3)	6/6 (100.0)
Functional improvement in NYHA class	13/14 (92.9)	4/4 (100.0)	32/33 (97.0)	8/8 (100.0)
Freedom from recurrent pulmonary stenosis	18/19 (94.7)	5/9 (55.6)	31/31 (100.0)	7/10 (70.0)
Improved gradient	7/8 (87.5)	3/3 (100.0)	7/8 (87.5)	2/2 (100.0)

NYHA: New York Heart Association.

Overall functional improvement was defined by the following 4 categories: (a) improved valve function demonstrated by a decrease in pulmonary regurgitation to mild or less per TTE at visit for patients with moderate or more (>2) pulmonary regurgitation at baseline, (b) functional improvement from baseline of 1 or more NYHA functional classes at visit for patients with baseline NYHA functional class of 2 or higher, (c) freedom from recurrent pulmonary stenosis at visit, and (d) improved valve function demonstrated by a decrease in pulmonary stenosis mean gradient to less than 30 mm Hg for patients with pulmonary stenosis mean gradient greater than 30 mm Hg at baseline. Patients with mild or less (≤2+) pulmonary regurgitation at baseline only use categories b, c, and d to determine overall functional improvement. Patients with an NYHA functional class of less than 2 at baseline only use categories a, c, and d to determine overall functional improvement. Patients treated for indications other than pulmonary stenosis only use categories a, b, and d for overall functional improvement. Patients with pulmonary stenosis mean gradient less than 30 mm Hg at baseline only use categories a, b, and c for overall functional improvement.

Harmony Transcatheter Pulmonary Valve

Pivotal Study

A summary of the US FDA Summary of Safety and Effectiveness (2021)[16,] for the Harmony TPV is shown in Tables 5 and 6.

There were 70 patients in the implanted cohort, 20 were from the feasibility phase, 31 were in the pivotal phase with the current TPV 22 and TPV 25 devices, and 19 were in the pivotal cohort with an earlier version (cTPV 25). Technical success was achieved in 95.7% of implantations, and the clinical endpoint of acceptable hemodynamic function without reintervention at 6 months was met in 89.2% of patients. The proportion of patients with severe pulmonary regurgitation decreased from 84.4% at baseline to 1.7% at 6 months. Four out of 70 patients (5.7%), required explant of the TPV; 2 were in the feasibility phase and 2 were with a prior version of the device. There were no explants with the current devices in the pivotal study and no mortalities up to the 6 month follow-up. Quality of life, measured by the 36-item short form survey, was improved most in the areas of physical functioning and role limitations due to physical health. Follow-up to 5 years is continuing.

Table 5. Summary of Pivotal Study Characteristics

Study	Country	Participants	Treatment Delivery	Follow-Up
US FDA SSED (2021)[16,]	US	70 patients with severe pulmonary regurgitation and a	Harmony TPV	5 years

Study	Country	Participants	Treatment Delivery	Follow-Up
		clinical indication for surgical placement of a pulmonary artery conduit or prosthetic valve		

FDA SSED: Food and Drug Administration Summary of Safety and Effectiveness; TPV: Transcatheter pulmonary valve

Table 6. Summary of Pivotal Study Results

Study	Acceptable Hemodynamic Function at 6 mo[a]	Technical Success	Freedom From Device Failure at 6 mo	Mortality at 6 mo	Explant of the TPV
US FDA SSED (2021)[16,]					
N	68	70	70	70	71
	58 (89.2%)	67 (95.7%)	84.3%	0%	5.7%
95% CI	79.1% to 95.6%				

CI: confidence interval; FDA SSED: Food and Drug Administration Summary of Safety and Effectiveness; TPV: Transcatheter pulmonary valve
[a] Acceptable hemodynamic function at 6 mo was defined as a mean right ventricular outflow tract gradient ≤ 40 mm Hg AND pulmonary regurgitant fraction < 20%, without reintervention

Section Summary: Food and Drug Administration-Approved Device and Indications
The evidence for the use of TPVI with the Melody valve, SAPEIN XT, and Harmony systems consists of the prospective, interventional, noncomparative pivotal studies on which each device's FDA approval was based, along with post approval registry studies and additional case series. Overall, the evidence would suggest that TPVI is associated with high rates of short-term technical success and improvements in heart failure-related symptoms and hemodynamic parameters. Studies with postprocedure follow-up extending to a maximum of 7 years have suggested that the functional and hemodynamic improvements are durable, with a number of earlier devices (20% to 30%) requiring reintervention on the pulmonary valve.

Non-Food and Drug Administration-Approved Indications
Nonrandomized Studies
A variety of potential off-label uses of TPVI have been reported in the literature.

Data from the Valve-in-Valve International Database multicenter registry have been evaluated for the off-label use of transcatheter aortic and TPVI prostheses for tricuspid valve-in-valve implantation.[17,] One hundred fifty of 156 patients in the registry had successful tricuspid valve-in-valve with a Melody (n=93) or a SAPIEN (n=57) valve. During a median 13.3-month follow-up, 22 (15%) patients died, all with NYHA class III or IV. There were 10 (6.6%) tricuspid valve reinterventions and 3 (2%) other patients who had significant recurrent dysfunction of the valve. Preintervention, 71% of patients were in NYHA class III or IV; at follow-up, 77% of surviving patients were in NYHA class I or II (p<.001).

A few case series have been on use of the Melody valve in patients with clinical characteristics not corresponding to FDA-approved indications.[18,19,] These indications have included the use of valves in positions other than pulmonic, patients with conduit sizes inconsistent with FDA indications, and patients with prior congenital heart repair surgery not involving the construction of an RVOT conduit. In general, these case series have reported high rates of procedural success with low rates of periprocedural complications, but longer term outcomes are lacking.

Although most studies have evaluated the use of TPVI in patients with a constructed RVOT conduit, a few have evaluated TPVI with either the Melody valve or the Edwards SAPIEN THV in a native RVOT or RVOT without a circumferential conduit. Meadows et al (2014) reported on results from a retrospective, 5-center review of patients who underwent TPV placement in a nonconduit RVOT, with the native tissue comprising at least part of the circumference.[20] Thirty-one patients were included, with indications for RVOT intervention including primarily valvular insufficiency in 14 (45%), obstruction in 3 (10%), and mixed obstruction and insufficiency in 14 (45%). TPVI was successful in all patients, with serious complications in 2 (6%). At a median follow-up of 15 months (range, 1 month to 3.8 years), all patients were alive, and none reported greater than mild pulmonary regurgitation. Among the 19 patients with adequate imaging at follow-up, 6 (32%) had evidence of stent fracture. Three patients were treated for endocarditis or bloodstream infection. Malekzadeh-Milani (2014) reported on outcomes for 34 patients with a native or patched noncircular RVOT who underwent Melody TPV insertion at a single center.[21] The procedure was technically successful in all patients, with early complications occurring in 8.8%. At a mean follow-up of 2.6 years, no patients had stent fracture or migration, and 32 (94.1%) of 34 had no or trivial pulmonary regurgitation.

Adverse Events

A publication focusing on adverse events from the US Melody TPV trial was published in 2011.[22] This report assessed adverse events at a median follow-up of 30 months in 150 patients. Stent fracture occurred in 26% (39/150) of patients. The estimated freedom from stent fracture was 77% at 14 months and 60% at 39 months. Freedom from reinterventions for all patients was estimated to be 86% at 27 months, and freedom from reinterventions for patients with stent fracture was estimated at 49% at 2 years.

Boudjemline et al (2016) conducted a prospective observational study to evaluate predictors of conduit rupture during the preparation of the RVOT for TPVI in a cohort of patients older than age 5 years with RVOT obstruction, pulmonary regurgitation, or mixed lesions, who underwent transcatheter therapies, including balloon dilatation, bare metal stent placement, or TPV placement.[23] Ninety-nine patients were included, 56 of whom were adults. Of the total cohort, 83.8% underwent Melody TPVI. Conduit rupture occurred in 9 (9.09%) patients. In 2 of the 9 patients, conduit rupture was angiographically obvious and severe with extension, causing hemodynamic instability. All conduit ruptures occurred during balloon dilatation and occurred in patients with RVOT obstruction. Heavy calcification and the presence of a homograft were associated with conduit rupture risk.

Coronary artery compression during balloon angioplasty or stent placement in the RVOT conduit is considered a relative contraindication to TPV placement. Several studies have evaluated the incidence of coronary artery compression with TPVI. Morray et al (2013) reported on the incidence of coronary artery compression in a 4-center series of 404 patients who underwent attempted TPVI.[24] Three hundred forty-three (85%) patients underwent TPVI, and 21 (5%) patients had evidence of coronary artery compression. Most (n=19) patients with coronary artery compression did not undergo TPV placement. Fraisse et al (2014) reported on the incidence, diagnosis, and outcome of coronary compression among patients treated with transcatheter RVOT interventions for RVOT obstruction, pulmonary regurgitation, or mixed lesions.[25] All patients underwent balloon dilatation and coronary assessment with angiography, which was followed by TPV placement if RVOT dysfunction was ongoing. Of 100 patients evaluated, 83% had implantation of a Melody TPV. Coronary artery compression occurred in 6 cases, all of which could be diagnosed by selective coronary angiogram and/or aortic root angiogram during balloon dilation of the RVOT. No specific risk factors for coronary artery compression were identified.

Summary of Evidence

For individuals who have a history of congenital heart disease and current RVOT obstruction who receive TPVI with a U.S. FDA approved device and indication, the evidence includes a systematic review of retrospective comparative studies and prospective, interventional, noncomparative studies. Relevant outcomes are overall survival, symptoms, functional outcomes, quality of life, hospitalizations, and treatment-related mortality and morbidity. Results of the case series have indicated that there is a high rate of procedural success and low procedural mortality, although the rates of serious procedural adverse events reported ranged from 3.0% to 7.4%. Most valves have demonstrated competent functioning by Doppler echocardiography at 6- to 12-month follow-ups. Publications with longer follow-up have reported stent fractures in up to 26% of patients; however, most stent fractures did not require reintervention. Studies with follow-up extending to a maximum of 7 years post-procedure have suggested that the functional and hemodynamic improvements are durable, but a relatively high proportion of patients (20% to 30%) have required reintervention on the pulmonary valve. Retrospective comparative studies have been reported, but are limited by differences in patient characteristics between those who are treated with percutaneous and open heart procedures. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who have a history of congenital heart disease and current RVOT obstruction who receive TPVI with a non-FDA-approved device or indication, the evidence includes case series. Relevant outcomes are overall survival, symptoms, functional outcomes, quality of life, hospitalizations, and treatment-related mortality and morbidity. There is limited evidence on the off-label use of TPVI including the use of a non-FDA-approved valve or use of an approved valve for a non-FDA-approved indication. The published case series enrolled relatively few patients and are heterogeneous regarding devices used and indications for TPVI. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

Supplemental Information
The purpose of the following information is to provide reference material. Inclusion does not imply endorsement or alignment with the evidence review conclusions.

Clinical Input From Physician Specialty Societies and Academic Medical Centers
While the various physician specialty societies and academic medical centers may collaborate with and make recommendations during this process, through the provision of appropriate reviewers, input received does not represent an endorsement or position statement by the physician specialty societies or academic medical centers, unless otherwise noted.

2018 Input
Clinical input was sought to help determine whether the use of transcatheter pulmonary valve implantation (TPVI) for individuals with congenital heart disease and current right ventricular outflow tract (RVOT) obstruction or regurgitation would provide a clinically meaningful improvement in the net health outcome and whether its use is consistent with generally accepted medical practice. In response to requests, clinical input on the use of TPVI was received from 2 specialty society-level respondents while this policy was under review in 2018. The combined clinical input response incorporated input from a panel including physicians affiliated with academic medical centers.

Clinical input was provided by the following specialty societies:

- American College of Cardiology (ACC) and Society for Cardiovascular Angiography and Interventions (SCAI)[a]

[a] Indicates that conflicts of interest related to the topic where clinical input is being sought were identified by this respondent (see Appendix).

The clinical input supports that the following indications provide a clinically meaningful improvement in the net health outcome and are consistent with generally accepted medical practice:

- Use of TPVI for individuals with right ventricle-to-pulmonary artery conduit with or without bioprosthetic valve with at least moderate pulmonic regurgitation;
- Use of TPVI for individuals with native or patched RVOT with at least moderate pulmonic regurgitation;

- Use of TPVI for individuals with right ventricle-to-pulmonary artery conduit with or without bioprosthetic valve with pulmonic stenosis (mean RVOT gradient at least 35 mm Hg); or
- Use of TPVI for individuals with native or patched RVOT with pulmonic stenosis (mean RVOT gradient at least 35 mm Hg).

Practice Guidelines and Position Statements

Guidelines or position statements will be considered for inclusion in 'Supplemental Information' if they were issued by, or jointly by, a US professional society, an international society with US representation, or National Institute for Health and Care Excellence (NICE). Priority will be given to guidelines that are informed by a systematic review, include strength of evidence ratings, and include a description of management of conflict of interest.

Society for Cardiovascular Angiography and Interventions and the Adult Congenital Heart Association

In 2020, the Society for Cardiovascular Angiography and Interventions and the Adult Congenital Heart Association published a position statement on operator and institutional recommendations for TPVI.[26] Included were recommendations for interventional training, practicing physician competency, ongoing education and training, and institutional and team requirements.

American College of Cardiology, American Heart Association, et al

In 2018, the American College of Cardiology and American Heart Association and 6 other societies published comprehensive guidelines on the management of patients with congenital heart disease.[27] Included are recommendations for treatment of pulmonary stenosis, pulmonary regurgitation and tetralogy of Fallot (Table 7).

Table 7. ACC/AHA Guidelines on the Management of Patients with Tetralogy of Fallot

Recommendation	SOR	LOE
"Pulmonary valve replacement (surgical or percutaneous) for relief of symptoms is recommended for patients with repaired TOF and moderate or greater PR with cardiovascular symptoms not otherwise explained."	Strong	B-NR
"Pulmonary valve replacement (surgical or percutaneous) is reasonable for preservation of ventricular size and function in asymptomatic patients with repaired TOF and ventricular enlargement or dysfunction and moderate or greater PR."	Moderate	B-NR
"Surgical pulmonary valve replacement may be reasonable for adults with repaired TOF and moderate or greater PR with other lesions requiring surgical interventions."	Weak	C-EO
"Pulmonary valve replacement, in addition to arrhythmia management, may be considered for adults with repaired TOF and moderate or greater PR and ventricular tachyarrhythmia."	Weak	C-EO

ACC/AHA: American College of Cardiology/American Heart Association; B-NR: Non-randomized (moderate quality evidence); C-EO: consensus of expert opinion; LOE: level of evidence, PR: pulmonary regurgitation; SOR: strength of recommendation; TOF: tetralogy of Fallot

U.S. Preventive Services Task Force Recommendations

Not applicable.

Medicare National Coverage

There is no national coverage determination. In the absence of a national coverage determination, coverage decisions are left to the discretion of local Medicare carriers.

Ongoing and Unpublished Clinical Trials

Some currently unpublished trials that might influence this review are listed in Table 8.

Table 8. Summary of Key Trials

NCT No.	Trial Name	Planned Enrollment	Completion Date
Ongoing			
NCT02744677[a]	COngenital Multicenter Trial of Pulmonic vAlve Dysfunction Studying the SAPIEN 3 interventIONal THV (COMPASSION S3)	108	Dec 2027
NCT02979587	The Medtronic Harmony™ Transcatheter Pulmonary Valve Clinical Study	50	Jan 2031
NCT02987387[a]	New Enrollment SAPIEN XT Post-Approval Study (COMPASSION XT PAS)	57	Sep 2025
NCT04860765[a]	Congenital Multicenter Trial of Pulmonic Valve Dysfunction Studying the SAPIEN 3 Interventional THV Post-Approval Study	150	Aug 2030

NCT: national clinical trial.
[a] Denotes industry-sponsored or cosponsored trial.

Appendix 1

2018 Clinical Input

Objective

Clinical input was sought to help determine whether the use of transcatheter pulmonary valve implantation for individuals with congenital heart disease and current right ventricular outflow tract (RVOT) obstruction or regurgitation would provide a clinically meaningful improvement in the net health outcome and whether its use is consistent with generally accepted medical practice.

Respondents

Clinical input was provided by the following specialty societies:

- American College of Cardiology (ACC) and Society for Cardiovascular Angiography and Interventions (SCAI)[a]

[a] Indicates that conflicts of interest related to the topic where clinical input is being sought were identified by this respondent (see Appendix).

Ratings

		Confidence Level That Clinical Use Expected to Provide Clinically Meaningful Improvement in Net Health Outcome											Confidence Level that Clinical Use is Consistent with Generally Accepted Medical Practice										
			NO (High – Intermediate – Low)					YES (Low – Intermediate – High)						NO (High – Intermediate – Low)					YES (Low – Intermediate – High)				
Clinical Indication	Respondent	Yes or No	5	4	3	2	1	1	2	3	4	5	Yes or No	5	4	3	2	1	1	2	3	4	5
TPVI using Melody® Transcatheter Pulmonary Valve (TPV)																							
RV-PA conduit with or without bioprosthetic valve with at least moderate pulmonic regurgitation	ACC[a] / SCAI[a]	YES										■	YES										■
Native or patched RVOT with at least moderate pulmonic regurgitation	ACC[a] / SCAI[a]	YES									■		YES									■	
Q1c: RV-PA conduit with or without bioprosthetic valve with pulmonic stenosis (mean RVOT gradient at least 35 mm Hg)	ACC[a] / SCAI[a]	YES										■	YES										■
Native or patched RVOT with pulmonic stenosis (mean RVOT gradient at least 35 mm Hg)	ACC[a] / SCAI[a]	YES									■		YES									■	
TPVI using SAPIEN XT™ Transcatheter Heart Valve (pulmonic) or SAPIEN 3 Transcatheter Heart Valve[b]																							
RV-PA conduit with or without bioprosthetic valve with at least moderate pulmonic regurgitation	ACC[a] / SCAI[a]	YES										■	YES										■
Native or patched RVOT with at least moderate pulmonic regurgitation	ACC[a] / SCAI[a]	YES									■		YES									■	
RV-PA conduit with or without bioprosthetic valve with pulmonic stenosis (mean RVOT gradient at least 35 mm Hg)	ACC[a] / SCAI[a]	YES										■	YES										■
Native or patched RVOT with pulmonic stenosis (mean RVOT gradient at least 35 mm Hg)	ACC[a] / SCAI[a]	YES									■		YES									■	

ACC: American College of Cardiology; SCAI: Society for Cardiovascular Angiography and Interventions; RV-PA: right ventricle-to-pulmonary artery; TPVR: transcatheter pulmonary valve replacement.
[a] Indicates that conflicts of interest related to the topic where clinical input is being sought were identified by this respondent.

[b] The choice of SAPIEN transcatheter heart valve may be based on clinical judgment such as size needed for patient anatomy.

Respondent Profile

	Specialty Society	
No.	**Name of Organization**	**Clinical Specialty**
1	American College of Cardiology and Society for Cardiovascular Angiography and Interventions	Cardiology and Cardiovascular Angiography and Interventions

Respondent Conflict of Interest Disclosure

No.	Conflict of Interest Policy Statement
1	The ACC and SCAI typically strive to have less than 50% of participants in clinical writing workgroups with conflicts of interest. For this project, four of the five (80%) physicians comprising the ACC-SCAI workgroup completing this document report that they have no conflicts of interest. The one member of the workgroup that does have a COI serves as a proctor/consultant for both Medtronic and Edwards Life Sciences, the two companies with TPVI devices

Individual physician respondents answered at individual level. Specialty Society respondents provided aggregate information that may be relevant to the group of clinicians who provided input to the Society-level response.
ACC: American College of Cardiology; SCAI: Society for Cardiovascular Angiography and Interventions; TPVI: transcatheter pulmonary valve implantation.

Responses

- Based on the evidence and your clinical experience, describe for each clinical indication listed below the narrative rationale that includes: (1) relevant authoritative scientific evidence and/or relevant clinical scenarios (e.g., a chain of evidence) supporting that use of the technology provides clinical meaningful improvement in net health outcome; and (2) any relevant patient inclusion/exclusion criteria or clinical context important to achieve a clinically meaningful improvement in net health outcome. Please include the PMID for any relevant references. As applicable, please discuss the role of TPVI compared with open surgical valve replacement or reconstruction, particularly when patients are not considered good candidates for open valve surgery due to one or more of the following conditions: (a) high risk for surgery due to concomitant medical comorbidities; or (b) poor surgical candidate due to multiple prior sternotomy procedures for open heart surgery.
  - o Right ventricle-to-pulmonary artery connection (RV-PA conduit) with or without bioprosthetic valve with at least moderate pulmonic regurgitation: This includes individuals with at least moderate pulmonary regurgitation and an RV-PA conduit that supports placement of the TPV device in the pulmonary position.

No.	Rationale
1	TPVI is a well accepted and FDA-approved therapy for RV-PA conduit and bioprosthetic valve (BPV) regurgitation, regardless of the surgical risk, because of 5-7 year follow-up data from multiple prospective studies showing excellent results and durability. • Cabalka AK, Hellenbrand WE, Eicken A, et al. Relationships Among Conduit Type, Pre-Stenting, and Outcomes in Patients Undergoing Transcatheter Pulmonary Valve Replacement in the Prospective North American and European Melody Valve Trials. JACC Cardiovasc Interv. Sep 11 2017;10(17):1746-1759. PMID 28823778 • Cheatham JP, Hellenbrand WE, Zahn EM, et al. Clinical and hemodynamic outcomes up to 7 years after transcatheter pulmonary valve replacement in the US melody valve investigational device exemption trial. Circulation. Jun 2 2015;131(22):1960-70. PMID 25944758 Freedom from TPVI valve dysfunction is comparable to that for surgical conduits and BPVs, particularly when comparing age-matched studies, as valve dysfunction is age-related (). • Batlivala SP, Emani S, Mayer JE, et al. Pulmonary valve replacement function in adolescents: a comparison of bioprosthetic valves and homograft conduits. The Annals of Thoracic Surgery. May 04 2012;93(6):2007-2016. PMID 22560964 • Buber J, Assenza GE, Huang A, et al. Durability of large diameter right ventricular outflow tract conduits in adults with congenital heart disease. Int J Cardiol. Aug 20 2014; 175(3):455-63. PMID 25002319

No.	Rationale
	Comparing valve dysfunction is more useful than comparing reintervention rates, as many surgical patients were left with dysfunction without undergoing reoperation, prior to the availability of TPVI therapy. One of the great benefits of TPVI therapy is treatment of conduit and BPV dysfunction without open heart surgery and redo sternotomy operations. STS-CHSD data show that unadjusted mortality and other complications increase with the increasing number of prior cardiopulmonary bypass (CPB) operations. • Khanna AD, Hill KD, Pasquali SK, et al. Benchmark Outcomes for Pulmonary Valve Replacement Using The Society of Thoracic Surgeons Databases. Ann Thorac Surg. Jul 2015;100(1):138-45. PMID 26007205 Therefore, it is beneficial to decrease the number of CPB operations over a patient's lifetime. In addition, TPVI has fewer complications of death/stroke/early reoperation than surgical valve replacement (0.8% vs. 4.3%). • Bishnoi RN, Jones TK, Kreutzer J, et al. NuMED Covered Cheatham-Platinum Stent™ for the treatment or prevention of right ventricular outflow tract conduit disruption during transcatheter pulmonary valve replacement. Catheter Cardiovasc Interv. Feb 15 2015;85(3):421-7. PMID 25459038 • Batlivala SP, Emani S, Mayer JE, et al. Pulmonary valve replacement function in adolescents: a comparison of bioprosthetic valves and homograft conduits. The Annals of Thoracic Surgery. May 04 2012;93(6):2007-2016. PMID 22560964 Furthermore, hospital length of stay averages 1 day with TPVI compared to 4-7 days with surgical conduit or valve replacement. Cost effectiveness studies have shown TPVI cost to be comparable to or less than surgical pulmonary valve replacement. • Vergales JE, Wanchek T, Novicoff W, et al. Cost-analysis of percutaneous pulmonary valve implantation compared to surgical pulmonary valve replacement. Catheter Cardiovasc Interv. Dec 1 2013;82(7):1147-53. PMID 23857801 • O'Byrne ML, Gillespie MJ, Shinohara RT, et al. Cost comparison of Transcatheter and Operative Pulmonary Valve Replacement (from the Pediatric Health Information Systems Database). Am J Cardiol. Jan 1 2016;117(1):121-6. PMID 26552510 • Steinberg ZL, Jones TK, Verrier E, et al. Early outcomes in patients undergoing transcatheter versus surgical pulmonary valve replacement. Heart (British Cardiac Society). Mar 28 2017;103(18):1455-1460. PMID 28351873

- o Native or patched RVOT with at least moderate pulmonic regurgitation: This includes individuals with at least moderate pulmonary regurgitation and native or patched RVOT that supports placement of the TPV device in the pulmonary position.

No.	Rationale
1	While there are no transcatheter valves FDA-approved for use in a native or patched RVOT, this therapy is considered a reasonable alternative to surgical pulmonary valve replacement (SPVR), regardless of surgical risk. Levi et al presented 10 patients with a patched RVOT who were taken to the catheterization laboratory for TPVI with a Sapien XT valve, and 7 patients underwent successful valve implantation with no residual stenosis or regurgitation. Three were excluded due to an inadequate landing zone or coronary compression risk. • Levi DS, Sinha S, Salem MM, et al. Transcatheter native pulmonary valve and tricuspid valve replacement with the Sapien XT: Initial experience and development of a new delivery platform. Catheter Cardiovasc Interv. Sep 2016;88(3):434-43. PMID 27142960 At this time, the literature is limited to case reports and case series, but larger retrospective and prospective studies are forthcoming. This practice is currently considered standard-of-care in many centers, when a landing zone is adequate, in order to decrease the number of cardiopulmonary bypass operations, hospital length of stay, and time off of work for patients.

- o Right ventricle-to-pulmonary artery connection (RV-PA conduit) with or without bioprosthetic valve with pulmonic stenosis (mean RVOT gradient at least 35 mm Hg): This includes individuals with pulmonic stenosis with a mean RVOT gradient greater or equal to 35 mm Hg and RV-PA conduit that supports placement of the TPV device.

No.	Rationale
1	Transcatheter pulmonary valve placement in the setting of stenosis has been reported to have excellent procedural success and has been noted to have durable improvements in patient status.

No.	Rationale
	Perhaps one argument against transcatheter pulmonary valve placement when compared to surgical intervention is the published rate of reintervention with TPVR. This is an effect of the pre-stent era and in this population of stenotic conduits, reinterventions were often a result of stent fracture. Additionally, previously reported risk in this population of a stenotic conduit includes conduit rupture, now able to be adequately treated with covered stents now available following the COAST and PARCS trials in nearly all cases. Eliminating at least one sternotomy, often more, in patients that will require several reentry stenotomies most arguably can be lifesaving. A recent paper by Calbalka et al describes outcomes in prospective North American and European Melody valve trials. In this study, freedom from reintervention in 358 patients was 85% at 3 years. This improved rate of freedom from reintervention was attributed to the adopted practice of prestenting, thus reducing Melody frame fracture. In this study, 162 patients had stenosis or mixed disease (stenosis and regurgitation) with good results. • Cabalka AK, Hellengrand WE, Eicken A, et al. Relationships Among Conduit Type, Pre-Stenting, and Outcomes in Patients Undergoing Transcatheter Pulmonary Valve Replacement in the Prospective North American and European Melody Valve Trials. JACC Cardiovasc Interv. Sep 11 2017;10(17):1746-1759. PMID 28823778 A recent metaanalysis by Chatterjee et al. entitled Transcatheter Pulmonary Valve Implantation: A Comprehensive Systematic Review and Meta-Analyses of Observational Studies pooling 19 studies describes the improved reintervention rates post pre-stent era (4.8 per 100 patient year). Taking current practices of prestenting into account, longevity of the valve has been shown to be comparable to surgical conduits. • Chatterjee A, Bajaj NS, McMahon WS, et al. Transcatheter Pulmonary Valve Implantation: A Comprehensive Systematic Review and Meta-Analyses of Observational Studies. J Am Heart Assoc. Aug 4 2017;6(8). pii: e006432. PMID 28778940

- Native or patched RVOT with pulmonic stenosis (mean RVOT gradient at least 35 mm Hg): This includes individuals with pulmonic stenosis with a mean RVOT gradient greater or equal to 35 mm Hg and native or patched RVOT that supports placement of the TPV device in the pulmonary position.

No.	Rationale
1	The stenotic native RVOT carries fewer risks for transcatheter valve placement compared to dilated RVOT and severely stenotic conduit cohort. This group additionally has highly variable and dynamic RVOT anatomy which can make patient selection key in success. This was outlined in a recent article by Meadows et al (2014). This study highlights the importance of selection in this native RVOT population. In this population of patients from 5 centers, 3 of the 31 patients had stenosis as the primary indication and were mixed (stenosis and regurgitation) in an additional 14 patients. All implants were successful without risk of stent migration in the stenotic group. Follow up results were good with median gradient across the RVOT of 23 mmHg and mild TPV insufficiency. Stent fracture was associated with higher gradients. This population can undergo transcatheter pulmonary valve insertion safely, thus offering an alternative to surgical intervention. • Meadows JJ, Moore PM, Berman DP, et al. Use and Performance of the Melody Transcatheter Pulmonary Valve in Native and Postsurgical, Nonconduit Right Ventricular Outflow Tracts. Circ Cardiovasc Interv. Jun 2014;7(3):374-80. PMID 24867892

- Based on the evidence and your clinical experience for each of the clinical indications described in Question 1a-1d when performing TPVI using the Melody Transcatheter Pulmonary Valve (TPV):
  - Clinically Meaningful Improvement in Net Health Outcome
    - Respond YES or NO for each clinical indication whether the use of TPVI would be expected to provide a clinically meaningful improvement in net health outcome; AND
    - Rate your level of confidence in your YES or NO response using the 1 to 5 scale outlined below.

No.	Indications	Yes/No	Low Confidence		Intermediate Confidence		High Confidence
			1	2	3	4	5
1	Q1a: RV-PA conduit with or without bioprosthetic valve with at least moderate pulmonic regurgitation	Yes					X
	Q1b: Native or patched RVOT with at least moderate pulmonic regurgitation	Yes				X	
	Q1c: RV-PA conduit with or without bioprosthetic valve with pulmonic stenosis (mean RVOT gradient at least 35 mm Hg)	Yes					X
	Q1d: Native or patched RVOT with pulmonic stenosis (mean RVOT gradient at least 35 mm Hg)	Yes				X	

- o Generally Accepted Medical Practice
  - Respond YES or NO for each clinical indication whether the use of TPVI is consistent with generally accepted medical practice; AND
  - Rate your level of confidence in your YES or NO response using the 1 to 5 scale outlined below.

No.	Indications	Yes/No	Low Confidence		Intermediate Confidence		High Confidence
			1	2	3	4	5
1	Q1a: RV-PA conduit with or without bioprosthetic valve with at least moderate pulmonic regurgitation	Yes					X
	Q1b: Native or patched RVOT with at least moderate pulmonic regurgitation	Yes				X	
	Q1c: RV-PA conduit with or without bioprosthetic valve with pulmonic stenosis (mean RVOT gradient at least 35 mm Hg)	Yes					X
	Q1d: Native or patched RVOT with pulmonic stenosis (mean RVOT gradient at least 35 mm Hg)	Yes				X	

- Based on the evidence and your clinical experience for each of the clinical indications described in Question 1a-1d when performing TPVI using the SAPIEN XT Transcatheter Heart Valve (pulmonic) or SAPIEN 3 Transcatheter Heart Valve[a]:
  - o Clinically Meaningful Improvement in Net Health Outcome
    - Respond YES or NO for each clinical indication whether the use of TPVI would be expected to provide a clinically meaningful improvement in net health outcome; AND
    - Rate your level of confidence in your YES or NO response using the 1 to 5 scale outlined below.

No.	Indications	Yes/No	Low Confidence		Intermediate Confidence		High Confidence
			1	2	3	4	5
1	Q1a: RV-PA conduit with or without bioprosthetic valve with at least moderate pulmonic regurgitation	Yes					X
	Q1b: Native or patched RVOT with at least moderate pulmonic regurgitation	Yes				X	
	Q1c: RV-PA conduit with or without bioprosthetic valve with pulmonic stenosis (mean RVOT gradient at least 35 mm Hg)	Yes					X
	Q1d: Native or patched RVOT with pulmonic stenosis (mean RVOT gradient at least 35 mm Hg)	Yes				X	

- Generally Accepted Medical Practice
  - Respond YES or NO for each clinical indication whether the use of TPVI is consistent with generally accepted medical practice; AND
  - Rate your level of confidence in your YES or NO response using the 1 to 5 scale outlined below.

No.	Indications	Yes/No	Low Confidence 1	2	Intermediate Confidence 3	4	High Confidence 5
1	Q1a: RV-PA conduit with or without bioprosthetic valve with at least moderate pulmonic regurgitation	Yes					X
	Q1b: Native or patched RVOT with at least moderate pulmonic regurgitation	Yes				X	
	Q1c: RV-PA conduit with or without bioprosthetic valve with pulmonic stenosis (mean RVOT gradient at least 35 mm Hg)	Yes					X
	Q1d: Native or patched RVOT with pulmonic stenosis (mean RVOT gradient at least 35 mm Hg)	Yes				X	

- Additional narrative rationale or comments and/or any relevant scientific citations (including the PMID) supporting your clinical input on this topic.

No.	Additional Comments
1	Not applicable to TPVI

- Is there any evidence missing from the attached draft review of evidence that demonstrates clinically meaningful improvement in net health outcome?

No.	Yes/No	Citations of Missing Evidence
1	No	

[a] The choice of SAPIEN transcatheter heart valve may be based on clinical judgment such as size needed for patient anatomy.

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Documentation for Clinical Review

Please provide the following documentation:

- History and physical and/or consultation notes including:
  - All previous surgeries, treatments, and responses pertaining to request
  - New York Heart Association Classification of symptoms
  - Pulmonary valve stenosis severity description
  - Reason for procedure
- Echocardiogram within last six months
- Any other pertinent imaging or diagnostic studies

Post Service (in addition to the above, please include the following):

- Operative report(s)

Coding

This Policy relates only to the services or supplies described herein. Benefits may vary according to product design; therefore, contract language should be reviewed before applying the terms of the Policy.

The following codes are included below for informational purposes. Inclusion or exclusion of a code(s) does not constitute or imply member coverage or provider reimbursement policy. Policy Statements are intended to provide member coverage information and may include the use of some codes for clarity. The Policy Guidelines section may also provide additional information for how to interpret the Policy Statements and to provide coding guidance in some cases.

Type	Code	Description
CPT®	33477	Transcatheter pulmonary valve implantation, percutaneous approach, including pre-stenting of the valve delivery site, when performed
HCPCS	None	

Policy History

This section provides a chronological history of the activities, updates and changes that have occurred with this Medical Policy.

Effective Date	Action
03/30/2012	New Policy Adoption
06/30/2015	Coding update
02/01/2016	Policy revision without position change Coding update
08/01/2016	Policy revision without position change
09/01/2017	Policy revision without position change
07/01/2018	Policy revision without position change
09/01/2019	Policy revision without position change
08/01/2020	Annual review. No change to policy statement. Literature review updated.
08/01/2021	Annual review. Policy statement and literature review updated.
08/01/2022	Annual review. Policy statement and literature review updated.

Definitions of Decision Determinations

Medically Necessary: Services that are Medically Necessary include only those which have been established as safe and effective, are furnished under generally accepted professional standards to treat illness, injury or medical condition, and which, as determined by Blue Shield, are: (a) consistent with Blue Shield medical policy; (b) consistent with the symptoms or diagnosis; (c) not furnished primarily for the convenience of the patient, the attending Physician or other provider; (d) furnished at the most appropriate level which can be provided safely and effectively to the patient; and (e) not more costly than an alternative service or sequence of services at least as likely to produce equivalent therapeutic or diagnostic results as to the diagnosis or treatment of the Member's illness, injury, or disease.

Investigational/Experimental: A treatment, procedure, or drug is investigational when it has not been recognized as safe and effective for use in treating the particular condition in accordance with generally accepted professional medical standards. This includes services where approval by the federal or state governmental is required prior to use, but has not yet been granted.

Split Evaluation: Blue Shield of California/Blue Shield of California Life & Health Insurance Company (Blue Shield) policy review can result in a split evaluation, where a treatment, procedure, or drug will be considered to be investigational for certain indications or conditions, but will be deemed safe and effective for other indications or conditions, and therefore potentially medically necessary in those instances.

Prior Authorization Requirements (as applicable to your plan)

Within five days before the actual date of service, the provider must confirm with Blue Shield that the member's health plan coverage is still in effect. Blue Shield reserves the right to revoke an authorization prior to services being rendered based on cancellation of the member's eligibility. Final determination of benefits will be made after review of the claim for limitations or exclusions.

Questions regarding the applicability of this policy should be directed to the Prior Authorization Department at (800) 541-6652, or the Transplant Case Management Department at (800) 637-2066 ext. 3507708 or visit the provider portal at www.blueshieldca.com/provider.

Disclaimer: This medical policy is a guide in evaluating the medical necessity of a particular service or treatment. Blue Shield of California may consider published peer-reviewed scientific literature, national guidelines, and local standards of practice in developing its medical policy. Federal and state law, as well as contract language, including definitions and specific contract provisions/exclusions, take precedence over medical policy and must be considered first in determining covered services. Member contracts may differ in their benefits. Blue Shield reserves the right to review and update policies as appropriate.

Appendix A

POLICY STATEMENT	
BEFORE Red font: Verbiage removed	AFTER Blue font: Verbiage Changes/Additions
Transcatheter Pulmonary Valve Implantation 7.01.131 **Policy Statement:** Transcatheter pulmonary valve implantation (TPVI), with a Food and Drug Administration-approved valve may be considered **medically necessary** for patients with congenital heart disease and current right ventricular outflow tract obstruction (RVOT) or regurgitation including **one or more** of the following indications: • Individuals with right ventricle-to-pulmonary artery conduit with or without bioprosthetic valve with at least moderate pulmonic regurgitation • Individuals with native or patched RVOT with at least moderate pulmonic regurgitation • Individuals with right ventricle-to-pulmonary artery conduit with or without bioprosthetic valve with pulmonic stenosis (mean RVOT gradient at least 35 mm Hg) • Individuals with native or patched RVOT with pulmonic stenosis (mean RVOT gradient at least 35 mm Hg) Transcatheter pulmonary valve implantation is considered **investigational** for all other indications.	**Transcatheter Pulmonary Valve Implantation 7.01.131** **Policy Statement:** I. Transcatheter pulmonary valve implantation (TPVI), with a Food and Drug Administration-approved valve may be considered **medically necessary** for individuals with congenital heart disease and current right ventricular outflow tract obstruction (RVOT) or regurgitation including **one or more** of the following indications: A. Individuals with right ventricle-to-pulmonary artery conduit with or without bioprosthetic valve with at least moderate pulmonic regurgitation B. Individuals with native or patched RVOT with at least moderate pulmonic regurgitation C. Individuals with right ventricle-to-pulmonary artery conduit with or without bioprosthetic valve with pulmonic stenosis (mean RVOT gradient at least 35 mm Hg) D. Individuals with native or patched RVOT with pulmonic stenosis (mean RVOT gradient at least 35 mm Hg) II. Transcatheter pulmonary valve implantation is considered **investigational** for all other indications.