TRANSCATHETER HEART VALVE PROCEDURES

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COMMERCIAL & MEDICAID COVERAGE RATIONALE

Aortic Valve
Transcatheter aortic heart valve replacement is medically necessary for treating high risk patients, when used according to U.S. Food and Drug Administration (FDA) labeled indications, contraindications, warnings and precautions, and ALL of the following criteria are met:
- Severe calcific native aortic valve stenosis as indicated by ONE of the following:
  - Mean aortic valve gradient >40 mmHg; or
  - Peak aortic jet velocity >4.0 m/s; or
  - Aortic valve area of ≤ 0.8 cm²
- Patient is symptomatic (New York Heart Association [NYHA] class II or greater) and symptoms are due to aortic valve stenosis
• Patient requires valve replacement surgery but is at high risk for serious surgical complications or death from open valve replacement surgery as determined by an interventional cardiologist and an experienced cardiothoracic surgeon. According to the FDA approval, high risk is defined as a Society of Thoracic Surgeons (STS) predicted operative risk score of >8% or an estimated >15% mortality risk for surgical aortic valve replacement (SAVR).

For a complete list of indications, contraindications, warnings and precautions by device, see the FDA section.

**Pulmonary Valve**
Transcatheter pulmonary heart valve replacement is medically necessary when used according to FDA labeled indications, contraindications, warnings and precautions, in patients with right ventricular outflow tract (RVOT) dysfunction who meet the following criteria:
- Existence of a full (circumferential) dysfunctional RVOT conduit that was equal to or greater than 16 mm in diameter when originally implanted, and
- Dysfunctional RVOT conduit with one of the following clinical indications for intervention:
  - Moderate or greater pulmonary regurgitation, or
  - Pulmonary stenosis with a mean RVOT gradient ≥ 35 mmHg.

**Mitral Valve**
Percutaneous transcatheter mitral valve leaflet repair is not medically necessary. There is insufficient evidence in the clinical literature demonstrating the long-term efficacy of catheter-delivered mitral valve leaflet repair devices for treating mitral regurgitation. Further results from prospective, randomized controlled trials are needed to determine device durability and the ideal candidates for the procedure. See Benefit Considerations for coverage of not medically necessary services when certain conditions are met.

Percutaneous transcatheter mitral valve annuloplasty via the coronary sinus is not medically necessary and investigational due to lack of FDA approval. There is insufficient evidence in the clinical literature demonstrating the long-term efficacy of coronary sinus annuloplasty devices for treating mitral regurgitation. Further results from prospective, randomized controlled trials are needed to determine safety, efficacy, durability and the ideal candidates for the procedure.

**Valve-in-Valve (ViV) Procedures**
Transcatheter heart valve replacement within a failed bioprosthesis (valve-in-valve procedure) is not medically necessary. There is insufficient evidence in the clinical literature demonstrating the long-term efficacy of ViV procedures. Further results from prospective studies are needed to determine the ideal candidates for this procedure.

**MEDICARE COVERAGE RATIONALE**
Medicare covers transcatheter aortic valve replacement (TAVR) when criteria are met. Refer to the National Coverage Determination (NCD) for Transcatheter Aortic Valve Replacement (TAVR) (20.32) and Transcatheter Mitral Valve Repair (20.33). Local Coverage Determinations (LCDs) for Nevada do not exist at this time.
Medicare does not have an NCD for transcatheter pulmonary heart valve replacement procedures. There is no LCD for Nevada at this time (Accessed January 2017).

Transcatheter Aortic Valve Replacement (20.32)

Item/Service Description

A. General

Transcatheter aortic valve replacement (TAVR - also known as TAVI or transcatheter aortic valve implantation) is used in the treatment of aortic stenosis. A bioprosthetic valve is inserted percutaneously using a catheter and implanted in the orifice of the aortic valve.

Indications and Limitations of Coverage

B. Nationally Covered Indications

The Centers for Medicare & Medicaid Services (CMS) covers transcatheter aortic valve replacement (TAVR) under Coverage with Evidence Development (CED) with the following conditions:

A. TAVR is covered for the treatment of symptomatic aortic valve stenosis when furnished according to a Food and Drug Administration (FDA)-approved indication and when all of the following conditions are met:

1. The procedure is furnished with a complete aortic valve and implantation system that has received FDA premarket approval (PMA) for that system's FDA approved indication.
2. Two cardiac surgeons have independently examined the patient face-to-face and evaluated the patient's suitability for open aortic valve replacement (AVR) surgery; and both surgeons have documented the rationale for their clinical judgment and the rationale is available to the heart team.
3. The patient (preoperatively and postoperatively) is under the care of a heart team: a cohesive, multi-disciplinary, team of medical professionals. The heart team concept embodies collaboration and dedication across medical specialties to offer optimal patient-centered care.

TAVR must be furnished in a hospital with the appropriate infrastructure that includes but is not limited to:

a. On-site heart valve surgery program,

b. Cardiac catheterization lab or hybrid operating room/catheterization lab equipped with a fixed radiographic imaging system with flat-panel fluoroscopy, offering quality imaging,

c. Non-invasive imaging such as echocardiography, vascular ultrasound, computed tomography (CT) and magnetic resonance (MR),

d. Sufficient space, in a sterile environment, to accommodate necessary equipment for cases with and without complications,

e. Post-procedure intensive care facility with personnel experienced in managing patients who have undergone open-heart valve procedures,

f. Appropriate volume requirements per the applicable qualifications below.
There are two sets of qualifications; the first set outlined below is for hospital programs and heart teams without previous TAVR experience and the second set is for those with TAVR experience.

Qualifications to begin a TAVR program for hospitals without TAVR experience:

The hospital program must have the following:

a. \( \geq 50 \) total AVRs in the previous year prior to TAVR, including \( 10 \) high-risk patients, and;

b. \( \geq 2 \) physicians with cardiac surgery privileges, and;

c. \( \geq 1000 \) catheterizations per year, including \( 400 \) percutaneous coronary interventions (PCIs) per year.

Qualifications to begin a TAVR program for heart teams without TAVR experience:

The heart team must include:

a. Cardiovascular surgeon with:
   i. \( \geq 100 \) career AVRs including \( 10 \) high-risk patients; or,
   ii. \( \geq 25 \) AVRs in one year; or,
   iii. \( \geq 50 \) AVRs in \( 2 \) years; and which include at least \( 20 \) AVRs in the last year prior to TAVR initiation; and,

b. Interventional cardiologist with:
   i. Professional experience with \( 100 \) structural heart disease procedures lifetime; or,
   ii. \( 30 \) left-sided structural procedures per year of which \( 60\% \) should be balloon aortic valvuloplasty (BAV). Atrial septal defect and patent foramen ovale closure are not considered left-sided procedures; and,

c. Additional members of the heart team such as echocardiographers, imaging specialists, heart failure specialists, cardiac anesthesiologists, intensivists, nurses, and social workers; and,

d. Device-specific training as required by the manufacturer.

Qualifications for hospital programs with TAVR experience:

The hospital program must maintain the following:

a. \( \geq 20 \) AVRs per year or \( \geq 40 \) AVRs every \( 2 \) years; and,

b. \( \geq 2 \) physicians with cardiac surgery privileges; and,

c. \( \geq 1000 \) catheterizations per year, including \( \geq 400 \) percutaneous coronary interventions (PCIs) per year.

Qualifications for heart teams with TAVR experience:

The heart team must include:

a. cardiovascular surgeon and an interventional cardiologist whose combined experience maintains the following:
   i. \( \geq 20 \) TAVR procedures in the prior year, or,
   ii. \( \geq 40 \) TAVR procedures in the prior \( 2 \) years; and,

b. Additional members of the heart team such as echocardiographers, imaging specialists, heart failure specialists, cardiac anesthesiologists, intensivists, nurses, and social workers.
4. The heart team's interventional cardiologist(s) and cardiac surgeon(s) must jointly participate in the intra-operative technical aspects of TAVR.

5. The heart team and hospital are participating in a prospective, national, audited registry that: 1) consecutively enrolls TAVR patients; 2) accepts all manufactured devices; 3) follows the patient for at least one year; and, 4) complies with relevant regulations relating to protecting human research subjects, including 45 CFR Part 46 and 21 CFR Parts 50 & 56. The following outcomes must be tracked by the registry; and the registry must be designed to permit identification and analysis of patient, practitioner and facility level variables that predict each of these outcomes:
   i. Stroke;
   ii. All cause mortality;
   iii. Transient Ischemic Attacks (TIAs);
   iv. Major vascular events;
   v. Acute kidney injury;
   vi. Repeat aortic valve procedures;
   vii. Quality of Life (QoL).

The registry should collect all data necessary and have a written executable analysis plan in place to address the following questions (to appropriately address some questions, Medicare claims or other outside data may be necessary):
- When performed outside a controlled clinical study, how do outcomes and adverse events compare to the pivotal clinical studies?
- How do outcomes and adverse events in subpopulations compare to patients in the pivotal clinical studies?
- What is the long term (5 year) durability of the device?
- What are the long term (5 year) outcomes and adverse events?
- How do the demographics of registry patients compare to the pivotal studies?

B. TAVR is **covered** for uses that are not expressly listed as an FDA-approved indication when performed within a clinical study that fulfills all of the following.

1. The heart team's interventional cardiologist(s) and cardiac surgeon(s) must jointly participate in the intra-operative technical aspects of TAVR.

2. As a fully-described, written part of its protocol, the clinical research study must critically evaluate not only each patient's quality of life pre- and post-TAVR (minimum of 1 year), but must also address at least one of the following questions:
   - What is the incidence of stroke?
   - What is the rate of all-cause mortality?
   - What is the incidence of transient ischemic attacks (TIAs)?
   - What is the incidence of major vascular events?
   - What is the incidence of acute kidney injury?
   - What is the incidence of repeat aortic valve procedures?

3. The clinical study must adhere to the following standards of scientific integrity and relevance to the Medicare population:
a. The principal purpose of the research study is to test whether a particular intervention potentially improves the participants' health outcomes.
b. The research study is well supported by available scientific and medical information or it is intended to clarify or establish the health outcomes of interventions already in common clinical use.
c. The research study does not unjustifiably duplicate existing studies.
d. The research study design is appropriate to answer the research question being asked in the study.
e. The research study is sponsored by an organization or individual capable of executing the proposed study successfully.
f. The research study is in compliance with all applicable Federal regulations concerning the protection of human subjects found in the Code of Federal Regulations (CFR) at 45 CFR Part 46. If a study is regulated by the Food and Drug Administration (FDA), it also must be in compliance with 21 CFR Parts 50 and 56. In particular, the informed consent includes a straightforward explanation of the reported increased risks of stroke and vascular complications that have been published for TAVR.
g. All aspects of the research study are conducted according to appropriate standards of scientific integrity (see http://www.icmje.org).
h. The research study has a written protocol that clearly addresses, or incorporates by reference, the standards listed as Medicare coverage requirements.
i. The clinical research study is not designed to exclusively test toxicity or disease pathophysiology in healthy individuals. Trials of all medical technologies measuring therapeutic outcomes as one of the objectives meet this standard only if the disease or condition being studied is life threatening as defined in 21 CFR §312.81(a) and the patient has no other viable treatment options.
j. The clinical research study is registered on the www.ClinicalTrials.gov website by the principal sponsor/investigator prior to the enrollment of the first study subject.
k. The research study protocol specifies the method and timing of public release of all pre-specified outcomes to be measured including release of outcomes if outcomes are negative or study is terminated early. The results must be made public within 24 months of the end of data collection. If a report is planned to be published in a peer reviewed journal, then that initial release may be an abstract that meets the requirements of the International Committee of Medical Journal Editors (http://www.icmje.org). However a full report of the outcomes must be made public no later than three (3) years after the end of data collection.
l. The research study protocol must explicitly discuss subpopulations affected by the treatment under investigation, particularly traditionally underrepresented groups in clinical studies, how the inclusion and exclusion criteria affect enrollment of these populations, and a plan for the retention and reporting of said populations on the trial. If the inclusion and exclusion criteria are expected to have a negative effect on the recruitment or retention of underrepresented populations, the protocol must discuss why these criteria are necessary.
m. The research study protocol explicitly discusses how the results are or are not expected to be generalizable to the Medicare population to infer whether Medicare patients may benefit from the intervention. Separate discussions in the protocol may be necessary for populations eligible for Medicare due to age, disability or Medicaid eligibility.
C. Nationally Non-Covered Indications
TAVR is not covered for patients in whom existing co-morbidities would preclude the expected benefit from correction of the aortic stenosis.

Transcatheter Mitral Valve Repair (20.33)
General
Transcatheter mitral valve repair (TMVR) is used in the treatment of mitral regurgitation. A TMVR device involves clipping together a portion of the mitral valve leaflets as treatment for reducing mitral regurgitation (MR); currently, Abbott Vascular's MitraClip® is the only one with Food and Drug Administration (FDA) approval.

Indications and Limitations of Coverage
Nationally Covered Indications
The Centers for Medicare & Medicaid Services (CMS) covers TMVR for MR under Coverage with Evidence Development (CED) with the following conditions:

A. Treatment of significant symptomatic degenerative MR when furnished according to an FDA-approved indication and when all of the following conditions are met
1. The procedure is furnished with a complete TMVR system that has received FDA premarket approval (PMA) for that system's FDA-approved indication.
2. Both a cardiothoracic surgeon experienced in mitral valve surgery and a cardiologist experienced in mitral valve disease have independently examined the patient face-to-face and evaluated the patient's suitability for mitral valve surgery and determination of prohibitive risk; and both surgeons have documented the rationale for their clinical judgment and the rationale is available to the heart team.
3. The patient (pre-operatively and post-operatively) is under the care of a heart team: a cohesive, multi-disciplinary, team of medical professionals. The heart team concept embodies collaboration and dedication across medical specialties to offer optimal patient-centered care.

TMVR must be furnished in a hospital with the appropriate infrastructure that includes but is not limited to:

a. On-site active valvular heart disease surgical program with >2 hospital-based cardiothoracic surgeons experienced in valvular surgery;
b. Cardiac catheterization lab or hybrid operating room/catheterization lab equipped with a fixed radiographic imaging system with flat-panel fluoroscopy, offering catheterization laboratory-quality imaging,
c. Non-invasive imaging expertise including transthoracic/transesophageal/3D echocardiography, vascular studies, and cardiac CT studies;
d. Sufficient space, in a sterile environment, to accommodate necessary equipment for cases with and without complications;
e. Post-procedure intensive care facility with personnel experienced in managing patients who have undergone open-heart valve procedures;
f. Adequate outpatient clinical care facilities
g. Appropriate volume requirements per the applicable qualifications below
There are institutional and operator requirements for performing TMVR. The hospital must have the following:

a. A surgical program that performs > 25 total mitral valve surgical procedures for severe MR per year of which at least 10 must be mitral valve repairs;
b. An interventional cardiology program that performs > 1000 catheterizations per year, including > 400 percutaneous coronary interventions (PCIs) per year, with acceptable outcomes for conventional procedures compared to National Cardiovascular Data Registry (NCDR) benchmarks;
c. The heart team must include
   1. An interventional cardiologist(s) who:
      • performs > 50 structural procedures per year including atrial septal defects (ASD), patent foramen ovale (PFO) and trans-septal punctures; and,
      • must receive prior suitable training on the devices to be used; and,
      • must be board-certified in interventional cardiology or board-certified/eligible in pediatric cardiology or similar boards from outside the United States;
   2. Additional members of the heart team, including: cardiac echocardiographers, other cardiac imaging specialists, heart valve and heart failure specialists, electrophysiologists, cardiac anesthesiologists, intensivists, nurses, nurse practitioners, physician assistants, data/research coordinators, and a dedicated administrator;
d. All cases must be submitted to a single national database;
e. Ongoing continuing medical education (or the nursing/technologist equivalent) of 10 hours per year of relevant material;
f. The cardiothoracic surgeon(s) must be board-certified in thoracic surgery or similar foreign equivalent.

4. The heart team’s interventional cardiologist or a cardiothoracic surgeon must perform the TMVR. Interventional cardiologist(s) and cardiothoracic surgeon(s) may jointly participate in the intra-operative technical aspects of TMVR as appropriate.

5. The heart team and hospital are participating in a prospective, national, audited registry that: 1) consecutively enrolls TMVR patients; 2) accepts all manufactured devices; 3) follows the patient for at least one year; and, 4) complies with relevant regulations relating to protecting human research subjects, including 45 Code of Federal Regulations (CFR) Part 46 and 21 CFR Parts 50 & 56. The following outcomes must be tracked by the registry; and the registry must be designed to permit identification and analysis of patient-, practitioner-, and facility-level variables that predict each of these outcomes:
   • All-cause mortality;
   • Stroke;
   • Repeat mitral valve surgery or other mitral procedures;
   • Worsening MR;
   • Transient ischemic events (TIAs);
   • Major vascular events;
   • Renal complications;
   • Functional capacity;
   • Quality of Life (QoL)
The registry should collect all data necessary and have a written executable analysis plan in place to address the following questions (to appropriately address some questions, Medicare claims or other outside data may be necessary):

- When performed outside a controlled clinical study, how do outcomes and adverse events compare to the pivotal clinical studies?
- How do outcomes and adverse events in subpopulations compare to patients in the pivotal clinical studies?
- What is the long-term (.5 year) durability of the device?
- What are the long-term (.5 year) outcomes and adverse events?
- How do the demographics of registry patients compare to the pivotal studies?

B. TMVR for MR uses that are not expressly listed as an FDA-approved indication when performed within an FDA-approved randomized controlled trial that fulfills all of the following:

1. TMVR must be performed by an interventional cardiologist or a cardiac surgeon. Interventional cardiologist(s) and cardiothoracic surgeon(s) may jointly participate in the intra-operative technical aspects of TMVR as appropriate.

2. As a fully-described, written part of its protocol, the clinical research trial must critically evaluate the following questions at 12 months or longer follow-up:

   - What is the rate of all-cause mortality in the group randomized to TMVR compared to the patients randomized to control (surgical repair, optimal medical therapy, or other specified control group)?
   - What is the rate of re-operations (open surgical or transcatheater) of the mitral valve in the group randomized to TMVR compared to the patients randomized to control (surgical repair or other specified control group)?
   - What is the rate of severe MR in the group randomized to TMVR compared to the patients randomized to control (surgical repair or other specified control group)?

3. The randomized controlled trial must address all of the following questions at one year post-procedure

   - What is the incidence of stroke?
   - What is the incidence of TIAs?
   - What is the incidence of major vascular events?
   - What is the incidence of renal complications?
   - What is the incidence of worsening MR?
   - What is the patients post-TMVR QoL?
   - What is the patient’s post-TMVR functional capacity?

Nationally Non-Covered Indications
TMVR is non-covered for the treatment of MR when not furnished under CED according to the above-noted criteria. TMVR used for the treatment of any non-MR indications are non-covered.

For Medicare and Medicaid Determinations Related to States Outside of Nevada:
Please review Local Coverage Determinations that apply to other states outside of Nevada.
Important Note: Please also review local carrier Web sites in addition to the Medicare Coverage database on the Centers for Medicare and Medicaid Services’ Website.

DESCRIPTION OF SERVICES

The four natural valves of the heart (aortic, pulmonary, mitral and tricuspid) act as one-way valves to direct the flow of blood to the lungs and aorta. Heart valves with congenital defects or those that become diseased over time can result in either a leaky valve (regurgitation/incompetence/insufficiency) or a valve that does not open wide enough (stenosis).

Conventional treatment of structural heart valve disorders is surgical repair or replacement requiring open-heart surgery using cardiopulmonary bypass. Transcatheter (percutaneous or catheter-based) valve procedures use catheter technology to access the heart and manage heart valve disorders without the need for open-heart surgery and cardiopulmonary bypass. During the procedure, a compressed artificial heart valve or other device is attached to a wire frame and guided by a catheter to the heart. Once in position, the wire frame expands, allowing the device to fully open.

Aortic Valve
The aortic valve directs blood flow from the left ventricle into the aorta. Aortic valve stenosis, a common valvular disorder in older adults, is a narrowing or obstruction of the aortic valve that prevents the valve leaflets from opening normally. When the aortic valve does not open properly, the left ventricle has to work harder to pump enough blood through the narrowed opening to the rest of the body. Reduced blood flow can cause chest pain, shortness of breath, excess fluid retention and other symptoms. Left untreated, severe aortic stenosis can lead to left ventricular hypertrophy and heart failure (ECRI, 2012; updated 2014). The various stages of valvular aortic stenosis are addressed by Nishimura et al. (2014).

The gold standard for treating severe, symptomatic aortic stenosis is surgical replacement with a prosthetic valve. However, some patients are not candidates for open-heart surgery because they are too old, too frail or they suffer from another condition that would make the surgery too risky. Transcatheter aortic valve replacement (TAVR) is a minimally invasive alternative to surgical valve replacement. Transcatheter aortic valves feature a metal, stent-like scaffold that contains a bioprosthetic valve. Depending on patient anatomy, possible access routes to the aortic valve include transfemoral (percutaneous or endovascular approach), transapical, subaxillary or transaortic approaches. The procedure is done without removing the diseased native valve (ECRI, 2015; Williams et al., 2010).

Pulmonary Valve
The pulmonary valve directs blood flow from the right ventricle into the lungs. Disorders of the pulmonary valve are often due to congenital heart disease such as tetralogy of Fallot, pulmonary atresia, transposition of the great arteries and double-outlet right ventricle. Surgery to replace the valve with a bioprosthesis may also include a conduit (graft) to open the RVOT. Over time, the valved conduit may fail, leading to pulmonary valve stenosis (narrowing), pulmonary valve regurgitation
Transcatheter heart valve implantation, a minimally invasive alternative to surgical valve repair or replacement, is designed to reduce the number of surgeries needed throughout a patient’s lifetime. Transcatheter pulmonary valves feature a metal, stent-like scaffold that contains a bioprosthetic valve. Access to the pulmonary valve is achieved via the femoral vein. The replacement valve is usually positioned within a preexisting pulmonary conduit (graft) (ECRI, 2015; NICE, 2013; Medtronic Melody website).

Mitral Valve
The mitral valve directs blood flow from the left atrium into the left ventricle. Mitral regurgitation (MR) occurs when the mitral valve does not close properly, allowing blood to flow backwards from the ventricle to the atrium. MR is sometimes referred to as mitral incompetence or mitral insufficiency. Primary, or degenerative, MR is usually caused by damage to the valve components (e.g., leaflets, attached chords or adjacent supporting tissue). Secondary, or functional, MR is typically due to changes in the shape of the left ventricle that pull the leaflets apart, preventing complete closure (Hayes, 2014; updated 2016). Left untreated, moderate to severe MR can lead to congestive heart failure. MR that cannot be managed conservatively may require surgical valve repair or replacement (NICE, 2009).

Transcatheter leaflet repair and percutaneous annuloplasty are two minimally invasive approaches to repair damaged mitral valves. Transcatheter leaflet repair keeps the two valve leaflets more closely fitted together, thereby reducing regurgitation. The procedure, based on the surgical edge-to-edge technique, creates a double orifice using a clip instead of a suture to secure the leaflets. The device consists of a steerable guide catheter, including a clip delivery device and a two-armed, flexible metal clip covered in polyester fabric. A transseptal puncture is required to implant the device in the left side of the heart. Access to the mitral valve is achieved via the femoral vein.

Percutaneous transcatheter annuloplasty attempts to replicate the functional effects of open surgical annuloplasty by reshaping the mitral annulus from within the coronary sinus. The coronary sinus is a large vein located along the heart's outer wall, between the left atrium and left ventricle, adjacent to the mitral valve.

Valve-in-Valve Procedures
Transcatheter heart valve implantation within an existing bioprosthetic valve, also called a valve-in-valve procedure, replaces a previously implanted bioprosthetic heart valve that has failed or degenerated over time.

CLINICAL EVIDENCE

Aortic Valve
A Hayes report concluded that there is sufficient evidence to support the use of TAVR in patients with severe aortic stenosis who are deemed by a heart team to be at high or greater surgical risk. The overall quality of the evidence is moderate. Most studies showed no difference in mortality rates between TAVR and SAVR in patients with aortic stenosis. Bleeding complications or events occurred less in TAVR-treated patients. Stroke and myocardial infarction rates between TAVR and SAVR did not
differ; however, pacemaker implantation rates were higher in TAVR-treated patients. Renal
impairment or injury rates were inconsistent. Definitive patient selection criteria for TAVR in patients
with severe aortic stenosis have not been established (Hayes, 2016).

Nagaraja et al. (2014) conducted a systematic review and meta-analysis of 39 studies comparing
TAVR and SAVR in patients with aortic stenosis. Among three randomized controlled trials,
differences between the two cohorts were not statistically significant for the frequency of stroke,
incidence of myocardial infarction, 30-day mortality rate, 1-year mortality rate and acute kidney injury.
The remaining non-randomized controlled trials demonstrated that the TAVR group had an amplified
frequency of aortic regurgitation at discharge. While differences between the two cohorts were not
statistically significant for the incidence of myocardial infarction, stroke, acute renal failure requiring
hemodialysis, 30-day mortality and the need for a pacemaker, fewer TAVR patients needed
transfusions or experienced new-onset atrial fibrillation.

Biondi-Zoccai et al. (2014) performed a meta-analysis of four randomized controlled trials (n=1805)
comparing survival rates and complications between TAVR and SAVR. Separate TAVR procedures
were considered, including CoreValve, transfemoral SAPIEN and transapical SAPIEN. After a median
of 8 months, risk of death and myocardial infarction was not different when comparing surgery versus
transcatheter procedures, irrespective of device or access. Conversely, surgery was associated with
higher rates of major bleeding and acute kidney injury, but lower rates of pacemaker implantation and
moderate or severe aortic regurgitation. Strokes were less frequent with CoreValve than with
transfemoral SAPIEN or transapical SAPIEN, whereas pacemaker implantation was more common
with CoreValve. The authors concluded that survival after transcatheter or surgical aortic valve
replacement is similar, but there might be differences in the individual safety and effectiveness profile
between the treatment strategies and the individual devices used in TAVR.

PARTNER (Placement of AoRTic traNscatheterER valves) Study
The PARTNER trial is a two-part, multicenter, randomized controlled trial funded by Edwards
Lifesciences. Cohort A compared transcatheter aortic valve replacement to surgical valve replacement.
Cohort B compared transcatheter aortic valve replacement to medical therapy in patients with severe
aortic stenosis who were unable to undergo surgery. Clinicaltrials.gov number NCT00530894.

Cohort A
In a multicenter, randomized controlled trial, Smith et al. (2011) randomly assigned 699 high-risk
patients with severe aortic stenosis to undergo either TAVR with a balloon-expandable bovine
pericardial valve (n=348; transfemoral n=244; transapical n=104) or surgical replacement (n=351).
The primary end point was death from any cause at 1 year. The rates of death from any cause were
3.4% in the transcatheter group and 6.5% in the surgical group at 30 days and 24.2% and 26.8%,
respectively, at 1 year. The rates of major stroke were 3.8% in the transcatheter group and 2.1% in the
surgical group at 30 days and 5.1% and 2.4%, respectively, at 1 year. At 30 days, major vascular
complications were significantly more frequent with transcatheter replacement (11.0% vs. 3.2%).
Adverse events that were more frequent after surgical replacement included major bleeding (9.3% vs.
19.5%) and new-onset atrial fibrillation (8.6% vs. 16.0%). The authors concluded that in high-risk
patients with severe aortic stenosis, transcatheter and surgical procedures for aortic-valve replacement
were associated with similar rates of survival at 1 year, although there were important differences in
periprocedural risks.
A 2-year follow-up of patients in Cohort A reported similar outcomes in the two groups with respect to mortality, reduction in cardiac symptoms and improved valve hemodynamics. Paravalvular regurgitation was more frequent after TAVR and was associated with increased late mortality. An early increase in the risk of stroke with TAVR was attenuated over time. The authors concluded that these results support TAVR as an alternative to surgery in high-risk patients (Kodali et al., 2012).

At 5 years, the risk of death was 67.8% in the TAVR group compared with 62.4% in the surgical group. There were no structural valve deteriorations requiring surgical valve replacement in either group. Moderate or severe aortic regurgitation occurred in 40 (14%) of 280 patients in the TAVR group and two (1%) of 228 in the surgical group, and was associated with increased 5-year risk of mortality in the TAVR group (72.4% for moderate or severe aortic regurgitation versus 56.6% for those with mild aortic regurgitation or less) (Mack et al., 2015).

**Cohort B**

In the same multicenter, randomized controlled trial, Leon et al. (2010) evaluated TAVR in patients with severe aortic stenosis who were not candidates for surgery. A total of 358 patients were randomized to standard therapy (including balloon aortic valvuloplasty) (n=179) or transfemoral transcatheter implantation of a balloon-expandable bovine pericardial valve (n=179). At 1 year, the rate of death from any cause was 30.7% with TAVR, as compared with 50.7% with standard therapy. The rate of the composite end point of death from any cause or repeat hospitalization was 42.5% with TAVR as compared with 71.6% with standard therapy. Among survivors at 1 year, the rate of cardiac symptoms (NYHA class III or IV) was lower among patients who had undergone TAVR than among those who had received standard therapy (25.2% vs. 58.0%). At 30 days, TAVR, as compared with standard therapy, was associated with a higher incidence of major strokes (5.0% vs. 1.1%) and major vascular complications (16.2% vs. 1.1%). In the year after TAVR, there was no deterioration in the functioning of the bioprosthetic valve. The authors concluded that in patients with severe aortic stenosis who were not suitable candidates for surgery, TAVR, as compared with standard therapy, significantly reduced the rates of death from any cause, the composite end point of death from any cause or repeat hospitalization and cardiac symptoms, despite the higher incidence of major strokes and major vascular events (Leon et al., 2010).

At 2 years, the mortality rates in Cohort B were 43.3% in the TAVR group and 68.0% in the standard therapy group. The corresponding rates of cardiac death were 31.0% and 62.4%. The survival advantage associated with TAVR at 1 year remained significant among patients who survived beyond the first year. The rate of stroke was higher after TAVR than with standard therapy (13.8% vs. 5.5%). There was an increased frequency of early ischemic strokes (≤30 days) but little change in the rate of late ischemic strokes (>30 days). At 2 years, the rate of rehospitalization was 35.0% in the TAVR group and 72.5% in the standard-therapy group. TAVR, as compared with standard therapy, was also associated with improved functional status. The data suggest that the mortality benefit after TAVR may be limited to patients who do not have extensive coexisting conditions. The authors concluded that among appropriately selected patients with severe aortic stenosis who were not suitable candidates for surgery, TAVR reduced the rates of death and hospitalization, with a decrease in symptoms and an improvement in valve hemodynamics that were sustained at 2 years of follow-up (Makkar et al., 2012).
PARTNER II Study

The PARTNER II study is a two-part, multicenter, randomized controlled trial, also funded by Edwards Lifesciences, evaluating a second-generation transcatheter valve system. The newer, low-profile SAPIEN XT system was developed to reduce adverse events noted in the PARTNER study. Cohort A compared TAVR to conventional surgery in patients with severe aortic stenosis and intermediate surgical risk. Cohort B compared the SAPIEN XT valve with the first-generation SAPIEN valve in patients with severe aortic stenosis who were unable to undergo surgery. ClinicalTrials.gov number NCT01314313.

Cohort A

Leon et al. (2016) evaluated TAVR and SAVR in a multicenter, randomized controlled trial involving intermediate-risk patients. A total of 2032 intermediate-risk patients with severe aortic stenosis were randomly assigned to undergo either TAVR with the SAPIEN XT valve (n=1011) or SAVR (n=1021). The primary end point was death from any cause or disabling stroke at 2 years. The primary hypothesis was that TAVR would not be inferior to surgical replacement. Before randomization, patients were entered into one of two cohorts on the basis of clinical and imaging findings: transfemoral access (76.3%) and transthoracic access (23.7%). The rate of death from any cause or disabling stroke was similar in the TAVR group and the surgery group. At 2 years, the event rates were 19.3% in the TAVR group and 21.1% in the surgery group. In the transfemoral access cohort, TAVR resulted in a lower rate of death or disabling stroke than surgery, whereas in the transthoracic access cohort, outcomes were similar in the two groups. TAVR resulted in larger aortic-valve areas than did surgery and also resulted in lower rates of acute kidney injury, severe bleeding and new-onset atrial fibrillation. Surgery resulted in fewer major vascular complications and less paravalvular aortic regurgitation. Further studies assessing long-term outcomes in this patient population are needed to confirm these results.

Cohort B

Webb et al. (2015) evaluated the safety and effectiveness of the SAPIEN XT versus SAPIEN valve systems in patients with symptomatic, severe aortic stenosis who were not candidates for surgery. The primary endpoint was a composite of all-cause mortality, major stroke and rehospitalization. Secondary endpoints included cardiovascular death, NYHA functional class, myocardial infarction, stroke, acute kidney injury, vascular complications, bleeding, 6-min walk distance and valve performance. A total of 560 patients were randomized to receive the SAPIEN (n=276) or SAPIEN XT (n=284) systems. At 1-year follow-up, there was no difference in all-cause mortality, major stroke or rehospitalization between SAPIEN and SAPIEN XT, but the SAPIEN XT was associated with less vascular complications and bleeding requiring transfusion. No differences in the secondary endpoints were found. The authors concluded that in inoperable patients with severe, symptomatic aortic stenosis, the lower-profile SAPIEN XT system provided an incremental improvement from the prior generation of TAVR technology.

In a multicenter, randomized, noninferiority trial, Adams et al. (2014) reported that TAVR, using a self-expanding bioprosthesis (CoreValve), had a significantly higher rate of survival at one year than SAVR in patients with severe aortic stenosis and an increased surgical risk. A total of 795 patients were randomly assigned in a 1:1 ratio to TAVR with the CoreValve (TAVR group) or to SAVR (surgical group). The rate of death from any cause at one year was significantly lower in the TAVR group than in the surgical group (14.2% vs. 19.1%) with an absolute reduction in risk of 4.9 percent. Results were similar in the intention-to-treat analysis where the event rate was 13.9 percent in the
Transcatheter Heart Valve Procedures

TAVR group compared to 18.7 percent in the surgical group. The survival benefit with TAVR was consistent across clinical subgroups. ClinicalTrials.gov number NCT01240902.

In a prospective, multicenter, nonrandomized study, Popma et al. (2014) evaluated the safety and efficacy of the CoreValve transcatheter heart valve for the treatment of severe aortic stenosis in patients at extreme risk for surgery. Forty-one sites recruited 506 patients, of whom 489 underwent treatment with the CoreValve device. The rate of all-cause mortality or major stroke at 12 months was 26.0% vs. 43.0%. Individual 30-day and 12-month events included all-cause mortality (8.4% and 24.3%, respectively) and major stroke (2.3% and 4.3%, respectively). Procedural events at 30 days included, life threatening/disabling bleeding (12.7%), major vascular complications (8.2%) and need for permanent pacemaker placement (21.6%). The frequency of moderate or severe paravalvular aortic regurgitation was lower 12-months after self-expanding TAVR (4.2%) than at discharge (9.7%).

Two nonrandomized studies compared specific TAVR devices (Attias et al., 2010; Wenaweser et al., 2011). Although there were no significant differences in mortality between the different treatment groups, further studies are needed to draw conclusions regarding the superiority of one device over another.

Several national TAVR registries were identified in the literature. Published results indicate that use of the SAPIEN and CoreValve devices was fairly equal, and the transfemoral approach was used approximately 3 times as often as the transapical approach. Conversion to surgical valve replacement occurred in 0.4% to 4% of procedures. Procedural success was very high and ranged from 91% to 99%. Procedural mortality was low and ranged from 0.4% to 3%. Survival at 30 days ranged from 87% to 95% and at 1 year from 63% to 100%, depending on the device and approach used (Walther et al., 2015; Gilard et al., 2012; Ussia et al., 2012; Bosmans et al., 2011; Thomas et al., 2011; Eltchaninoff et al., 2011; Zahn et al., 2011; Moat et al., 2011; Rodés-Cabau et al., 2010).

A meta-analysis of the adverse effects associated with TAVR included over 16,000 patients in 49 studies. Khatri et al. (2013) found that the need for a permanent pacemaker was the most common adverse outcome (13.1%) and was 5 times more common with the CoreValve than the Edwards SAPIEN valve. Vascular complications were also common (10.4%) and was highest with the transarterial implantation of the Edwards SAPIEN valve (22.3%). Acute renal failure was the third most common complication, occurring in 4.9% of patients. Overall 30-day and 1-year survival after TAVR were 91.9% and 79.2%, respectively.

A National Institute for Health and Care Excellence (NICE) guidance document states that the evidence on the safety of TAVR for aortic stenosis shows the potential for serious but well-recognized complications. For patients with aortic stenosis who are considered to be unsuitable for SAVR, the evidence on the efficacy of TAVR is adequate. For patients with aortic stenosis for whom SAVR is considered suitable but poses a high risk, the evidence on the efficacy of TAVR is inadequate. NICE encourages clinicians to enter suitable patients into a clinical trial. For patients with aortic stenosis for whom SAVR is considered suitable and does not pose a high risk, the evidence on the efficacy of TAVR is inadequate. NICE encourages clinicians to enter suitable patients into a clinical trial (NICE, 2012).
The Valve Academic Research Consortium (VARC), an independent collaboration between academic research organizations and specialty societies (cardiology and cardiac surgery) in the United States and Europe, is focused on creating consistent endpoint definitions and consensus recommendations for TAVR. In an effort to improve the quality of clinical research and to enable meaningful comparisons between clinical trials, consensus criteria were developed for the following endpoints: mortality, myocardial infarction, stroke, bleeding, acute kidney injury, vascular complications and prosthetic valve performance. Composite endpoints for safety and effectiveness were also recommended. The consensus document is not intended as a ‘guidelines’ or ‘guidance’ document and although thoroughly reviewed by individuals from seven cardiology and cardiac surgery societies, the content has not been subjected to a formal society guidelines review process (Leon et al. 2011). In a subsequent consensus document, Kappetein et al. (2012) provided additional detail on definitions to further standardize endpoint definitions.

**Pulmonary Valve**

An ECRI emerging technology evidence report states that studies using the Melody system indicate that percutaneous pulmonary valve implantation (PPVI) improves symptoms as indexed by the NYHA Classification system in the short-term (<6 months), but longer-term results are not available. Studies using the Melody system also indicate that PPVI improves cardiac function on several measures (i.e., decreases RVOT pressure gradient, decreases regurgitation fraction through the pulmonary valve, and decreases right ventricular end-diastolic volume; data on maximal oxygen consumption are not consistent). No data were available to assess how PPVI affects quality of life. Ongoing clinical trials should help clarify questions not addressed by the available literature, including quality of life and long-term clinical outcomes (ECRI, 2012b).

A Hayes report concluded that the evidence evaluating PPVI was of low quality and consisted entirely of observational studies. Sample sizes were small, long-term follow-up was available for very few patients and there was considerable overlap in patient populations. No randomized or quasi-randomized controlled trials were identified in the literature. Study results showed consistent improvement in hemodynamics for patients with pulmonary valve insufficiency, stenosis or both, and for pulmonary regurgitation patients with pulmonary insufficiency following PPVI. Heart function was improved to a lesser extent while overall pulmonary function did not improve. Mid- to long-term follow-up was available in very few patients; however, the preliminary evidence suggests that in most patients, the benefits are maintained for a number of years. Valve failure rates range from 25% to 32% at 5 years. Additional evidence is needed to determine the impact of PPVI on disease-related survival and mortality. Complications were few, but some were potentially life threatening. There is a learning curve associated with PPVI, and experience with this technique improves outcomes and reduces the risk for complications. Although there is very limited evidence at this time, PPVI fills a gap in the management of patients with RVOT dysfunction following surgical repair for congenital heart defects. Although PPVI can cause severe complications, it is a treatment option used for patients who cannot undergo open heart surgery or to prolong the need for surgical valve replacement with its associated risks (Hayes, 2016).

Armstrong et al. (2014) conducted a one-year follow-up of the Melody transcatheter pulmonary valve (TPV) multicenter post-approval study to determine if real-world experience was equivalent to the historical results established in the initial Investigational Device Exemption trial. Patients with dysfunctional RVOT conduits were entered in this prospective, nonrandomized study at 10 centers.
The primary endpoint was acceptable hemodynamic function at 6 months post-implantation, defined as a composite of RVOT echocardiographic mean gradient ≤30 mm Hg, pulmonary regurgitation less than moderate as measured by echocardiography, and freedom from conduit reintervention and reoperation. Cardiac catheterization was performed in 120 patients for potential implantation of the Melody TPV; of these, 100 patients were implanted, with a 98.0% procedural success rate. There were no procedure-related deaths. Acceptable hemodynamic function at 6 months was achieved in 96.7% of patients with evaluable data (87.9% of the entire implanted cohort), with results maintained through one year. No patient had moderate or severe pulmonary regurgitation after implantation. No patient required catheter reintervention in the first year after implantation, and 2 patients required reoperation for conduit replacement. The rate of freedom from TPV dysfunction was 96.9% at one year.

Butera et al. (2013) conducted a prospective, multicenter web-based registry study of percutaneous pulmonary valve implantation (PPVI). Between October 2007 and October 2010, 63 patients were included in the registry (median age: 24 years; range 11-65 years). Results suggest that PPVI has good procedural and mid-term success and might delay surgical intervention in more than 80% of patients. However, serious complications can occur and valve failure occurred in almost 20% of patients during follow-up. The authors concluded that longer follow-up and larger series are needed.

Eiken et al. (2011) reported on a two-center experience with percutaneous pulmonary valve implantation (PPVI) in 102 patients with RVOT dysfunction. Median weight was 63 kg (54.2-75.9 kg). Median age was 21.5 years (16.2-30.1 years). The median peak systolic RVOT gradient decreased from 37 mmHg (29-46 mmHg) to 14 mmHg (9-17 mmHg), and the ratio right ventricular (RV) pressure/aortic pressure (AoP) decreased from 62% (53-76%) to 36% (30-42%). The median end-diastolic RV-volume index decreased from 106 mL/m(2) (93-133 mL/m(2)) to 90 mL/m(2) (71-108 mL/m(2)). Pulmonary regurgitation was significantly reduced in all patients. One patient died due to compression of the left coronary artery. The incidence of stent fractures was 5 of 102 (5%). During follow-up [median: 352 days (99-390 days)] one percutaneous valve had to be removed surgically 6 months after implantation due to bacterial endocarditis. In 8 of 102 patients, a repeated dilatation of the valve was done due to a significant residual systolic pressure gradient, which resulted in a valve-in-valve procedure in four patients. The authors concluded that percutaneous pulmonary valve implantation can be performed by experienced interventionalists with similar results to previously published studies. The procedure is technically challenging and longer clinical follow-up is needed.

McElhinney et al. (2010) conducted a multicenter trial of 136 patients (median age, 19 years) who underwent catheterization for intended Melody valve implantation. Implantation was attempted in 124 patients. In the other 12, transcatheter pulmonary valve placement was not attempted because of the risk of coronary artery compression (n=6) or other clinical or protocol contraindications. There was 1 death and 1 explanted valve after conduit rupture. The median peak RVOT gradient was 37 mmHg before implantation and 12 mmHg immediately after implantation. Before implantation, pulmonary regurgitation was moderate or severe in 92 patients. No patient had more than mild pulmonary regurgitation early after implantation or during follow-up. Freedom from stent fracture was 77.8+/-.4.3% at 14 months. Freedom from valve dysfunction or reintervention was 93.5+/-.2.4% at 1 year. A higher RVOT gradient at discharge and younger age were associated with shorter freedom from dysfunction. The results demonstrated an ongoing high rate of procedural success and encouraging short-term valve function. All re-interventions in this series were for RVOT obstruction, highlighting the importance of patient selection, adequate relief of obstruction, and measures to prevent and manage stent fracture. Clinicaltrials.gov number NCT00740870.
Zahn et al. (2009) evaluated the safety, procedural success and short-term effectiveness of the Melody transcatheter pulmonary valve in patients with dysfunctional RVOT conduits. Thirty four patients underwent catheterization for intended Melody valve implantation at 3 centers. Mean age was 19.4 +/- 7.7 years. Initial conduit Doppler mean gradient was 28.8 +/- 10.1 mmHg, and 94% of patients had moderate or severe pulmonary regurgitation (PR). Implantation was successful in 29 of 30 attempts and not attempted in 4 patients. Procedural complications included conduit rupture requiring urgent surgery and device removal (n = 1), wide-complex tachycardia (n = 1) and distal pulmonary artery guidewire perforation (n = 1). Peak systolic conduit gradient fell acutely from 37.2 +/- 16.3 mmHg to 17.3 +/- 7.3 mmHg, and no patient had more than mild PR. There were no deaths or further device explants. At 6-month follow-up, conduit Doppler mean gradient was 22.4 +/- 8.1 mmHg, and PR fraction by magnetic resonance imaging was significantly improved (3.3 +/- 3.6% vs. 27.6 +/- 13.3%). Stent fracture occurred in 8 of 29 implants; 3 of these were treated with a second Melody valve for recurrent stenosis later in follow-up. The authors concluded that implantation of the Melody valve for RVOT conduit dysfunction has encouraging acute and short-term outcomes when performed by experienced operators.

In a retrospective case series, Lurz et al. (2008) evaluated percutaneous pulmonary valve implantation in 155 patients with stenosis and/or regurgitation. The procedure led to significant reduction in right ventricular systolic pressure and RVOT gradient. Follow-up ranged from 0 to 83.7 months (median 28.4 months). Freedom from reoperation was 93% (+/-2%), 86% (+/-3%), 84% (+/-4%) and 70% (+/-13%) at 10, 30, 50 and 70 months, respectively. Freedom from transcatheter reintervention was 95% (+/-2%), 87% (+/-3%), 73% (+/-6%) and 73% (+/-6%) at 10, 30, 50 and 70 months, respectively. Survival at 83 months was 96.9%. The first series of 50 patients and patients with a residual gradient >25 mmHg were associated with a higher risk of reoperation.

In a retrospective case series, Khambadkone et al. (2005) evaluated percutaneous pulmonary valve implantation (PPVI) in 59 patients with pulmonary regurgitation with or without stenosis after repair of congenital heart disease. PPVI was performed successfully in 58 patients (32 male; median age of 16 years and median weight of 56 kg). The right ventricular (RV) pressure, RVOT gradient and pulmonary regurgitation (PR) decreased significantly after percutaneous pulmonary valve implantation. In 28 patients, magnetic resonance imaging showed significant reduction in PR fraction and in RV end-diastolic volume (EDV) and a significant increase in left ventricular EDV and effective RV stroke volume.

A National Institute for Health and Care Excellence (NICE) guidance document states that the evidence on percutaneous pulmonary valve implantation for RVOT dysfunction shows good short-term efficacy. There is little evidence on long-term efficacy but it is well documented that these valves may need to be replaced in the longer term. With regard to safety there are well-recognized complications, particularly stent fractures in the longer term, which may or may not have clinical effects. Patients having this procedure are often very unwell and might otherwise need open heart surgery (typically reoperative) with its associated risks (NICE, 2013).

Post-approval clinical trials are ongoing to assess the long-term clinical performance of the Melody transcatheter pulmonary valve.
Mitral Valve
Percutaneous Leaflet Repair

Evidence from one large randomized controlled trial suggests that transcatheter mitral valve repair using the MitraClip device is not as effective as conventional surgery for patients who are candidates for conventional surgery. Although patient survival and decrease in MR were similar for the MitraClip procedure versus conventional open surgery at 4 years follow-up, MitraClip implantation was associated with a statistically significant increase in the need for additional surgery. A small number of nonrandomized comparison studies and several uncontrolled studies provide weak evidence that the MitraClip device may be more effective than standard treatment for high-risk patients who are not candidates for conventional surgery. Additional studies are needed to determine the long-term risks versus benefits of MitraClip implantation in these high-risk patients (Hayes, 2014; updated 2016).

Bail (2015) performed a meta-analysis of the safety and efficacy of the MitraClip device. Twenty-six studies (n=3821) were included in the analysis. Based on the analysis, the authors reported that treatment with MitraClip is associated with good short-term success and low mortality. The procedure is safe and effective for patients with limited surgical options. The results are comparable with open mitral valve repair, but patients are markedly older and have a higher risk profile than patients who undergo open mitral valve repair. Prospective randomized controlled trials are warranted to determine potential adverse events, device durability and long-term follow-up.

A Blue Cross Blue Shield (BCBS) technology assessment concluded that percutaneous mitral valve repair does not meet the Technology Evaluation Center (TEC) criteria. The scientific evidence is insufficient to permit conclusions about MitraClip’s impact on health outcomes. In 2 higher quality studies (Lim et al., 2013; Reichenspurner et al., 2013) reporting outcomes for patients receiving the device, 30-day mortality rates were 6.0% and 6.3% and 12-month mortality rates were 17.1% and 23.6%, respectively. In evaluable patients surviving to 12 months, 83.3% and 74.6% of patients in these 2 studies, respectively, had an MR grade of 2+ or less, 81% and 87% had a NYHA class I/II, and 68% and 88% improved at least 1 NYHA class. Although improvement in NYHA class is a measure of a better health outcome, due to lack of control groups, reviewers were not able to determine whether the mortality rate improved, was equivalent or worsened compared with no treatment (BCBS, 2014).

Munkholm-Larsen et al. (2014) performed a systematic review to assess the safety and efficacy of the MitraClip system for high surgical risk candidates with severe organic and/or functional MR. Twelve prospective observational studies were included. Immediate procedural success ranged from 72-100%. Thirty day mortality ranged from 0-7.8%. The authors noted a significant improvement in hemodynamic profile and functional status after implantation. One year survival ranged from 75-90%. The authors concluded that further prospective trials with mid- to long-term follow-up are required.

Using registry data from the EVEREST II High-Risk registry and the REALISM Continued Access Study High-Risk Arm registry, Glower et al. (2014) reported 12-month outcomes in high-risk patients treated with the MitraClip device for MR. Patients with grades 3 to 4+ MR and a surgical mortality risk of ≥12% were enrolled. In the studies, 327 of 351 patients completed 12 months of follow-up. Patients were elderly (76 ± 11 years of age), with 70% having functional MR and 60% having prior cardiac surgery. The mitral valve device reduced MR to ≤2+ in 86% of patients at discharge (n = 325). Major adverse events at 30 days included death in 4.8%, myocardial infarction in 1.1% and stroke in 2.6%. At 12 months, MR was ≤2+ in 84% of patients (n = 225). From baseline to 12 months, left
ventricular (LV) end-diastolic volume improved from 161 ± 56 ml to 143 ± 53 ml (n = 203) and LV end-systolic volume improved from 87 ± 47 ml to 79 ± 44 ml (n = 202). NYHA functional class improved from 82% in class III/IV at baseline to 83% in class I/II at 12 months (n = 234). Survival estimate at 12 months was 77.2%.

**EVEREST II (Endovascular Valve Edge-to-Edge Repair Study)**

EVEREST II is a two-part multicenter, randomized controlled trial to evaluate the safety and efficacy of endovascular mitral valve repair using the MitraClip device compared with conventional mitral valve surgery in patients with moderate to severe mitral regurgitation (MR). The study is funded by Abbott Vascular. EVEREST II consists of a randomized arm and a high-risk registry arm. Clinicaltrials.gov number NCT00209274.

**EVEREST II Randomized Arm**

Feldman et al. (2011) randomly assigned 279 patients with moderately severe or severe (grade 3-4+) MR in a 2:1 ratio to undergo either percutaneous repair (n=184) or conventional surgery (n=95) for repair or replacement of the mitral valve. The patients enrolled in this trial had a normal surgical risk and mainly degenerative MR with preserved left ventricular function. The primary end point for efficacy was freedom from death, from surgery for mitral-valve dysfunction and from grade 3-4+ MR at 12 months. The primary safety end point was a composite of major adverse events within 30 days. At 12 months, the rates of the primary end point for efficacy were 55% in the percutaneous-repair group and 73% in the surgery group. The respective rates of the components of the primary end point were as follows: death, 6% in each group; surgery for mitral-valve dysfunction, 20% versus 2%; and grade 3-4+ MR, 21% versus 20%. Major adverse events occurred in 15% of patients in the percutaneous-repair group and 48% of patients in the surgery group at 30 days. At 12 months, both groups had improved left ventricular size, NYHA functional class and quality-of-life measures, as compared with baseline. Although percutaneous repair was less effective at reducing MR than conventional surgery at 12 and 24 months, the procedure was associated with a lower adverse event rate and similar improvements in clinical outcomes.

At 4 years follow-up, Mauri et al. (2013) reported no significant differences between the MitraClip and conventional surgery treatment groups in all-cause mortality, presence of moderate or severe MR or event-free survival. However, at 4 years follow-up, additional mitral valve surgery was needed for 25% of MitraClip patients versus 6% of conventional surgery patients.

At 5 years follow-up, Feldman et al. (2015) reported that, although mitral valve repair surgery is superior to percutaneous mitral valve intervention using the MitraClip device in reducing the severity of MR, the device reduces symptoms, produces durable reduction of MR and promotes favorable reverse remodeling of the left ventricle 5 years after intervention.

**EVEREST II High Risk Registry Arm**

Whitlow et al. (2012) evaluated 78 high-risk symptomatic patients with severe (Grade 3 or 4+) MR and an estimated surgical mortality rate of ≥12%. Percutaneous mitral valve leaflet repair, using the MitraClip device, was compared with 36 patients with similar degrees of MR, risks and comorbidities who were screened for the study but were not enrolled for various reasons. The devices were successfully placed in 96% of patients. Procedure-related mortality rate at 30 days was similar in the patients who underwent MitraClip placement and the comparator group (7.7% versus 8.3%), but the MitraClip patients appeared to have a better 1-year survival (76% versus 55%). In surviving patients
with matched baseline and 12-month data, 78% had an MR grade of ≤2+. Left ventricular end-diastolic volume improved from 172 ml to 140 ml, and end-systolic volume improved from 82 ml to 73 ml. NYHA functional class improved from III/IV at baseline in 89% to class I/II in 74%. Quality of life improved (Short Form-36 physical component score increased from 32.1 to 36.1), and the mental component score increased from 45.5 to 48.7 at 12 months. The annual rate of hospitalization for congestive heart failure in surviving patients with matched data decreased from 0.59 to 0.32. The authors concluded that the MitraClip device reduced MR in a majority of patients deemed at high risk of surgery, resulting in improvement in clinical symptoms and significant left ventricular reverse remodeling over 12 months. The study has several limitations, most notably a lack of randomization and a questionable comparator group that was recruited retrospectively.

**EVEREST (Endovascular Valve Edge-to-Edge Repair Study)**

EVEREST is a multicenter, prospective single-arm study to evaluate the feasibility, safety and efficacy of a percutaneous mitral valve repair system (MitraClip) for treating MR. Patients will undergo 30-day, 6 month, 12 month and 5 year clinical follow-up. The study is funded by Abbott Vascular Clinicaltrials.gov number NCT00209339.

Feldman et al. (2009) conducted a prospective, multicenter single-arm study to evaluate the feasibility, safety and efficacy of the MitraClip system. A total of 107 patients with moderate to severe (grade 3-4+) MR or compromised left ventricular function (if asymptomatic) underwent percutaneous valve repair with the MitraClip device. Ten (9%) had a major adverse event, including 1 nonprocedural death. Freedom from clip embolization was 100%. Partial clip detachment occurred in 10 (9%) patients. Overall, 74% of patients achieved acute success and 64% were discharged with MR of ≤1+. Thirty-two patients (30%) had mitral valve surgery during the 3.2 years after clip procedures. When repair was planned, 84% (21 of 25) were successful. Thus, surgical options were preserved. A total of 50 of 76 (66%) successfully treated patients were free from death, mitral valve surgery or MR >2+ at 12 months (primary efficacy end point). Kaplan-Meier freedom from death was 95.9%, 94.0% and 90.1%, and Kaplan-Meier freedom from surgery was 88.5%, 83.2% and 76.3% at 1, 2 and 3 years, respectively.

Maisano et al. (2013) and Reichenspurner et al. (2013) reported early outcomes from the ACCESS-EU trial. The prospective, multicenter, nonrandomized post-approval study enrolled 567 patients with MR. Maisano et al. reported an implant success rate of 99.6%. Nineteen patients (3.4%) died within 30 days after the MitraClip procedure. Survival at 1 year was 81.8%. Thirty-six patients (6.3%) required mitral valve surgery within 12 months after the implant procedure. There was improvement in the severity of MR at 12 months, compared with baseline. In a subset of 117 patients with severe degenerative MR, Reichenspurner et al. reported that the MitraClip procedure resulted in significant reductions in MR and improvements in clinical outcomes at 12 months. Limitations of this study include lack of randomization, absence of a control group and short-term follow-up. Additionally, patient selection criteria varied at participating centers.

Cohort studies have compared the MitraClip procedure in high-risk patients with conventional surgery in patients at normal risk. The largest of these studies enrolled 171 patients with secondary MR and found that after 6 months, the MitraClip procedure was associated with lower survival (87% versus 96% of patients) and lower freedom from moderate or severe MR (88% versus 97% of patients). These differences may have been due to the poorer health status of patients who underwent the MitraClip procedure. Adjustment for these differences eliminated the statistically significant difference in
survival (Conradi et al., 2013). Similar results were obtained by Taramasso et al. (2012) in a cohort study that enrolled 143 patients and preferentially assigned higher-risk patients to the MitraClip procedure. At 1-year follow-up, there were no significant differences between the treatment groups in patient survival but the MitraClip group was more likely to have moderate or severe MR (21% versus 6% of patients). Again, these differences may have been due to the poorer health status of patients who underwent the MitraClip procedure.

A National Institute for Health and Care Excellence (NICE) guidance document states that the evidence on the safety and efficacy of percutaneous mitral valve leaflet repair for MR is currently inadequate in quality and quantity. Therefore, this procedure should only be used with special arrangements for patients who are well enough for surgical mitral valve repair or in the context of research for patients who are not well enough for surgical mitral valve repair (NICE, 2009).

Several clinical trials are ongoing.

**Percutaneous Annuloplasty**

A Hayes report concluded that there is insufficient evidence to evaluate the Carillon procedure for percutaneous mitral valve repair (Hayes, 2014; updated 2016).

Siminiak et al. (2012) evaluated whether percutaneous mitral annuloplasty (Carillon Mitral Contour System) could safely and effectively reduce functional mitral regurgitation (FMR) and yield durable long-term clinical benefit. Patients in whom the device was placed then acutely recaptured for clinical reasons served as a comparator group. Quantitative measures of FMR, left ventricular (LV) dimensions, NYHA class, 6 min walk distance (6MWD), and quality of life were assessed in both groups up to 12 months. Safety and key functional data were assessed in the implanted cohort up to 24 months. Thirty-six patients received a permanent implant; 17 had the device recaptured. The 30-day major adverse event rate was 1.9%. In contrast to the comparison group, the implanted cohort demonstrated significant reductions in FMR as represented by regurgitant volume. There was a corresponding reduction in LV diastolic volume and systolic volume compared with progressive LV dilation in the comparator. The 6MWD markedly improved for the implanted patients by $102.5 \pm 164$ m at 12 months and $131.9 \pm 80$ m at 24 months. The authors concluded that percutaneous reduction of FMR using a coronary sinus approach is associated with reverse LV remodelling. Significant clinical improvements persisted up to 24 months. While this study provides a comparator group with which to evaluate the hemodynamic and clinical significance of treating FMR, the lack of a randomized and blinded comparator also remains the primary limitation of the study. According to the authors, a randomized trial comparing intervention with a medically managed control group is warranted.

Schofer et al. (2009) evaluated patients with moderate heart disease who were enrolled in the CARILLON Mitral Annuloplasty Device European Union Study (AMADEUS). Percutaneous mitral annuloplasty was achieved through the coronary sinus with the CARILLON Mitral Contour System. Of the 48 patients enrolled in the trial, 30 received the CARILLON device. Eighteen patients did not receive a device because of access issues, insufficient acute FMR reduction, or coronary artery compromise. Echocardiographic FMR grade, exercise tolerance, NYHA class, and quality of life were assessed at baseline and 1 and 6 months. The major adverse event rate was 13% at 30 days. At 6 months, the degree of FMR reduction among 5 different quantitative echocardiographic measures ranged from 22% to 32%. Six-minute walk distance improved from $307 +/- 87$ m at baseline to $403 +/-$
137 m at 6 months. Quality of life, measured by the Kansas City Cardiomyopathy Questionnaire, improved from 47+/−16 points at baseline to 69+/−15 points at 6 months. The authors concluded that percutaneous reduction in FMR with a novel coronary sinus-based mitral annuloplasty device is feasible in patients with heart failure, is associated with a low rate of major adverse events, and is associated with improvement in quality of life and exercise tolerance. Study limitations include the lack of a randomized, blinded control group with whom to compare safety and efficacy results.

A National Institute for Health and Care Excellence (NICE) guidance document states that the current evidence on the safety and efficacy of percutaneous mitral valve annuloplasty is inadequate in quality and quantity. Therefore this procedure should only be used in the context of research, which should clearly describe patient selection, concomitant medical therapies and safety outcomes. Both objective measurements and clinical outcomes should be reported (NICE, 2010).

**Valve-in-Valve Procedures**

The evidence base for transcatheter heart valve implantation within an existing bioprosthetic valve consists primarily of case series.

Using registry data, Dvir et al. (2014) determined the survival of patients after transcatheter ViV implantation inside failed surgical bioprosthetic valves. Correlates for survival were evaluated using a multinational registry that included 459 patients with degenerated bioprosthetic valves undergoing ViV implantation. Modes of bioprosthesis failure were stenosis (n = 181), regurgitation (n = 139) and combined (n = 139). The stenosis group had a higher percentage of small valves (37% vs 20.9% and 26.6% in the regurgitation and combined groups, respectively). Within 1 month following ViV implantation, 35 (7.6%) patients died, 8 (1.7%) had major stroke and 313 (92.6%) of surviving patients had good functional status (NYHA class I/II). The overall 1-year survival rate was 83.2%; 62 death events; 228 survivors). Patients in the stenosis group had worse 1-year survival (76.6%; 34 deaths; 86 survivors) in comparison with the regurgitation group (91.2%; 10 deaths; 76 survivors) and the combined group (83.9%; 18 deaths; 66 survivors). Similarly, patients with small valves had worse 1-year survival (74.8%; 27 deaths; 57 survivors) versus with intermediate-sized valves (81.8%; 26 deaths; 92 survivors) and with large valves (93.3%; 7 deaths; 73 survivors). Factors associated with mortality within 1 year included having small surgical bioprosthesis (≤21 mm) and baseline stenosis (vs regurgitation).

Raval et al. (2014) performed a systematic review to evaluate the effectiveness and outcomes of ViV implantation. Sixty-one studies were included: aortic (n=31), mitral (n=13), tricuspid (n=12) and pure native aortic valve regurgitation (n=9). The authors reported that ViV implantation can be considered an acceptable alternative to conventional open heart surgery for elderly high-risk surgical patients with bioprosthetic degeneration; however, most of the studies included were case reports with some case series. Long-term follow-up of treated patients will be necessary to establish the true role of ViV implantation for bioprosthetic degeneration.

Webb et al. (2010) evaluated transcatheter ViV implantation for failed bioprosthetic heart valves. ViV implantations were performed in 24 high-risk patients. Failed valves were aortic (n=10), mitral (n=7), pulmonary (n=6) or tricuspid (n=1) bioprostheses. Implantation was successful with immediate restoration of satisfactory valve function in all but one patient. No patient had more than mild regurgitation after implantation. No patients died during the procedure. Thirty-day mortality was 4.2%.
Mortality was related primarily to learning-curve issues early in this high-risk experience. At baseline, 88% of patients were in NYHA functional class III or IV. At the last follow-up, 88% of patients were in class I or II. At a median follow-up of 135 days and a maximum follow-up of 1045 days, 91.7% of patients remained alive with satisfactory valve function. This study is limited by a small patient population and a lack of randomization and control.

A NICE guidance document states that for patients with aortic bioprosthetic valve dysfunction for whom SAVR is considered to be unsuitable, the evidence on the safety and efficacy of valve-in-valve (ViV) TAVR is adequate. For patients with aortic bioprosthetic valve dysfunction for whom SAVR is considered to be suitable but to pose a high risk, the evidence on the safety and efficacy of ViV TAVR is inadequate. For patients with aortic bioprosthetic valve dysfunction for whom SAVR is considered to be suitable and not to pose a high risk, the evidence on the safety and efficacy of ViV TAVR is inadequate (NICE, 2014).

A NICE guidance document states that the current evidence on the safety of transapical transcatheter mitral valve-in-valve implantation for a failed surgically implanted mitral valve bioprosthesis shows the potential for serious complications. However, this is in patients for whom open surgical valve implantation is unsuitable, who have severe symptoms and a high risk of death. The evidence on efficacy shows generally good symptom relief in the short term, but is based on very small numbers of patients. Therefore, this procedure should only be used with special arrangements for clinical governance, consent and audit or research (NICE, 2015).

Professional Societies
American College of Cardiology (ACC) / American Heart Association (AHA)
ACC/AHA guidelines for the management of patients with valvular heart disease (Nishimura et al., 2014) make the following recommendations regarding transcatheter valve replacement:

Aortic
- Transcatheter aortic valve replacement (TAVR) is recommended in patients who meet an indication for aortic valve replacement (AVR) for aortic stenosis who have a prohibitive surgical risk and a predicted post-TAVR survival >12 mo. (Class I recommendation, level of evidence B – procedure is useful/effective based on evidence from a single randomized trial or nonrandomized studies.)
- TAVR is a reasonable alternative to surgical AVR in patients who meet an indication for AVR and who have high surgical risk. (Class IIa recommendation, level of evidence B – procedure is reasonable but based on conflicting evidence from a single randomized trial or nonrandomized studies.)
- TAVR is not recommended in patients in whom existing comorbidities would preclude the expected benefit from correction of aortic stenosis. Class III: no benefit, level of evidence B – procedure has no proven benefit based on evidence from a single randomized trial or nonrandomized studies.)
- For patients in whom TAVR or high-risk surgical AVR is being considered, members of a Heart Valve Team should collaborate to provide optimal patient care. (Class I recommendation, level of evidence C - based on expert opinion, case studies or standard of care.)
Mitral
Transcatheter mitral valve repair may be considered for severely symptomatic patients (NYHA class III to IV) with chronic severe primary MR (stage D) who have favorable anatomy for the repair procedure and a reasonable life expectancy but who have a prohibitive surgical risk because of severe comorbidities and remain severely symptomatic despite optimal guideline-directed medical therapy for heart failure. (Class IIb recommendation, level of evidence B - procedure may be considered but usefulness/efficacy is less well established based on conflicting evidence from a single randomized trial or nonrandomized studies.)

Pulmonary
Transcatheter pulmonary valve replacement is outside the scope of these guidelines. See Warnes et al., 2008.

The ACC and STS, along with the Society for Cardiovascular Angiography and Interventions (SCAI) and the American Association for Thoracic Surgery (AATS), released an expert consensus statement outlining operator and institutional requirements for creating and maintaining transcatheter aortic valve replacement programs. The recommendations are aimed at ensuring optimal patient care (Tommaso et al., 2012). The same organizations released a similar statement addressing transcatheter therapies for MR (O’Gara et al., 2014).

In a separate publication, these organizations provide additional expert consensus recommendations for patient selection, screening and post-procedural care. These recommendations specify that TAVR is recommended for adults with severe, symptomatic, calcific stenosis of a trileaflet aortic valve who have aortic and vascular anatomy suitable for TAVR and a predicted survival of 12 months. TAVR is recommended in patients with prohibitive surgical risk and is a reasonable alternative to SAVR in patients at high surgical risk. Prohibitive surgical risk is defined by an estimated ≥ 50% risk of mortality or irreversible morbidity at 30 days or other factors such as frailty, prior radiation therapy, porcelain aorta and severe hepatic or pulmonary disease (Holmes et al., 2012).

In a joint consensus document, ACC and STS state that transcatheter valve therapy is a transformational technology with the potential to significantly impact the clinical management of patients with valvular heart disease in a less invasive manner. Although the initial experience is positive, evidence exists from only 1 randomized clinical trial in patients with aortic stenosis and 1 in patients with mitral insufficiency. Adoption of these techniques to populations beyond those studied in these randomized trials, therefore, is not appropriate at the current time. However, in view of the promising results obtained in these limited population subsets, conduct of further randomized trials in other patient groups is strongly encouraged.

Both ACC and STS strongly recommend the use of a “heart team” approach in which both a cardiothoracic surgeon and a cardiologist actively participate in the procedure. The consensus document makes recommendations for populating the heart team.

Participation in a national registry is also strongly recommended. The STS/ACCF TVT Registry is now enrolling participant sites (https://www.ncdr.com/TVT/Home/Default.aspx. Accessed January 2017). Data from this registry will provide clinical short-term and long-term follow-up information
necessary to monitor outcomes as well as quality-of-life. The registry will also provide information that can be used to assess appropriateness of care as well as overuse (Holmes and Mack, 2011).

ACC guidelines on the management of adults with congenital heart disease address percutaneous therapies for reintervention in patients with RVOT dysfunction. Therapies include balloon dilation, stenting or percutaneous valve replacement. While promising, percutaneous valve replacement is considered investigational as it has yet to be proven in larger clinical trials (Warnes et al., 2008).

**American Heart Association (AHA)**

In a scientific statement, the AHA states that percutaneous valve therapy devices and techniques require significant changes before widespread clinical use is possible. Randomized comparisons with existing standard of care treatments and registries for high-risk patients will define the roles of these new technologies. For the near term, percutaneous techniques will likely remain investigational and will be limited in use to patients considered to be high risk or to inoperable surgical candidates. Even after FDA approvals, percutaneous devices should be used in only a small number of centers with excellent surgical and catheter experience until they are thoroughly tested in the clinical arena. The AHA also states that less invasive and percutaneous valve therapies will likely have a major impact on the management of patients with valvular heart disease over the next several years (Rosengart et al., 2008).

An AHA scientific statement on interventions for pediatric cardiac disease concluded that it is reasonable to consider percutaneous pulmonary valve replacement in a patient with a right ventricular-pulmonary artery conduit with associated moderate to severe pulmonary regurgitation or stenosis provided the patient meets inclusion/exclusion criteria for the available valve (Feltes et al., 2011). (Class IIa recommendation, level of evidence B – although there is conflicting evidence and/or a divergence of opinion about the usefulness/efficacy of procedure, weight of evidence/opinion is in favor of usefulness/efficacy based on data derived from a single randomized trial or nonrandomized studies.)

**European Association of Cardio-Thoracic Surgery (EACTS) / European Society of Cardiology (ESC)**

EACTS and ESC guidelines on the management of valvular heart disease make the following recommendations regarding TAVR:

- TAVR should only be undertaken with a multidisciplinary ‘heart team’ including cardiologists and cardiac surgeons and other specialists if necessary.

- TAVR should only be performed in hospitals with cardiac surgery on-site.

- TAVR is indicated in patients with severe symptomatic aortic stenosis who are not suitable for aortic valve replacement as assessed by a ‘heart team’ and who are likely to gain improvement in their quality of life and to have a life expectancy of more than 1 year after consideration of their comorbidities.

- TAVR should be considered in high-risk patients with severe symptomatic aortic stenosis who may still be suitable for surgery, but in whom TAVR is favored by a ‘heart team’ based on the individual risk profile and anatomic suitability.

The guidelines also address percutaneous edge-to-edge repair for patients with primary MR. The EVEREST trials and other studies suggest that percutaneous edge-to-edge mitral valve repair is relatively safe, usually well tolerated even by patients in poor clinical condition and has a success rate
of approximately 75%. Despite these benefits, percutaneous mitral valve repair does not reduce MR as effectively as mitral valve surgery. The guidelines caution that valve replacement may be necessary in up to 50% of patients who have unsuccessful clip implantation. Experience from a limited number of patients suggests that percutaneous edge-to-edge mitral valve repair is feasible in patients with secondary or functional MR. The procedure may provide short-term improvement in functional condition and LV function. These findings have to be confirmed in larger series with longer follow-up and with a randomized design.

The guidelines only briefly mention that data on coronary sinus annuloplasty is limited (Vahanian et al., 2012).

EACTS and ESC, in collaboration with the European Association of Percutaneous Cardiovascular Interventions (EAPCI), published a position statement on transcatheter valve implantation for patients with aortic stenosis. The document states that currently available results obtained with TAVR suggest that these techniques are feasible and provide hemodynamic and clinical improvement for up to 2 years in patients with severe symptomatic aortic stenosis at high risk or with contraindications for surgery. Pending questions concern safety and long-term durability. A careful commercialization process, including training and post-market surveillance, is crucial to avoid the risk of uncontrolled diffusion. The group acknowledges that the conclusions rely on limited data reported mostly in oral communications and few in peer-reviewed journals (Vahanian et al., 2008).

**European Society of Cardiology (ESC)**
ESC guidelines for the management of adult congenital heart disease state that the decision to perform a percutaneous pulmonary valve implantation should involve a process of rigorous peer review and multidisciplinary discussion, as currently few data exist to demonstrate non-inferiority over surgery for many of these approaches. Mid-/long-term outcome data are not available yet for this procedure. Surgery is preferred over percutaneous methods when additional interventions are being considered (Baumgartner et al., 2010).

**U.S. FOOD AND DRUG ADMINISTRATION (FDA)**

**Aortic**
The Edwards SAPIEN Transcatheter Heart Valve received FDA premarket approval (P100041) on November 2, 2011. The device is indicated for transfemoral delivery in patients with severe, symptomatic native aortic valve stenosis who have been determined by a cardiac surgeon to be inoperable for open aortic valve replacement and in whom existing comorbidities would not preclude the expected benefit from correction of the aortic stenosis. The device is contraindicated in patients who cannot tolerate an anticoagulation/antiplatelet regimen or who have active bacterial endocarditis or other active infections. Labeling also states that implantation of the transcatheter heart valve should be performed only by physicians who have received Edwards Lifesciences training. The implanting physician should be experienced in balloon aortic valvuloplasty. Additional information is available at: [http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfTopic/pma/pma.cfm?num=P100041](http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfTopic/pma/pma.cfm?num=P100041). Accessed January 2017.

On October 19, 2012, the FDA approved an expanded indication for the Edwards SAPIEN valve to include patients with aortic stenosis who are eligible for surgery but who are at high risk for serious

On September 23, 2013, the FDA approved revised labeling for the SAPIEN valve. The new labeling removes references to specific access points now making the device available for inoperable patients who need an alternate access point. The device is now indicated for patients with severe symptomatic calcified native aortic valve stenosis without severe aortic insufficiency and with ejection fraction >20% who have been examined by a heart team including an experienced cardiac surgeon and a cardiologist and found to be: 1) inoperable and in whom existing co-morbidities would not preclude the expected benefit from correction of the aortic stenosis; or 2) be operative candidates for aortic valve replacement but who have a predicted operative risk score ≥8% or are judged by the heart team to be at a ≥15% risk of mortality for SAVR.

The Edwards SAPIEN XT Transcatheter Heart Valve and accessories received FDA premarket approval (P130009) on June 16, 2014. The device is indicated for relief of aortic stenosis in patients with symptomatic heart disease due to severe native calcific aortic stenosis (aortic valve area ≤1.0 cm² or aortic valve area index ≤0.6 cm²/m², a mean aortic valve gradient of ≥40 mmHg or a peak aortic-jet velocity of ≥4.0 m/s), and with native anatomy appropriate for the 23, 26 or 29 mm valve system, who are judged by a heart team, including a cardiac surgeon, to be at high or greater risk for open surgical therapy (i.e., STS operative risk score ≥8% or at a ≥15% risk of mortality at 30 days). Additional information is available at: http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfTopic/pma/pma.cfm?id=P130009. Accessed January 2017.

On October 9, 2015 the FDA granted expanded approval of the SAPIEN XT Transcatheter Heart Valve to include aortic valve-in-valve procedures.

The Edwards SAPIEN 3 Transcatheter Heart Valve and accessories received FDA premarket approval (P140031) on June 17, 2015. The device is indicated for relief of aortic stenosis in patients with symptomatic heart disease due to severe native calcific aortic stenosis who are judged by a heart team, including a cardiac surgeon, to be at high or greater risk for open surgical therapy (i.e., STS operative risk score ≥8% or at a ≥15% risk of mortality at 30 days). Additional information is available at: http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpmia/pma.cfm?id=P140031. Accessed January 2017.

On August 18, 2016, the FDA granted expanded approval of the SAPIEN XT and SAPIEN 3 valves to include patients with intermediate surgical risk for aortic valve replacement.

The Medtronic CoreValve System received FDA premarket approval (P130021) on January 17, 2014. The device is indicated for relief of aortic stenosis in patients with symptomatic heart disease due to severe native calcific aortic stenosis (aortic valve area ≤0.8 cm², a mean aortic valve gradient of >40 mm Hg, or a peak aortic-jet velocity of >4.0 m/s) and with native aortic annulus diameters between 18 and 29 mm who are judged by a heart team, including a cardiac surgeon, to be at extreme risk or inoperable for open surgical therapy (predicted risk of operative mortality and/or serious irreversible
morbidity ≥50% at 30 days). The device is contraindicated for patients presenting with any of the following conditions:

- known hypersensitivity or contraindication to aspirin, heparin (HIT/HITTS) and bivalirudin, ticlopidine, clopidogrel, Nitinol (titanium or nickel), or sensitivity to contrast media, which cannot be adequately premedicated
- ongoing sepsis, including active endocarditis
- preexisting mechanical heart valve in aortic position

Additional information is available at:

On June 12, 2014, the FDA approved an expanded indication for the Medtronic CoreValve System to include patients at high or greater risk for open surgical therapy (i.e., STS operative risk score ≥8% or at a ≥15% risk of mortality at 30 days).

On March 30, 2015, the FDA approved a second indication for the Medtronic CoreValve System. The device is approved for valve-in-valve replacement and is indicated for use in selected high-surgical risk patients with a degenerated bioprosthetic aortic valve who require another valve replacement procedure.

On June 22, 2015, the FDA approved Medtronic’s next-generation CoreValve Evolut® System which allows for the device to be recaptured and repositioned.

On February 12, 2013, the FDA granted the STS and the American College of Cardiology (ACC) a unique investigational device exemption (IDE) to study “alternative access” approaches for transcatheter aortic valve replacement (TAVR) using the STS/ACC TVT Registry™. Currently, only the transfemoral approach to TAVR using the Edwards SAPIEN valve has been approved for inoperable patients. Both the transfemoral and transapical approaches have been approved for high risk patients. An estimated 1 in 4 patients is ineligible for these procedures because of inadequate vessel size, vessel disease or other considerations. The new STS/ACC study protocol, as approved by CMS, allows Medicare reimbursement for alternative access to the aortic valve via the heart muscle or the aorta (transaortic approach) in inoperable patients involved in the study. The goal of the study is controlled off-label use of an approved device (STS press release, 2013). Available at:

**Pulmonary**

The Melody Transcatheter Pulmonary Valve (TPV) and the Ensemble Transcatheter Valve Delivery System received FDA premarket approval (P140017) on January 27, 2015. The Melody TPV is indicated 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) dysfunctional right ventricular outflow tract (RVOT) conduit that was equal to or greater than 16 mm in diameter when originally implanted AND
- Dysfunctional RVOT conduit with a clinical indication for intervention, and:
  - Regurgitation: ≥ moderate regurgitation AND/OR
  - Stenosis: mean RVOT gradient ≥ 35 mmHg


On February 29, 2016, the FDA granted expanded approval of the Edwards SAPIEN XT Transcatheter Heart Valve to include use in percutaneous pulmonary valve implantation procedures (P130009).

**Mitral**

The MitraClip Mitral Valve Repair System received FDA premarket approval (P100009) on October 24, 2013. The device is indicated for the percutaneous reduction of significant symptomatic mitral regurgitation (MR ≥ 3+) due to primary abnormality of the mitral apparatus [degenerative MR] in patients who have been determined to be at prohibitive risk for mitral valve surgery by a heart team, which includes a cardiac surgeon experienced in mitral valve surgery and a cardiologist experienced in mitral valve disease, and in whom existing comorbidities would not preclude the expected benefit from reduction of the mitral regurgitation. Additional information is available at: http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfTopic/pma/pma.cfm?num=P100009. Accessed January 2017.

**Additional Products**

Carillon® Mitral Contour System™ for percutaneous annuloplasty – not FDA approved
Portico™ (St. Jude Medical) – not FDA approved

### APPLICABLE CODES

The following list(s) of procedure and/or diagnosis codes is provided for reference purposes only and may not be all inclusive. Listing of a code in this policy does not imply that the service described by the code is a covered or non-covered health service. Benefit coverage for health services is determined by the member specific benefit plan document and applicable laws that may require coverage for a specific service. The inclusion of a code does not imply any right to reimbursement or guarantee claim payment. Other Policies and Coverage Determination Guidelines may apply.

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Transcatheter Heart Valve Procedures
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*CPT® is a registered trademark of the American Medical Association*

**REFERENCES**


**PROTOCOL HISTORY/REVISION INFORMATION**

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The foregoing Health Plan of Nevada/Sierra Health & Life Health Operations protocol has been adopted from an existing UnitedHealthcare coverage determination guideline that was researched, developed and approved by the UnitedHealthcare Coverage Determination Committee.