



Louisiana

Transcatheter Mitral Valve Repair

Policy # 00494

Original Effective Date: 02/17/2016

Current Effective Date: 02/21/2018

Applies to all products administered or underwritten by Blue Cross and Blue Shield of Louisiana and its subsidiary, HMO Louisiana, Inc. (collectively referred to as the "Company"), unless otherwise provided in the applicable contract. Medical technology is constantly evolving, and we reserve the right to review and update Medical Policy periodically.

When Services May Be Eligible for Coverage

Coverage for eligible medical treatments or procedures, drugs, devices or biological products may be provided only if:

- Benefits are available in the member's contract/certificate, and
- Medical necessity criteria and guidelines are met.

Based on review of available data, the Company may consider transcatheter mitral valve (MV) repair with a device approved by the U.S. Food and Drug Administration (FDA) for use in mitral valve (MV) repair to be **eligible for coverage**, for patients with symptomatic degenerative mitral regurgitation (DMR) who are considered at prohibitive risk for open surgery.

When Services Are Considered Investigational

Coverage is not available for investigational medical treatments or procedures, drugs, devices or biological products.

Based on review of available data, the Company considers transcatheter mitral valve (MV) repair in all other situations to be **investigational**.*

Note: "Prohibitive risk" for open surgery may be determined based on:

- Presence of a Society for Thoracic Surgeons predicted mortality risk of 12% or greater; and/or
- Presence of a logistic EuroSCORE of 20% or greater.

Background/Overview

MITRAL REGURGITATION

Epidemiology and Classification

Mitral regurgitation (MR) is the second most common valvular heart disease, occurring in 7% of people older than age 75 years and accounting for 24% of all patients with valvular heart disease. MR can result from a heterogeneous set of disease processes that may affect 1 or more parts of the MV complex. The functional anatomy of the MV complex includes the left ventricular (LV) myocardium, the subvalvular apparatus including the papillary muscles and chordae tendineae, the mitral annulus, the MV leaflets, and the left atrium. The underlying cause of MR and the portion of the MV complex involved determine the underlying treatment strategy.

MR is classified into degenerative and functional MV disease. In DMR, disease results from a primary structural abnormality of the MV complex. Common causes of DMR include MV prolapse syndrome with subsequent myxomatous degeneration, rheumatic heart disease, coronary artery disease, infective

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endocarditis, and collagen vascular disease. In contrast, in functional mitral regurgitation (FMR), the primary abnormality is a dilated LV due to ischemic or dilated cardiomyopathy, which leads to secondary dilatation of an anatomically normal MV. MR severity is classified as mild, moderate, or severe disease on the basis of echocardiographic and/or angiographic findings (1+, 2+, and 3-4+ angiographic grade, respectively).

MR with accompanying valvular incompetence leads to LV volume overload with secondary ventricular remodeling, myocardial dysfunction, and left heart failure. Clinical signs and symptoms of dyspnea and orthopnea may also present in patients with valvular dysfunction. MR can be acute or chronic. Acute MR can result from conditions such as ruptured chordae tendineae or infectious endocarditis; and when severe, it can present with simultaneous shock and pulmonary congestion. Chronic MR may remain asymptomatic over a long period of time due to compensatory LV hypertrophy secondary to the LV overload. This leads to increased LV end-diastolic volume and, in turn, increased stroke volume (to restore forward cardiac output) and increased LV and left atrial size (to accommodate the regurgitant volume at lower filling pressure). Eventually, prolonged volume overload leads to contractile dysfunction, with increased end-systolic volume, further LV dilatation, and increased LV filling pressure. These changes ultimately lead to reduced forward cardiac output and signs and symptoms of pulmonary congestion.

Standard Management

Medical Management

Medical management has a role in a subset of MR cases. Among patients with chronic DMR, there is no generally accepted medical management. In FMR, medical management plays a much greater role because the underlying pathophysiology is related to LV dysfunction and dilatation. Primary treatment of the LV systolic dysfunction with angiotensin-converting enzyme inhibitors, β -blockers, and biventricular pacing can reduce LV pressures, decrease LV dilatation, improve cardiac output, and thus ameliorate clinical symptoms.

Surgical Management

In patients with symptoms of MR with preserved LV function (DMR), surgery is the main therapy. In most cases, repair of the MV is preferred over replacement, as long as the valve is suitable for repair and personnel with appropriate surgical expertise are available. The American College of Cardiology and the American Heart Association have issued joint guidelines for the surgical management of MV, which are outlined in Table 1.

Table 1. Guidelines on Mitral Value Surgery

Recommendation	COR	LOE
MV surgery is recommended for the symptomatic patient with acute severe MR.	I	B
MV surgery is beneficial for patients with chronic severe MR and NYHA functional class II, III, or IV symptoms in the absence of severe LV dysfunction (severe LV dysfunction is defined as ejection fraction less than 0.30) and/or end-systolic dimension greater than 55 mm.	I	B
MV surgery is beneficial for asymptomatic patients with chronic severe MR and mild-to-moderate LV dysfunction, ejection fraction 0.30 to 0.60, and/or end systolic dimension greater than or equal to 40 mm.	I	B

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MV repair is recommended over MV replacement in the majority of patients with severe chronic MR who require surgery, and patients should be referred to surgical centers experienced in MV repair.	I	C
MV repair is also reasonable for asymptomatic patients with chronic severe MR with preserved LV function ... in whom the high likelihood of successful MV repair without residual MR is greater than 90%.	Ila	B
MV surgery is reasonable for asymptomatic patients with chronic severe MR, preserved LV function, and new onset of atrial fibrillation	Ila	C
MV surgery is reasonable for asymptomatic patients with chronic severe MR,* preserved LV function, and pulmonary hypertension....	Ila	C
MV surgery is reasonable for patients with chronic severe MR due to a primary abnormality of the mitral apparatus and NYHA functional class III–IV symptoms and severe LV dysfunction ... in whom MV repair is highly likely	Ila	C

COR: class of recommendation; LOE: level of evidence; LV: left ventricular; MR: mitral regurgitation; MV: mitral valve; NYHA: New York Heart Association.

Standard open MV repair includes quadrangular leaf resection (if MV prolapse is present), transposition of normal valve chords to other areas of prolapsing leaflet, and a remodeling annuloplasty with a ring prosthesis. Multiple types of annuloplasty rings and bands specific to the underlying cause of the MR are commercially available. Introduced in the 1990s, the edge-to-edge approximation technique (Alfieri repair), typically combined with an annuloplasty, involves suturing the anterior and posterior MV leaflets together at their midpoint, creating a double-orifice MV.

However, there are limitations to the open surgical approaches for MV repair. While surgical MV repair is durable, its use is limited by the requirement for thoracotomy and cardiopulmonary bypass, which may not be tolerated by patients who are elderly or debilitated due to their underlying cardiac disease or other conditions. In a 2007 study of 396 patients in Europe with severe, symptomatic MR, Mirabel et al found that about half of patients did not undergo surgical repair, specifically 56% of patients with DMR and 32% with FMR did not. Older age, impaired LV ejection fraction, and presence of comorbidities were all associated with the decision not to operate. In a single-center evaluation of 5737 patients with severe MR in the United States, Goel et al (2014) found that 53% of patients did not have MV surgery performed. Compared with those who received surgery, patients who did not had lower ejection fractions (27% vs 42%, p<0.001) and were at higher surgical risk, as judged by a higher Society of Thoracic Surgeons score (median, 5.8 vs 4.0, p<0.001). These findings suggest that there is an unmet need for less invasive procedures for MV repair.

Transcatheter MV Repair

Transcatheter approaches have been investigated to address the unmet need for less invasive MV repair, particularly among patients who face prohibitively high surgical risks due to age or comorbidities. MV repair devices under development address various components of the MV complex and generally are performed on the beating heart without the need for cardiopulmonary bypass. Approaches to MV repair include direct leaflet repair, repair of the mitral annulus via direct annuloplasty, or indirect repair based on the annulus's

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proximity to the coronary sinus. There are also devices in development to counteract ventricular remodeling, and systems designed for complete MV replacement via catheter.

Direct Leaflet Approximation

One device that undertakes direct leaflet repair, the MitraClip Clip Delivery System (Abbott Vascular, Menlo Park, CA), has been approved through the premarket approval process by the U.S. Food and Drug Administration for use in certain patients with symptomatic MR (see Regulatory Status section). Of the transcatheter MV repair devices under investigation, MitraClip has the largest body of evidence evaluating its use and has been in use in Europe since 2008. The MitraClip system is deployed percutaneously and approximates the open Alfieri edge-to-edge repair approach to treating MR. The delivery system consists of a catheter, a steerable sleeve, and the MitraClip device, which is a 4-mm wide clip fabricated from a cobalt-chromium alloy and polypropylene fabric. MitraClip is deployed via a transfemoral approach, with transseptal puncture used to access the left side of the heart and the MV. Placement of MitraClip leads to coapting of the mitral leaflets, thus creating a double-orifice valve.

Other MV Repair Devices

Additional devices for transcatheter MV repair that use different approaches are in development. Techniques to repair the mitral annulus include those that target the annulus itself (direct annuloplasty) and those that tighten the mitral annulus via manipulation of the adjacent coronary sinus (indirect annuloplasty). Indirect annuloplasty devices include the Carillon[®] Mitral Contour System (Cardiac Dimension, Kirkland, WA) and the Monarc[™] device (Edwards Lifesciences, Irvine, CA). The CE-marked Carillon Mitral Contour System is comprised of self-expanding proximal and distal anchors connected with a nitinol bridge, with the proximal end coronary sinus ostium and the distal anchor in the great cardiac vein. The size of the connection is controlled by manual pullback on the catheter (CE marked). The Carillon system was evaluated in the Carillon Mitral Annuloplasty Device European Union Study (AMADEUS) and the follow-up Tighten the Annulus Now (TITAN) study, with further studies planned. The Monarc system also involves 2 self-expanding stents connected by a nitinol bridge, with 1 end implanted in the coronary sinus via internal jugular vein and the other in the great cardiac vein. Several weeks following implantation, a biologically degradable coating over the nitinol bridge degrades, allowing the bridge to shrink and the system to shorten. It has been evaluated in the Clinical Evaluation of the Edwards Lifesciences Percutaneous Mitral Annuloplasty System for the Treatment of Mitral Regurgitation (EVOLUTION I) trial.

Direct annuloplasty devices include the Mitralign Percutaneous Annuloplasty System (Mitralign, Tewksbury, MA) and the AccuCinch[®] System (Guided Delivery Systems, Santa Clara, CA), both of which involve transcatheter placement of anchors in the MV, which are cinched or connected to narrow the mitral annulus. Other transcatheter direct annuloplasty devices under investigation include the enCorTC[™] device (MiCardia, Irvine, CA), which involves a percutaneously insertable annuloplasty ring that is adjustable using radiofrequency energy, a variation on its CE-marked enCor_{sq}[™] Mitral Valve Repair System, and the Cardioband[™] Annuloplasty System (Valtech Cardio, Or-Yehuda, Israel), an implantable annuloplasty band with a transfemoral venous delivery system.

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Transcatheter MV Replacement

Several devices are under development for transcatheter MV replacement, including the Endovalve™[‡] (MicroInterventional Devices, Langhorne, PA), the CardiAQ™[‡] (CardiAQ Valve Technologies, Irvine, CA) valve, the Cardiovalve (Valtech Cardio, Or-Yehuda, Israel), and the Fortis Transcatheter Mitral Valve (Edwards Lifesciences, Irvine, CA).

FDA or Other Governmental Regulatory Approval

U.S. Food and Drug Administration (FDA)

In October 2013, the MitraClip®[‡] Clip Delivery System (Abbott Vascular, Menlo Park, CA) was approved by the U.S. FDA through the premarket approval process for treatment 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 a prohibitive risk for mitral valve surgery by a heart team.” FDA product code: NKM.

Centers for Medicare and Medicaid Services (CMS)

In April 2015, the CMS issued a national coverage decision for the use of TMVR.

CMS determined that it would cover TMVR under Coverage with Evidence Development for the treatment of significant symptomatic MR when performed according to a FDA–approved indication and when all of the following conditions are met:

- “1. The procedure is performed 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 and 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;

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- 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[sic] 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 registry should collect all data necessary and have a written executable plan....

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- B. TMVR for MR uses that are not expressly listed as an FDA-approved indication when performed within a FDA-approved randomized clinical 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 study must critically evaluate the following questions at 12 months of longer follow-up:
 - What is the patient's post-TMVR quality of life (compared to pre-TMVR) at one year?
 - What is the patient's post-TMVR functional capacity (compared to pre-TMVR) at one year?"

In addition, the clinical research study must address a series of questions at 1 year postprocedure as outlined in the proposed decision memo.

Rationale/Source

The literature search for this evidence review focuses primarily on studies evaluating MitraClip, but evidence on other devices is discussed. Assessment of efficacy for therapeutic interventions such as MitraClip involves a determination of whether the intervention improves health outcomes. The optimal study design for this purpose is a randomized controlled trial (RCT) that includes clinically relevant measures of health outcomes. Intermediate outcome measures, also known as surrogate outcome measures, may be adequate if there is an established link between the intermediate outcome and true health outcomes. Nonrandomized comparative studies and uncontrolled studies can sometimes provide useful information on health outcomes, but are prone to biases. For MitraClip, the appropriate comparison group could be either open surgical repair (for surgical candidates) or best medical therapy (among persons at prohibitive surgical risk).

There are 2 major categories of patients with MR who are candidates for TMVR: those considered to be at prohibitively high risk for cardiac surgery and those considered surgical candidates. Studies addressing these 2 subsets of patients are outlined separately. Although outcomes and etiology differ for FMR and DMR, studies on MitraClip most often evaluate the device in mixed populations. The MitraClip device delivery system was approved by the FDA for use in patients with DMR who are not candidates for open surgery.

MITRACLIP IN PROHIBITIVE SURGICAL RISK CANDIDATES

Systematic Reviews

A 2014 TEC Assessment evaluated the evidence on the use of MitraClip for DMR, the FDA-approved indication. The Assessment included 5 case series reporting outcomes of patients with DMR considered at high risk of surgical mortality who underwent MitraClip placement. In the 2 studies the Assessment considered higher quality, 30-day mortality rates were 6.0% and 6.3%, and 12- and 25-month mortality rates were 17.1% and 23.6%, respectively. In evaluable patients at 12 months, the percentage of patients who had an MR grade of 2 or less was 83.3% and 74.6% in the 2 studies; the percentage of patients with

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New York Heart Association (NYHA) class I or II functional status was 81% and 87%; and improvement of at least 1 NYHA class was present in 68% and 88% of patients, respectively. Table 2 (adapted from the TEC Assessment) summarizes health outcomes for the 5 studies the Assessment evaluated.

Table 2. 12-Month Outcomes for Case Series of MitraClip for Degenerative Mitral Valve Disease

Study	Original N	MR Grade at 12 Months, % (n/N)	NYHA Class at 12 Months, % (n/N)	Other Pertinent Outcomes Assessed at 12 Months
Lim et al (2014)	127	MR ≤2+, 83.3% (70/84)	<ul style="list-style-type: none"> NYHA I/II, 86.9% (73/84) Improved ≥1 class, 86.9% (73/84) 	<ul style="list-style-type: none"> SF-36 PCS score change, 6.0 (95% CI, 4.0 to 8.0), n=76 SF-36 MCS score change, 5.6 (95% CI, 2.3 to 8.9), n=76
Reichenspurner et al (2013)	117	MR ≤2+, 74.6% (53/71)	<ul style="list-style-type: none"> NYHA I/II, 81% (63/78) Improved ≥1 class, 68% (53/78) 	<ul style="list-style-type: none"> Change in MLHFQ from baseline, 13.3 points (p=0.03), n=44 Change in 6MWT from baseline, 77.4 m (p<0.001), n=52
Estévez-Loureiro et al (2013)	79	NR	NR	
Grasso et al (2013)	28	NR	NR	Kaplan-Meier estimate of freedom from death, surgery, or ≥3+ MR, 70% (visual estimate from graph)
Chan et al (2012)	15	MR severity, 1.9 ^a	NYHA class, 2.1 ^a	

Adapted from the TEC Assessment.

CI: confidence interval; MCS: Mental Component Summary; MLHFQ: Minnesota Living with Heart Failure 10 Questionnaire; MR: mitral regurgitation; NR: not reported; NYHA: New York Heart Association; PCS: Physical Component Summary; 6MWT: Six-Minute Walk Test; SF-36: 36-Item Short-Form Health Survey.

^a Values are mean. Sample sizes unknown.

The Assessment reviewed evidence on the natural history of patients with MR who were considered at high risk for surgery in an attempt to determine an appropriate comparison group for the uncontrolled case series of MitraClip in high surgical risk patients. The evidence included 1 published study by Whitlow et al (2012) and data presented to FDA as part of the device's premarket approval application. The TEC Assessment concluded that these control groups may not provide unbiased or precise estimates of the natural history of patients eligible to receive MitraClip because most patients were not evaluated for anatomic eligibility for MitraClip or were ineligible. As such, the control groups likely had higher mortality rates than patients eligible to receive MitraClip.

Due to the lack of an appropriate control group or clear evidence about the natural history of patients with DMR considered at high risk for surgery, the Assessment concluded that it cannot be determined whether the mortality rate associated with MitraClip use was improved, equivalent, or worse than medical treatment. Also in 2014, Philip et al reported on results of a systematic review of studies evaluating MitraClip or surgical MV repair or replacement for severe symptomatic MR in patients at high surgical risk (logistic EuroSCORE >18 or Society for Thoracic Surgeons [STS] score >10). Reviewers included 21 studies that used MitraClip (n=3198 patients) and surgical MV repair (n=490) or MV replacement (n=2775). MitraClip

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patients had a mean STS score of 14 and a mean EuroSCORE of 23. Acute procedural success did not differ significantly between groups. However, the 30-day pooled technical failure rate was 3.2% (95% confidence interval [CI], 1.5% to 7%) for MitraClip patients compared with 0.6% (95% CI, 0.2% to 1.8%) for surgical repair/replacement patients ($p=0.002$). In pooled analysis, the 30-day mortality rate was 3% (95% CI, 2.6% to 4.2%) among MitraClip patients and 16% (95% CI, 13% to 20%) in surgical repair/replacement patients. Of the total sample, 1-year data were available for 1064 MitraClip patients (1-year data for surgical repair patients, limited to 47 patients, was not reported). Overall, among MitraClip patients, the 1-year mortality rate was 13.0% (95% CI, 9% to 18.3%), the 1-year stroke rate was 1.6% (95% CI, 0.8% to 3.2%), and the need for repeat MV surgery was 1.3% (95% CI, 0.7% to 2.6%).

A 2014 systematic review by Munkholm-Larsen et al summarized safety and efficacy results from 12 publications evaluating the efficacy of MitraClip in surgically high-risk patients. Reviewers included studies that evaluated high-risk surgical patients with significant MR who underwent TMVR with the MitraClip device, and excluded studies with surgical candidates. All were prospective, observational studies from specialized tertiary centers, with 3 multicenter studies and 9 single-institution studies. The 3 largest studies included 202, 117, and 100 patients, respectively, while the rest included fewer than 100 patients. Follow-up duration ranged from 1 to 14 months. Across the studies, 30-day mortality rates ranged from 0% to 7.8%. Most high surgical risk patients had successful reduction of MR of grade 2+ or less (73%-100% across studies). In studies that reported follow-up at 6 to 12 months, 61% to 99% of patients demonstrated continued MR reduction of grade 2+ or less, and 50% to 89% of patients demonstrated improvements in NYHA functional class to I to II. Reviewers suggested that MitraClip was associated with short-term improvements in echocardiographic parameters among high surgical risk patients, but did not provide evidence on clinical outcomes. In addition, most studies included both FMR and DMR, which limits ability to stratify outcomes by etiology.

Several other systematic reviews have also focused on the safety of MitraClip. In 2015, Bail et al reported results of a meta-analysis of the safety and efficacy of MitraClip placement, which included 26 studies (total $N=3821$ patients). Within the first 30 days postprocedure, 3.5% (95% CI, 2.9% to 4.2%) required open MV repair, 18.3% (95% CI 17.0% to 19.6%) experienced an adverse event, and 2.8% (95% CI, 2.3% to 4.4%) died. At 6 months, 4.5% (95% CI, 15.1% to 24.1%) required open MV repair, 18.9% (95% CI, 15.1% to 24.1%) experienced an adverse event, and the all-cause mortality rate was 11.9% (95% CI, 10.3 to 14.2%). By 12 months, 11.4% (95% CI, 9.6% to 13.5%) required open repair, and the all-cause mortality rate was 17.4% (95% CI, 15.1% to 18.9%).

In 2014, Vakil et al reported on results of a systematic review of the safety and efficacy of the MitraClip system for moderate-to-severe or severe FMR or DMR; it included 16 studies (total $N=2980$ patients). Based on calculated STS score, EuroSCORE, or surgeon discretion, 2689 patients in 14 studies were considered high risk for surgery and 291 patients in 2 studies were considered low risk for surgery. The pooled 30-day mortality rate (primary safety outcome) was 4.2%. During a mean follow-up of 310 days (range, 80 days to 4 years), 387 (15.8%) of 2457 deaths occurred. In the 8 studies reporting cause of death, the pooled incidence of cardiac mortality was 3.7%.

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Randomized Controlled Trials

No RCTs have been published evaluating MitraClip in prohibitive surgical risk populations.

Nonrandomized Comparative Studies

In 2014, Swaans et al on reported results of a study comparing survival for MR patients considered at high surgical risk who underwent MitraClip placement with high-risk patients who had conservative management and with patients who had surgical repair. MitraClip-treated patients (n=139) included those treated at a single institution with MitraClip for symptomatic MR whose high surgical risk was based on a logistic EuroSCORE of at least 20, or who were denied surgery based on other factors associated with increased mortality, as judged by the heart team. These patients were compared with a retrospectively defined cohort of patients with MR and indications for MV repair treated at the same institution in the 2 years prior to MitraClip availability who received conservative management (n=59) or open surgery (n=38). At baseline, patients treated with MitraClip had a higher logistic EuroSCORE (23.9 with MitraClip) than the other 2 groups (14.2 with surgical repair vs 18.7 with conservative treatment; $p < 0.001$). Rates of coronary artery disease and previous coronary artery bypass grafting were higher in the MitraClip group as well. At 1-year follow-up, survival rates were 85.8%, 82.2%, and 67.75% in the MitraClip, open surgery, and conservatively treated groups, respectively. Survival rates for the TMVR group were 75.5% and 62.3% after 2 and 3 years, respectively.

Single-Arm Studies

EVEREST High-Risk Registries

Concurrent with the EVEREST II RCT, described later in this review, investigators enrolled patients into the EVEREST II HRR study who were deemed ineligible for surgery due to prohibitively high surgical risks. In addition, a continued access study (EVEREST II REALISM), which included a high-risk and a non-high-risk arm, was conducted. For inclusion in the EVEREST II HRR, patients were considered high surgical risk if either their STS predicted operative mortality risk was 12% or higher or the surgeon investigator determined the patient to be high risk ($\geq 12\%$ predicted operative mortality risk) due to the presence of 1 of several prespecified risk factors. Patients were excluded from the registry if they had left ventricular ejection fraction (LVEF) less than 20%, left ventricular end-systolic diameter (LVESD) greater than 60 mm, MV orifice area less than 4 cm², or leaflet anatomy that might preclude MitraClip device implantation and/or proper MitraClip device positioning and/or sufficient reduction in MR. The REALISM registry high-risk arm had the same inclusion criteria as the EVEREST II HRR.

In 2014, Lim et al published outcomes from TMVR with MitraClip among high surgical risk patients with DMR who were included in the EVEREST II HRR and REALISM registries. For this analysis, prohibitive risk for surgical repair of DMR was defined as the presence of 1 or more of the following documented surgical risk factors: STS Risk Calculator predicted risk of 30-day mortality for MV replacement of 8% or greater, porcelain aorta or extensively calcified ascending aorta, frailty (assessed by ≥ 2 indices), hostile chest, severe liver disease or cirrhosis, severe pulmonary hypertension, severe pulmonary hypertension, or an "unusual extenuating circumstance" (eg, RV dysfunction with severe tricuspid regurgitation, chemotherapy for malignancy, major bleeding diathesis, AIDS, severe dementia). One hundred forty-one patients with

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severe ($\geq 3+$) DMR who met the definition of prohibitive surgical risk were identified, 127 of whom had follow-up data available at 1 year. Of these, 25 patients were from the EVEREST II HRR, 98 were from the high-risk arm of the EVEREST REALISM study, and 4 were treated under compassionate use and met the definition of prohibitive risk and all MV anatomic criteria for entry. At baseline, patients had poor functional status, with 87% in NYHA functional status class III or IV.

MitraClip was successfully placed in 95.3% of patients. Thirty-day and 12-month mortality rates were 6.3% and 23.6%, respectively. MitraClip reduced MR to grade 2+ or less in 86.1% of patients with baseline MR of 3+ and in 68.4% of patients with baseline MR of 4+. Fifty-eight percent of patients with grade 3+ MR at baseline and 36.8% of patients with grade 4+ MR at baseline had MR reduced to 1+. Of 91 patients who had procedural reduction of MR to grade 2+ or less, 64 (70.3%) patients had sustained MR grade 2+ or less at 1 year, 10 (11.0%) experienced worsening MR to grade 3+ or 4+, and 17 (18.7%) died. Of 59 patients who had a procedural reduction of MR to grade 1 or less, 21 (35.6%) patients had sustained MR of grade 1+ or less at 1 year, 20 (33.9%) had an increase in MR grade to 2+, 8 (13.6%) had an increase in MR grade to 3+ or 4+, and 10 (16.9%) died. There were no significant differences in 12-month survival between those discharged with an MR grade of 1+ or less compared to those with an MR grade of 2+. At 1 year, 30.6% of the 98 patients with baseline NYHA class III or IV had an improvement of at least 2 classes. In this high surgical risk population, MitraClip use was associated with a relatively low rate of procedural complications and a high rate of short-term improvements in MR grade to 2+ or less, along with improvements in functional status. However, a major limitation of this trial was the lack of a control group. In addition, the cohort of high-risk patients with DMR was retrospectively identified, so all analyses were post hoc. There are also questions about the validity of combining registry data from 2 separate registries that were collected over different time periods, along with the consistency of the inclusion criteria measures, because the STS Risk Calculator changed over time.

In 2014, Glower et al reported 12-month results for MitraClip use in the first 351 patients enrolled in the Everest HRR (n=78) or high-risk patients in the REALISM study (n=273), which had previously been presented to FDA. Seventy percent of patients had FMR. Following MitraClip implantation, 325 (86%) patients had MR reduced to 2+ or less. At 12 months, 225 (84%) patients had MR of grade 2+ or less. Using Kaplan-Meier analysis, survival at 12 months was 77.2%. Patients had improvements in quality of life scores and NYHA functional class.

In 2015, Velazquez et al published an industry-sponsored analysis comparing outcomes for patients from the Everest HRR and Everest REALISM registries who were matched with patients treated nonsurgically. The investigators used propensity-score matching to create groups with characteristics as similar as possible. In the optimal matched cohorts (239 high-risk MitraClip patients, 239 high-risk nonsurgical patients), baseline characteristics were similar for all but 3 variables: MR etiology, LV internal dimensions, and STS Risk Calculator score. Among patients in the optimally matched cohorts, Kaplan-Meier 1-year mortality estimates were significantly lower in the MitraClip group (22.4%) than in the nonsurgical control group (32.0%; adjusted hazard ratio [HR], 0.66; 95% CI, 0.45 to 0.99). Thirty-day mortality in the optimally

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matched cohorts was 4.2% in the MitraClip group and 7.2% in the nonsurgical group (HR and p values not reported).

Transcatheter Valve Therapy Registry

STS and American College of Cardiology's (ACC) Transcatheter Valve Therapy (TVT) registry includes patients who have had TMVR after initial FDA approval of MitraClip. Data on 564 patients, treated between November 2013 and August 2014 in the registry, were published by Sorajja et al in 2016. All patients had symptomatic primary MR and were at prohibitive surgical risk. All were treated at 1 of 61 hospitals, 42 of which had experience with the treatment prior to FDA approval. Postimplantation MR grade of 2 or less and no open heart surgery occurred in 514 (93.1%) of 526 patients. There were 13 (2.3%) in-hospital deaths and the 30-day mortality rate was 5.8% (26 deaths). Procedural success, defined as a reduction to MR grade 2 or less in the absence of cardiac surgery or in-hospital mortality, was 90.6%.

Section Summary: MitraClip in Prohibitive Surgical Risk Candidates

The evidence for the use of MitraClip among patients in patients with MR at prohibitive surgical risk consists primarily of single-arm cohort studies. The available single-arm studies include the pivotal EVEREST II HRR and EVEREST II REALISM trials. The trials have demonstrated that MitraClip implantation is feasible, with high rates (of at least 70% to 90%) of short-term reductions in MR grade of 2 or less and a reasonable safety profile. The TVT registry of patients treated in the United States after the MitraClip became commercially available had findings similar to the EVEREST trials. Moreover, an analysis matching patients in the EVEREST registries to similar nonsurgically treated patients found significantly lower 1-year mortality rates in MitraClip-treated patients.

MITRACLIP IN SURGICAL CANDIDATES

Systematic Reviews

A 2017 systematic review by Takagi et al identified 1 RCT and 6 nonrandomized comparative studies evaluating MitraClip and surgery. The RCT (EVEREST II) is described below. The systematic review conducted several pooled analyses. The meta-analysis did not detect a statistically significant difference in early (30-day or in-hospital) mortality between the MitraClip and surgery groups (pooled odds ratio [OR], 0.54; 95% CI, 0.27 to 1.08; p=0.08). Similarly, a pooled analysis of late survival (≥ 6 months) did not find a statistically significant difference between the MitraClip and surgery groups (pooled OR/HR, 1.17; 95% CI, 0.77 to 1.78; p=0.46). However, there was a significantly higher incidence of recurrent MR in the MitraClip than in the surgery group (pooled OR/HR, 4.80; 95% CI, 2.58 to 8.93; p<0.001).

Randomized Controlled Trials

One RCT evaluating use of MitraClip in surgical candidates has been published. The multicenter EVEREST II trial was designed to evaluate the efficacy of TMVR with MitraClip compared with open MV repair. Eligible patients had grade 3+ or 4+ MR and were all candidates for MV repair surgery. Symptomatic patients were required to have a LVEF of more than 25% and a LVESD of 55 mm or less; asymptomatic patients were required to have at least 1 of the following: LVEF between 25% and 60%; LVESD between 40 mm and 55 mm; new atrial fibrillation; or pulmonary hypertension. Patients were excluded if they had an MV orifice area

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less than 4.0 cm or leaflet anatomy that precluded MitraClip device implantation, proper MitraClip positioning, or sufficient reduction in MR. Two hundred seventy-nine patients were randomized 2:1 to transcatheter repair (184 patients) or standard MV surgery (95 patients).

The composite primary safety end point was major adverse events at 30 days, defined as freedom from death, myocardial infarction, nonelective cardiac surgery for adverse events, renal failure, transfusion of 2 or more units of blood, reoperation for failed surgery, stroke, gastrointestinal complications requiring surgery, ventilation for 48 or more hours, deep wound infection, septicemia, and new onset of permanent atrial fibrillation. The composite primary efficacy end point was freedom from MR at 2+ or higher, freedom from cardiac surgery for valve dysfunction, and survival beyond 12 months.

MitraClip was considered to have acute procedural success if the clip deployed and MR grade was reduced to less than 3+. The protocol's safety and efficacy analyses were reported on both an intention-to-treat (ITT) and a per-protocol basis. In the ITT analyses presented in the main article, crossover to surgery in the immediate postprocedure period if MitraClip failed to adequately reduce MR was considered a successful treatment strategy. Thus, in the ITT analysis, for patients who did not have acute procedural success (and may have undergone open MV repair), the efficacy end point was considered met for MitraClip group subjects if they were free from death, reoperation for MR, and MR grade greater than 2+ at 12 months.

For patients who did have acute procedural success, the efficacy end point was considered met for MitraClip group subjects if they were free from death, any MV surgery for MR, and MR greater than 2+ at 12 months. The trial had a predetermined efficacy end point of noninferiority of the MitraClip strategy, with a margin of 25% for the ITT analysis and 31% for prespecified per-protocol analyses. This implies that the MitraClip strategy would be noninferior to surgery at 12 months if the rate of the primary efficacy end point for the MitraClip group was not more than 25 percentage points less than that in the surgery group (for the ITT analysis).

Using ITT analysis, the study's primary combined efficacy end point (rates of freedom from death, MV surgery, and grade 3+/4+ MR at 12 months), was 55% in the MitraClip group and 73% in the surgery group (noninferiority, $p=0.007$). Rates of death and grade 3+ or 4+ MR at 12 months postprocedure were similar between groups; however, MitraClip group subjects were more likely to require surgery for MV dysfunction, either immediately post-MitraClip implantation or in the 12 months following. Twenty percent (37/181) of the MitraClip group and 2% (2/89) of the surgery group required reoperation for MV dysfunction ($p<0.001$). Although in the ITT analysis rates of grade 3+ or 4+ MR at 12 months were similar between groups, in the study's per-protocol analysis, patients in the MitraClip group were more likely to have grade 3+ or 4+ MR (17.2% [23/134] vs 4.1% [3/74], $p=0.01$), which suggests that a larger proportion of patients with grade 1+ or 2+ MR in the MitraClip group had had surgical repair.

Rates of major adverse events at 30 days were lower in the MitraClip group (15% [27/181]) than in the surgery group (48% [45/89]; $p<0.001$). Rates of transfusion of more than 2 units of blood were the largest

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component of major adverse events in both groups, occurring in 13% (24/181) of the MitraClip group and 45% (42/89, $p < 0.001$) of the surgery group.

In 2013, Mauri et al reported on 4-year follow-up results for patients enrolled in the EVEREST II trial. Of patients randomized to the percutaneous repair group, 161 (88%) were included in the 4-year efficacy analysis; of those in the surgery group, 73 (77%) were included in the 4-year efficacy analysis. At 4 years, 39.8% (64/161) of those in the MitraClip group achieved the primary efficacy end point of freedom from death, freedom from surgery for MV dysfunction, and freedom from grade 3+ or 4+ MR, compared with 53.4% (39/73) of the surgical group ($p = 0.070$). However, significantly more MitraClip patients required surgery for MV dysfunction during the follow-up period (24.85% [40/161] in the MitraClip group vs 5.5% [4/73] in the surgical group, $p < 0.001$); in the MitraClip group, most of the MV surgery occurred before 12 months.

Five-year results of EVEREST II were reported by Feldman et al in 2015. This analysis included patients who completed the 5-year follow-up visit and had data on their MR grade, or who had died or had MV surgery before withdrawing from the trial. As with the 4-year analysis (described above), significantly more patients in the MitraClip group had MV surgery or reoperation during the follow-up period (27.9%) compared to the surgical group (8.9%; $p = 0.003$). In addition, significantly more patients in the MitraClip group had grade 3+ or 4+ MR (12.3%) compared with the surgical group (1.8%; $p = 0.02$). The primary outcome was a composite of freedom from death, freedom from surgery for MV dysfunction, and freedom from grade 3+ or 4+ MR. The rate of this composite outcome was 44.2% (68/154) in the MitraClip group and 64.3% (36/56) in the surgical group ($p = 0.01$). The mortality rate did not differ significantly between groups (20.8% in the MitraClip group vs 26.8% in the surgical group; $p = 0.36$). As noted in previous analyses of EVEREST II data, most of the additional surgeries in the MitraClip group occurred early, in the first 6 to 12 months postprocedure. Among patients who were event-free at 1 year, there was no significant difference in the composite outcome at 5 years: 69% (60/87) in the MitraClip group and 75% (36/48) in the surgical group ($p = 0.55$).

Nonrandomized Comparative Studies

Several nonrandomized cohort studies have compared outcomes for MR treated with surgical or with TMVR using the MitraClip device. Two studies (Conradi et al [2013], Taramasso et al [2012]) included patients only with FMR, while Paranskaya et al (2013, 2017) reported results for a mixed DMR and FMR cohort.

In 2016, De Bonis et al published a study designed to verify whether findings from the EVEREST II trial that, for patients with an initially positive response to MitraClip, were sustained at long-term follow-up and were similar to surgery. The study included 85 patients with FMR and an initially good result after MitraClip implantation (ie, MR grade ≤ 1 at hospital discharge). Findings were compared with 58 consecutive surgical patients, treated before MitraClip was an option, who also had a MR grade of 1 or less at discharge. Patients were followed prospectively and data entered into a dedicated database. Patients in the 2 groups were comparable at baseline on most variables (eg, NYHA functional class, proportion with atrial fibrillation, LV dimensions); however, age and logistic EuroSCORE were significantly higher in the MitraClip group.

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At 1 year, echocardiographic prevalence of MR grade of 2 or more was 32.5% in the MitraClip group ($p < 0.001$ within group vs hospital discharge). In addition, among patients in the MitraClip group ($n=53$) with MR grade of 1 or less at 12 months, 8 (19%) of 42 with follow-up data had MR progression at least 1 grade at 2 years and 9 (33%) of 27 with follow-up data had MR grade 2 or more at 3 years. Compared with the surgery group, the 4-year freedom from grade 3+ MR (94% vs 75%) and freedom from grade 2+ MR (82% vs 37%) were significantly higher in the surgery group. Overall survival at 4 years was similar between groups (74% in MitraClip patients vs 77% in surgical patients). This analysis was limited by missing data and lack of randomization. However, it does suggest that, at least in this group of MitraClip patients, an initially successful outcome did not prevent progression of MR over time and that surgery may have greater long-term efficacy for MR control.

Section Summary: MitraClip in Surgical Candidates

The evidence for the use of MitraClip in patients who are considered candidates for open MV repair surgery includes 1 RCT (EVEREST II), a systematic review, and several comparative and noncomparative cohort studies. The RCT found that MitraClip was noninferior to open surgery in terms of safety and effectiveness at 1-year follow-up. At the 5-year follow-up, efficacy as assessed by a composite outcome, was significantly higher in the surgery group than in the MitraClip group. In EVEREST II, most patients who had persistent MV dysfunction after MitraClip developed it within the first year postprocedure and, among patients event-free at 1 year, 5-year efficacy did not differ significantly between the MitraClip and the surgery groups. EVEREST II had some methodologic limitations. The noninferiority margin of 25% was large, indicating that MitraClip could be somewhat inferior to surgery and the noninferiority margin still met. Crossover to surgery was allowed for patients who had a MR grade 3+ or higher prior to discharge, and 23% of patients assigned to MitraClip met this criterion. This large rate of crossover would bias results toward the null on ITT analysis, thus increasing the likelihood of meeting the noninferiority margin. In an analysis by treatment received, this crossover would result in a less severely ill population in the MitraClip group and bias the results in favor of MitraClip. A high proportion of patients required open MV replacement or repair during the first year postprocedure, thus limiting the number of patients who had long-term success without surgical intervention. As a result of these factors, this single trial is not definitive in demonstrating improved clinical outcomes with MitraClip compared to surgery. Further RCTs are needed to corroborate these results. A subsequent nonrandomized controlled trial that attempted to verify the findings of EVEREST II did not find the same low rates of long-term MR control in MitraClip patients with an initially positive response to treatment.

OTHER TRANSCATHETER MV REPAIR DEVICES

Several devices other than MitraClip are being investigated for TMVR, although none is FDA approved for use in the United States.

Several indirect annuloplasty devices, the Carillon Mitral Contour System (Cardiac Dimension, Kirkland, WA) and the Monarc device (Edwards Lifesciences, Irvine, CA), have been evaluated. A case series evaluating use of the Carillon device in 53 patients with grade 2+ FMR at 7 European centers was reported in 2012. Of the 53 patients who underwent attempted device implantation, 36 underwent permanent

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implantation and 17 had the device recaptured due to transient coronary compromise in 8 patients and less than 1 grade of FMR reduction in 9 patients. Echocardiographic measures of FMR improved in the implanted groups up through 12-month follow-up, along with improvements in 6-minute walk distance. An earlier feasibility study of the Carillon device in 48 patients with moderate-to-severe FMR demonstrated successful device placement in 30 patients, with 18 patients unable to be implanted due to access issues, insufficient acute FMR reduction, or coronary artery compromise. The Monarc device has been evaluated in a phase 1 safety trial at 8 European centers. Among 72 patients enrolled, the device was successfully implanted in 59 (82%) patients. The primary safety end point (freedom from death, tamponade, or myocardial infarction at 30 days) was met in 91% of patients at 30 days and in 82% at 1 year.

Section Summary: Other Transcatheter MV Repair Devices

The evidence for the use of TMVR devices other than the MitraClip for patients with MR includes only small case series and case reports. They are insufficient to determine the effects of these technologies on health outcomes.

SUMMARY OF EVIDENCE

For individuals who have symptomatic DMR or FMR and are at prohibitive risk for open surgery who receive TMVR using MitraClip, the evidence includes primarily single-arm cohort studies. Relevant outcomes are overall survival, morbid events, functional outcomes, and treatment-related morbidity. Several single-arm studies have demonstrated that MitraClip implantation is feasible, with high rates (at least 70% to 90%) of short-term reductions in MR grade to 2+ or less, and a reasonable safety profile. A nonrandomized analysis matching patients in the EVEREST registries to similar non-surgically-treated patients found significantly lower 1-year mortality rates in MitraClip-treated patients. However, the lack of concurrent control groups, especially in randomized trials, makes it difficult to draw conclusions on whether there is a net health benefit compared with alternative therapies in this population. There are no strong barriers to conducting controlled trials, including RCTs comparing MitraClip to continued medical management. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals who have symptomatic DMR or FMR and are surgical candidates who receive TMVR using MitraClip, the evidence includes a systematic review, an RCT, and several comparative and noncomparative cohort studies. Relevant outcomes are overall survival, morbid events, functional outcomes, and treatment-related morbidity. The RCT found that MitraClip was noninferior to open surgery in terms of safety and effectiveness at 1-year follow-up. At 5-year follow-up, efficacy, assessed using a composite outcome, was significantly higher in the surgery group than in the MitraClip group. The RCT had some methodologic limitations, including a wide noninferiority margin and permissibility of crossing over to surgery and still considered to have a positive outcome. This single trial does not definitively demonstrate improved clinical outcomes with MitraClip compared with surgery. Additional Other RCTs are needed to corroborate these results. A subsequent nonrandomized controlled trial, which attempted to verify the findings of the RCT, did not find the same low rates of long-term MR control in MitraClip patients with an initially positive response to treatment. The evidence is insufficient to determine the effects of the technology on health outcomes.

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For individuals who have DMR or FMR who receive TMVR using devices other than MitraClip, the evidence includes primarily noncomparative feasibility studies. Relevant outcomes are overall survival, morbidity events, functional outcomes, and treatment-related morbidity. The body of evidence consists only of very small case series and case reports. Controlled studies, preferably RCTs, are needed to draw conclusions about the net health benefit. The evidence is insufficient to determine the effects of the technology on health outcomes.

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02/04/2016 Medical Policy Committee review

02/17/2016 Medical Policy Implementation Committee approval. New Policy

01/01/2017 Coding update: Removing ICD-9 Diagnosis Codes

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02/02/2017 Medical Policy Committee review
 02/15/2017 Medical Policy Implementation Committee approval. No change to coverage.
 02/01/2018 Medical Policy Committee review
 02/21/2018 Medical Policy Implementation Committee approval. No change to coverage.
 Next Scheduled Review Date: 02/2019

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Code Type	Code
CPT	0345T, 33418, 33419, 93590, 93592 New codes eff 1/1/18: 0483T, 0484T
HCPCS	No codes
ICD-10 Diagnosis	All related diagnoses

*Investigational – A medical treatment, procedure, drug, device, or biological product is Investigational if the effectiveness has not been clearly tested and it has not been incorporated into standard medical practice. Any determination we make that a medical treatment, procedure, drug, device, or biological product is Investigational will be based on a consideration of the following:

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- B. Whether the medical treatment, procedure, drug, device, or biological product requires further studies or clinical trials to determine its maximum tolerated dose, toxicity, safety, effectiveness, or effectiveness as compared with the standard means of treatment or diagnosis, must improve health outcomes, according to the consensus of opinion among experts as shown by reliable evidence, including:
 1. Consultation with the Blue Cross and Blue Shield Association TEC or other nonaffiliated technology evaluation center(s);

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2. Credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community; or
3. Reference to federal regulations.

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- A. In accordance with nationally accepted standards of medical practice;
- B. Clinically appropriate, in terms of type, frequency, extent, level of care, site and duration, and considered effective for the patient's illness, injury or disease; and
- C. Not primarily for the personal comfort or convenience of the patient, physician or other health care provider, and not more costly than an alternative service or sequence of services at least as likely to produce equivalent therapeutic or diagnostic results as to the diagnosis or treatment of that patient's illness, injury or disease.

For these purposes, "nationally accepted standards of medical practice" means standards that are based on credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community, Physician Specialty Society recommendations and the views of Physicians practicing in relevant clinical areas and any other relevant factors.

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