Total Artificial Hearts and Implantable Ventricular Assist Devices

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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 Are 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.*

Bridge to Transplantation
Based on review of available data, the Company may consider implantable ventricular assist devices (VADs) with U.S. Food and Drug Administration (FDA) approval or clearance as a bridge to heart transplantation for patients who are currently listed as heart transplantation candidates and not expected to survive until a donor heart can be obtained, or are undergoing evaluation to determine candidacy for heart transplantation to be **eligible for coverage.**

Based on review of available data, the Company may consider implantable ventricular assist devices (VADs) with U.S. Food and Drug Administration (FDA) approval or clearance, including humanitarian device exemptions, as a bridge to heart transplantation in children 16 years old or younger who are currently listed as heart transplantation candidates and not expected to survive until a donor heart can be obtained, or are undergoing evaluation to determine candidacy for heart transplantation to be **eligible for coverage.**

Based on review of available data, the Company may consider total artificial hearts (TAHs) with U.S. Food and Drug Administration (FDA)-approved devices as a bridge to heart transplantation for patients with biventricular failure who have no other reasonable medical or surgical treatment options, who are ineligible for other univentricular or biventricular support devices, and are currently listed as heart transplantation candidates or are undergoing evaluation to determine candidacy for heart transplantation, and not expected to survive until a donor heart can be obtained to be **eligible for coverage.**

Destination Therapy
Based on review of available data, the Company may consider implantable ventricular assist devices (VADs) with U.S. Food and Drug Administration (FDA) approval or clearance as destination therapy with end-stage heart failure patients who are ineligible for human heart transplant and who meet the following "REMATCH Study" criteria to be **eligible for coverage**.

Patient Selection Criteria
Coverage eligibility will be considered when the following criteria are met:

- New York Heart Association (NYHA) class IV heart failure for ≥ 60 days, or patients in NYHA class III/IV for 28 days, received ≥ 14 days' support with intra-aortic balloon pump (IABP) or dependent on IV inotropic agents, with two failed weaning attempts.

In addition, patients must not be candidates for human heart transplant for one or more of the following reasons:

- Age > 65 years; or
- Insulin-dependent diabetes mellitus with end-organ damage; or
- Chronic renal failure (serum creatinine > 2.5 mg/dL for ≥ 90 days; or
- Presence of other clinically significant condition

Post-cardiotomy Setting/Bridge to Recovery
Based on review of available data, the Company may consider implantable ventricular assist devices (VADs) with U.S. Food and Drug Administration (FDA) approval or clearance in the postcardiotomy setting in patients who are unable to be weaned off cardiopulmonary bypass to be **eligible for coverage.**

When Services Are Considered Investigational
Coverage is not available for investigational medical treatments or procedures, drugs, devices or biological products.

Other Indications
Based on review of available data, the Company considers other applications of implantable ventricular devices or total artificial hearts (TAHs) including, but not limited to, the use of total artificial hearts (TAHs) as destination therapy. The use of non-U.S. Food and Drug Administration (non-FDA) approved or cleared implantable ventricular assist devices (VADs) or total artificial hearts (TAHs) is considered to be **investigational.***

Based on review of available data, the Company considers percutaneous ventricular assist devices (pVADs) for all indications to be **investigational.***

Policy Guidelines

Only 2 VADs have approval from the U.S. FDA for the pediatric population. The DeBakey VAD Child device and the Berlin Heart EXCOR Pediatric VAD have FDA approval through the humanitarian device exemption process. The DeBakey VAD is indicated for use in children ages 5 to 16 years who are awaiting a heart transplant (ie, a bridge to transplant) while the Berlin Heart EXCOR VAD is indicated for children with severe isolated left ventricular or biventricular dysfunction who are candidates for cardiac transplant and require circulatory support.

In general, candidates for bridge to transplant implantable VADs are those who are considered appropriate heart transplant candidates but who are unlikely to survive the waiting period until a human heart donor is available. Some studies have included the following hemodynamic selection criteria: either a left atrial

pressure of 20 mm Hg or a cardiac index of less than 2.0 L/min/m while receiving maximal medical support. Patients with VADs are classified by the United Network for Organ Sharing as status I (ie, persons who are most ill and are considered the highest priority for transplant).

The median duration for time on the device is between 20 days and 120 days.

Contraindications for bridge to transplant VADs and total artificial hearts include conditions that would generally exclude patients for heart transplant. Such conditions are chronic irreversible hepatic, renal, or respiratory failure; systemic infection; coagulation disorders, and inadequate psychosocial support. Due to potential problems with adequate function of the VAD or total artificial heart, implantation is also contraindicated in patients with uncorrected valvular disease.

In addition, patients must have sufficient space in the thorax and/or abdominal cavity for the device. In the case of the CardioWest Temporary Total Artificial Heart, this excludes patients with body surface areas less than 1.7 m^2 or who have a distance between the sternum and 10th anterior rib of less than 10 cm, as measured by computed tomography scan.

Background/Overview

HEART FAILURE

Heart failure may be the consequence of a number of differing etiologies, including ischemic heart disease, cardiomyopathy, congenital heart defects, or rejection of a heart transplant. The reduction of cardiac output is considered to be severe when systemic circulation cannot meet the body's needs under minimal exertion. Heart transplantation improves quality of life and has survival rates at 1, 5, and 10 years of 88%, 74%, and 55%, respectively. The supply of donor organs has leveled off, while candidates for transplants are increasing, compelling the development of mechanical devices.

Treatment

Ventricular Assist Devices

Implantable VADs are attached to the native heart, which may have enough residual capacity to withstand a device failure in the short term. In reversible heart failure conditions, the native heart may regain some function, and weaning and explanting of the mechanical support system after months of use has been described. VADs can be classified as internal or external, electrically or pneumatically powered, and pulsatile or continuous-flow. Initial devices were pulsatile, mimicking the action of a beating heart. More recent devices may use a pump, which provides continuous flow. Continuous devices may move blood in a rotary or axial flow.

At least 1 VAD system developed is miniaturized and generates an artificial pulse, the HeartMate 3 Left Ventricular Assist System.

Surgically implanted VADs represent a method of providing mechanical circulatory support for patients not expected to survive until a donor heart becomes available for transplant or for whom transplantation is contraindicated or unavailable. VADs are most commonly used to support the left ventricle, but right ventricular and biventricular devices may be used. The device is larger than most native hearts, and therefore the size of the patient is an important consideration; the pump may be implanted in the thorax or abdomen or remain external to the body. Inflow to the device is attached to the apex of the failed ventricle, while outflow is attached to the corresponding great artery (aorta for the left ventricle, a pulmonary artery for the right ventricle). A small portion of the ventricular wall is removed for insertion of the outflow tube; extensive cardiotomy affecting the ventricular wall may preclude VAD use.

Total Artificial Hearts

Initial research into mechanical assistance for the heart focused on the TAH, a biventricular device that completely replaces the function of the diseased heart. An internal battery required frequent recharging from an external power source. Many systems use a percutaneous power line, but a transcutaneous power-transfer coil allows for a system without lines traversing the skin, possibly reducing the risk of infection. Because the native heart must be removed, failure of the device is synonymous with cardiac death.

A fully bioprosthetic TAH, which is fully implanted in the pericardial sac and is electrohydraulically actuated, has been developed and tested in 2 patients but is currently experimental.

Percutaneous VADs

Devices in which most of the system's components are external to the body are for short-term use (6 hours to 14 days) only, due to the increased risk of infection and need for careful, in-hospital monitoring. Some circulatory assist devices are placed percutaneously (ie, are not implanted). They may be referred to as percutaneous VADs (pVADs). A pVAD is placed through the femoral artery. Two different pVADs have been developed, the TandemHeart and the Impella device. In the TandemHeart System, a catheter is introduced through the femoral vein and passed into the left atrium via transseptal puncture. Oxygenated blood is then pumped from the left atrium into the arterial system via the femoral artery. The Impella device is introduced through a femoral artery catheter. In this device, a small pump is contained within the catheter placed into the left ventricle. Blood is pumped from the left ventricle, through the device, and into the ascending aorta. Adverse events associated with pVAD include access site complications such as bleeding, aneurysms, or leg ischemia. Cardiovascular complications can also occur, such as perforation, myocardial infarction, stroke, and arrhythmias.

FDA or Other Governmental Regulatory Approval

A number of mechanical circulatory support devices have been approved or cleared for marketing by the U.S. FDA. These devices are summarized in Tables 1 and 2 and discussed in the following sections.

Table 1. Available Mechanical Circulatory Support Devices

Device	Manufacturer	Approval Date	FDA Clearance	PMA, HDE, or	Indication

				510(k) No.	
Thoratec® IVAD	Thoratec	Aug 2004	PMA Supp	P870072	Bridge to transplant and postcardiotomy
DeBakey VAD® Child	MicroMed	Feb 2004	HDE	H030003	Bridge to transplant in children 5-16 y
HeartMate II®	Thoratec	Apr 2008	PMA	P060040	Bridge to transplant and destination
CentriMag®	Levitronix (now Thoratec)	Oct 2008	HDE	H070004	Postcardiotomy
Berlin Heart EXCOR® Pediatric VAD	Berlin	Dec 2011	HDE	H100004	Bridge to transplant
HeartWare® Ventricular Assist System	HeartWare	Dec 2012	PMA	P100047	Bridge to transplant
HeartMate 3™ Left Ventricular Assist System	Thoratec	Aug 2017	PMA	P160054	Bridge to transplant and destination

FDA: U.S. Food and Drug Administration; HDE: humanitarian device exemption; PMA: premarket approval.

Ventricular Assist Devices

In 1995, the Thoratec®‡ Ventricular Assist Device System (Thoratec Corp.) was approved by FDA through the premarket approval process as a bridge to transplantation in patients suffering from end-stage heart failure. The patient should meet all of the following criteria:

- candidate for cardiac transplantation,
- imminent risk of dying before donor heart procurement, and
- dependence on, or incomplete response to, continuous vasopressor support.

In 1998, supplemental approval for this device was given for the indication of postcardiotomy patients unable to be weaned from cardiopulmonary bypass. In June 2001, supplemental approval was given for a portable external driver to permit excursions within a 2-hour travel radius of the hospital when accompanied by a trained caregiver. In 2003, supplemental approval was given to market the device as Thoratec®‡ Paracorporeal VAD. In 2004, supplemental approval was given to a modified device to be marketed as the Thoratec®‡ Implantable VAD for the same indications. In 2008, supplemental approval was given to rescind Paracorporeal VAD use.

In August 2016, HeartWare®‡ recalled its VAD Pumps due to a design flaw that was deemed by FDA as potentially causing serious injuries or death (class I recall). The devices affected were manufactured and distributed from March 2006 and May 2018. FDA product codes 204 and 017.

A class I recall was issued for the HeartMate 3™‡ in April 2018 affecting all manufacturing dates. FDA product code: DSQ.

Total Artificial Heart

In 2004, the temporary CardioWest™‡ Total Artificial Heart (SynCardia Systems) was approved by FDA through the premarket approval process for use as a bridge to transplant in cardiac transplant-eligible candidates at risk of imminent death from biventricular failure. This device is also intended for use inside the hospital. In 2010, FDA approved a name change to SynCardia Temporary Total Artificial Heart. FDA product code: LOZ.

In 2006, the AbioCor®‡ Implantable Replacement Heart System (Abiomed) was approved by FDA through the humanitarian device exemption (H040006) process in severe biventricular end-stage heart disease patients who are not cardiac transplant candidates and who:

- are younger than 75 years of age;
- require multiple inotropic support;
- are not treatable by left VAD destination therapy; and
- are not weanable from biventricular support if on such support.

In addition to meeting other criteria, patients who are candidates for the AbioCor®‡ TAH must undergo a screening process to determine if their chest volume is large enough to hold the device. The device is too large for approximately 90% of women and for many men.

Percutaneous VADs (Circulatory Assist Devices)

Table 2. Available Mechanical Circulatory Support Devices

Device	Manufacturer	Approval Date	FDA Clearance	PMA, 510(k) No.	Indication
TandemHeart®	Cardiac Assist	Sep 2005	510(k)	K110493	Temporary left ventricular bypass of ≤6 h
Impella® Recover LP 2.5	Abiomed	May 2008	510(k)	K063723	Partial circulatory support using extracorporeal bypass control unit for ≤6 h
Impella 2.5 System	Abiomed	Mar 2015	PMA	P140003	Temporary ventricular support for ≤6 h

FDA: U.S. Food and Drug Administration; PMA: premarket approval.

Comparative Efficacy of Left VAD Devices

The mechanism of operation of left VADs has changed since their introduction. The earliest devices were pulsatile positive displacement pumps. These pumps have been largely replaced by axial continuous-flow pumps. More recently centrifugal continuous-flow pumps have also been introduced.

The evidence of the comparative efficacy of centrifugal continuous-flow vs axial continuous-flow devices consists of 2 randomized controlled trials of 2 different centrifugal continuous-flow devices. The MOMENTUM 3 trial compared HeartMate 3 centrifugal continuous-flow device with the HeartMate II axial continuous-flow device in patients indicated for circulatory support as a bridge to transplant or destination

therapy. HeartMate 3 received PMA approval in August 2017 but was recalled in April 2018. The ENDURANCE trial compared HeartWare centrifugal continuous-flow device with the HeartMate II axial continuous-flow device in patients indicated for circulatory support as destination therapy. HeartWare is FDA-approved as a bridge to transplantation device. Both trials found the centrifugal device to be noninferior to the axial device for the primary, composite outcome including measures of survival, freedom from disabling stroke, and freedom from device failure. While there are fewer device failures with the centrifugal devices without a significant increase in disabling stroke, the HeartWare device was associated with increased risk of any stroke over a period of 2 years.

The evidence on the comparative efficacy of continuous-flow vs pulsatile-flow devices consists of a randomized controlled trial and several nonrandomized comparative studies. The randomized controlled trial reported fairly large differences in a composite outcome measure favoring the continuous-flow devices, with increases in revision and reoperation rates for the pulsatile device group being the largest factor driving the difference in outcomes. Other nonrandomized comparative studies, including a database study with large numbers of patients, have not reported important differences in clinical outcomes between devices.

Centers for Medicare and Medicaid Services (CMS)
Medicare has a national coverage determination (NCD) for artificial hearts and related devices, including VADs. The NCD, mandates coverage for VADs in the *postcardiotomy setting* as long as the following conditions are met:

- The VAD has “approval from the FDA” for post-cardiotomy support.
- The VAD is “used according to the FDA-approved labeling instructions.”

The NCD also mandates coverage for VADs as a *bridge to transplant* as long as the following conditions are met:

- The VAD has approval from FDA for the bridge to transplant indication.
- The VAD is “used according to the FDA-approved labeling instructions.”
- “The patient is approved for heart transplantation by a Medicare-approved heart transplant center….”
- “The implanting site, if different than the Medicare-approved transplant center, must receive written permission from the Medicare-approved heart transplant center under which the patient is listed prior to implantation of the VAD.”

The NCD mandates coverage for VADs as *destination therapy* as long as the following conditions are met:

- The VAD has approval from FDA for the destination therapy indication.
- Patient selection:
    - New York Heart Association class IV end-stage left ventricular failure
    - Not candidates for heart transplantation
    - Failed to respond to optimal medical management,
    - Left ventricular ejection fraction <25%, and,
    - Demonstrated functional limitation.

> "Beneficiaries receiving VADs for DT [destination therapy] must be managed by an explicitly identified cohesive, multidisciplinary team of medical professionals with the appropriate qualifications, training, and experience.... The team members must be based at the facility and must include individuals with experience working with patients before and after placement of a VAD."
>
> "Facilities must be credentialed by an organization approved by the Centers for Medicare & Medicaid Services."

The NCD mandates coverage for artificial hearts as a *bridge to transplant* or *destination therapy* when performed under coverage with evidence development when a clinical study meets the criteria outlined in the Medicare policy.

Rationale/Source

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

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

This literature review assesses 3 devices: (1) VADs, (2) TAHs, and (3) pVADs. This review addresses the short-term use of the devices as a bridge to recovery or transplantation. Left VADs (LVADs) and TAHs are also evaluated as longer term destination therapies for patients who are not transplant candidates.

VENTRICULAR ASSIST DEVICES AS A BRIDGE TO HEART TRANSPLANT FOR END-STAGE HEART FAILURE

Clinical Context and Therapy Purpose
The purpose of VADs as a bridge to heart transplant in patients who have end-stage heart failure is to provide a treatment option that is an alternative to or an improvement on existing therapies.

The question addressed in this evidence review is: Does the use of a VAD as a bridge to heart transplant improve the net health outcome in individuals with end-stage heart failure?

The following PICOTS were used to select literature to inform this review.

Patients
The relevant population of interest is individuals with end-stage heart failure. A subset of patients who receive a VAD as a bridge to transplantation have demonstrated improvements in their cardiac function, sometimes to the point that they no longer require the VAD. This results in the use of VAD as a bridge to recovery.

Interventions
The therapy being considered is a VAD as a bridge to heart transplant.

Comparators
The following therapy is currently being used to make decisions about individuals with end-stage heart failure: optimal medical therapy without VADs.

Outcomes
The general outcomes of interest are overall survival, device malfunction, heart failure, respiratory dysfunction, arrhythmias, and infection.

Timing
Time-to-transplant is of interest, as is the short-term outcome ranging from 30 days to 1 year.

Setting
Implantation of a VAD is performed in a hospital setting with specialized staff who are equipped to perform the surgical procedure and manage postsurgical intensive care.

VADs as Bridge to Recovery

Prospective Studies
VADs may have a role in bridging patients to recovery, particularly if there is reverse remodeling of the left ventricle. Several studies have investigated the role of VADs in bridging patients to decision for transplant eligibility. One clearly defined population in which the potential for myocardial recovery exists is in the postcardiotomy setting.

Acharya et al (2016) reported on patients who underwent VAD placement for acute myocardial infarction (AMI) who were enrolled in the Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS) registry, a prospective national registry of FDA–approved durable mechanical circulatory support (MCS) devices. Patients who had an AMI as the admitting diagnosis or a major myocardial infarction (MI) as a hospital complication that resulted in VAD implantation (n=502) were compared with patients who underwent VAD implantation for non-AMI indications (n=9727). Patients in the AMI group were generally sicker at baseline, with higher rates of smoking, severe diabetes, and peripheral vascular disease, but had fewer cardiac surgeries and recent cardiovascular hospitalizations. Most AMI patients (53.8%) were implanted with a "bridge to candidacy" strategy. At 1 month post-VAD, 91.8% of the AMI group were alive with the device in place. At 1 year post-VAD, 52% of the AMI group were alive with the device in place, 25.7% had received a transplant, 1.6% had their VAD explanted for recovery, and 20.7% died with the device in place.

Two additional 2016 publications from the INTERMACS registry reported on cardiac recovery in patients implanted with LVADs. Wever-Pinzon et al (2016) included adults registered between March 2006 and June 2015 excluding those who had a right VAD only, TAH, or prior heart transplant (n=15,631). One hundred twenty-five of these patients had an a priori bridge to recovery LVAD strategy. Cardiac recovery occurred in 192 (1.3%) of the LVAD patients overall and in 14 (11.2%) of the bridge to recovery patients. Topkara et al (2016) reported a similar analysis of 13,454 INTERMACS adults with implants between June 2006 and June 2015 without TAH or pulsatile-flow LVAD or heart transplant. Device explant rates for cardiac recovery were 0.9% at 1-year, 1.9% at 2-year, and 3.1% at 3-year follow-up. An additional 9% of patients demonstrated partial cardiac recovery.

In a prospective multicenter study to assess myocardial recovery in patients with LVAD implantation as a bridge to transplant, Maybaum et al (2007) evaluated 67 patients with heart failure who had LVAD implantation for severe heart failure. After 30 days, patients demonstrated significant improvements compared with their pre-LVAD state in left ventricular ejection fraction (17.1% vs 34.12%, $p<0.001$), left ventricular end-diastolic diameter (7.1 cm vs 5.1 cm, $p<0.001$), and left ventricular mass (320 g vs 194 g, $p<0.001$), respectively. However, only 9% of patients recovered sufficiently to have their LVAD explanted.

Retrospective Studies

Agrawal et al (2018) conducted a retrospective cohort study evaluating the 30-day readmissions of 2510 patients undergoing LVAD implantation. Of the patients who met the inclusion criteria, 788 (31%) were readmitted within 30 days after surviving initial index hospitalization. Cardiac causes accounted for 23.8% of readmissions, 13.4% due to heart failure, and 8.1% to arrhythmias. Infection (30.2%), bleeding (17.6%), and device-related causes (8.2%) comprised the 76.2% of noncardiovascular causes for readmission.

Takayama et al (2014) reported outcomes for a retrospectively defined cohort of 143 patients who received a CentriMag Right Ventricular Assist Device as a "bridge to decision" for refractory cardiogenic shock due to a variety of causes. Patients were managed with a bridge to decision algorithm. Causes of cardiogenic shock included failure of medical management (n=71), postcardiotomy shock (n=37), graft failure after heart

transplantation (n=2), and right ventricular failure postimplantable LVAD (n=13). The device configuration was biventricular in 67%, isolated right VAD in 26%, and isolated LVAD in 8%. After a mean duration of support of 14 days (interquartile range, 8-26 days), 30% of patients had myocardial recovery, 15% had device exchange to an implantable VAD, and 18% had a heart transplant.

VADs as Bridge to Heart Transplant
The insertion of a VAD will categorize its recipient as a high-priority heart transplant candidate. The available evidence on the efficacy of VADs in bridging patients with refractory heart failure to transplant includes single-arm series, which generally have reported high success rates in bridging to transplant.

Adult Patients
Systematic Reviews
Several older systematic reviews have that VADs can provide an effective bridge to transplantation.

Prospective Studies
Slaughter et al (2013) reported combined outcomes for patients included in the HeartWare bridge to transplant study previously described and a continued-access protocol granted by the FDA. The study included 322 patients with heart failure, eligible for heart transplant, who received the HeartWare (140 patients from the original study; 190 patients in the continue-access protocol who were monitored to the outcome or had completed 180-day follow-up at the time of analysis). Survival rates at 60, 180, and 360 days were 97%, 91%, and 84%, respectively. The most common adverse events were respiratory dysfunction, arrhythmias, sepsis, and driveline exit-site infections. Patients generally had improvements in quality of life measures.

Case Series
Strueber et al (2011) published a case series of 50 patients awaiting heart transplantation treated with HeartWare Ventricular Assist System, which is a smaller, continuous-flow centrifugal device implanted in the pericardial space. Patients were followed until transplantation, myocardial recovery, device explant, or death. The median duration of time on the VAD was 322 days. Nine patients died: 3 from sepsis, 3 from multiple organ failure, and 3 from hemorrhagic stroke. At the end of follow-up, 20 (40%) patients had undergone transplant, 4 (8%) had had the pump explanted, and the remaining 17 (34%) continued on pump support. The most common complications were infection and bleeding: 21 (42%) patients had infections, 5 (10%) had sepsis, while 15 (30%) patients had bleeding complications, 10 (20%) of whom required surgery.

Aaronson et al (2012) reported on results of a multicenter, prospective study of a newer generation LVAD, the HeartWare. The study enrolled 140 patients awaiting heart transplantation who underwent HeartWare implantation. A control group of 499 subjects comprised patients drawn from the INTERMACS database, which collects data on patients who receive FDA-approved durable MCS devices. The study's primary outcome was defined as survival on the originally implanted device, transplantation, or explantation for ventricular recovery at 180 days. Secondary outcomes were comparisons of survival between groups and functional, quality of life (QOL), and adverse event outcomes in the HeartWare group. Success on the

primary outcome occurred in 90.7% of the HeartWare group and 90.1% of controls (p<0.001, noninferiority with a 15% margin). Serious adverse events in the HeartWare group included, most commonly, bleeding, infections, and perioperative right heart failure.

In 5 reports published from 2007 to 2008, with sample sizes ranging from 32 to 279 patients, most participants received the continuous-flow device as a bridge to transplantation. Survival rates at 6 months ranged between 67% and 87%, and between 50% and 80% at 1 year. These rates were similar to those reported from the INTERMACS registry. A study by Patel et al (2008) compared HeartMate I with HeartMate II recipients at a single center, finding similar rates of 1-year survival and subsequent development of right heart failure. Serious adverse events occurring after HeartMate II implantation include bleeding episodes requiring reoperation, stroke, infection, and device failure.

Aissaoui et al (2018) published an observational study comparing 224 patients in Germany and France with end-stage heart failure who received VAD (group I, n=83) or heart transplantation or medical therapy as first treatment options (group II, n=141). The estimated 2-year survival was 44% for group I and 70% for group II (p<0.001).

Pediatric Patients
The FDA-approved EXCOR Pediatric VAD is available for use as a bridge to cardiac transplant in children. FDA approval was based on data from children who were part of the initial clinical studies of this device. Publications have reported positive outcomes for children using VADs as a bridge to transplantation.

Registry Studies
Bulic et al (2017) identified all U.S. children between 1 and 21 years of age at heart transplant between 2006 and 2015 who had dilated cardiomyopathy and were supported with an LVAD or vasoactive infusions alone at the time of transplant from the Organ Procurement and Transplant Network registry (n=701). Functional status as measured by the median Karnofsky Performance Scale score at heart transplant was higher for children receiving LVAD (6) compared with vasoactive infusion (5; p<0.001) and children receiving LVAD were more likely to be discharged from the hospital at the time of transplant. The percentage of children having a stroke at the time of transplant was higher in those receiving LVAD (3% vs 1%, p=0.04).

Wehman et al (2016) reported on posttransplant survival outcomes for pediatric patients who received a VAD, ECMO, or no mechanical circulatory support (MCS), in the pretransplant period. The study included 2777 pediatric patients who underwent heart transplant from 2005 to 2012 who were identified through the United Network for Organ Sharing database, of whom 428 were bridged with VADs and 189 were bridged with ECMO. In unadjusted analysis, the actuarial 5-year survival rate was highest in the direct-to-transplant group (77%), followed by the VAD group (49%) and then the ECMO group (35%). In a proportional hazards model to predict time to death, restricted to the first 4 months posttransplant, ECMO bridging was significantly associated with higher risk of death (adjusted hazard ratio, 2.77 vs direct-to-transplant; 95%

confidence interval [CI], 2.12 to 3.61; p<0.001). However, a model to predict time to death excluding deaths in the first 4 months posttransplant, the bridging group was not significantly associated with risk of death.

Fraser et al (2012) evaluated the EXCOR device among 48 children, ages 16 or younger, with 2-ventricle circulation who had severe heart failure, despite optimized treatment, and were listed for heart transplant. Patients were divided into 2 groups based on body surface area; a historical control group of children, receiving circulatory support with ECMO from the Extracorporeal Life Support Organization registry, were matched in a 2:1 fashion with study participants based on propensity-score matching. For participants in cohort 1 (body surface area <0.7 m^2), the median survival time had not been reached at 174 days, while in the matched ECMO comparison group, the median survival was 13 days (p<0.001). For participants in cohort 2 (body surface area range, 0.7 to <1.5 m^2), the median survival was 144 days compared with 10 days in the matched ECMO group (p<0.001). Rates of adverse events were high in both EXCOR device cohorts, including major bleeding (cohort 1, 42%; cohort 2, 50%), infection (cohort 1, 63%; cohort 2, 50%), and stroke (29% of both cohorts).

Noncomparative Studies
Blume et al (2016) published the first analysis of the Pediatric Interagency Registry for Mechanical Circulatory Support, which is a prospective, multicenter registry that collects data on patients who are under age 19 at the time of implant, and includes those implanted with either durable or temporary VADs. At analysis, the registry included 241 patients; of them, 41 were implanted with a temporary device only, leaving 200 patients implanted with VADs for this study. Most patients (73%) had an underlying diagnosis of cardiomyopathy. At the time of implantation, 64% were listed for transplant, while 29% were implanted with a “bridge to candidacy” strategy. A total of 7% were implanted with a destination therapy strategy. Actuarial survival at both 6 months and 1 year was 81%. By 6 months, 58% of patients had received transplants.

Almond et al (2013) reported results from a prospective, multicenter registry to evaluate outcomes in children who received the EXCOR device as a bridge to transplant. This study included a broader patient population than the Fraser et al (2012) study (discussed above). All patients were followed from the time of EXCOR implantation until transplantation, death, or recovery. The study included 204 children, 67% of whom received the device under compassionate use. Survival at 12 months on EXCOR support was 75%, including 64% who survived to transplantation, 6% who recovered (device explanted and the patient survived 30 days), and 5% who were alive with the device in place. In a follow-up study that evaluated 204 children from the same registry, Jordan et al (2015) reported relatively high rates of neurologic events in pediatric patients treated with the EXCOR device (29% of patients), typically early in the course of device use.

Chen et al (2016) reported on a retrospective, single-center series of pediatric patients with continuous-flow VADs, with a focus on outpatient experiences. The series included 17 children implanted with an intracorporeal device from 2010 to 2014. Eight (47%) patients were discharged after a median postimplant hospitalization duration of 49 days. Adverse events were common in outpatients, most frequently major device malfunction (31% [5/16] events) and cardiac arrhythmias (31% [5/16] events). At the time of

analysis, 4 patients had received an orthotopic heart transplant, two were on ongoing support, and one each had been transferred or died.

Another retrospective, single-center series of pediatric patients, conducted by Conway et al (2016), reported on outcomes with short-term continuous-flow VADs, including the Thoratec PediMag or CentriMag, or the Maquet RotaFlow. From 2015 to 2014, 27 children were supported with one of these devices, most commonly for congenital heart disease (42%). The median duration of support was 12 days, and 67% of all short-term continuous-flow VAD runs (19 of 28 runs) led to hospital discharge.

Effects of Pretransplant VADs on Transplant Outcomes

Published studies continue to report that the use of a VAD does not compromise the success of a subsequent heart transplant and, in fact, may improve posttransplant survival, thus improving the use of donor hearts. A systematic review by Alba et al (2011) examined the evidence on the effect of VADs on posttransplant outcomes. Reviewers included 31 observational studies that compared transplant outcomes in patients who did and did not have pretransplant VAD. Survival at 1 year was more likely in patients who had VAD treatment, but this benefit was specific to patients who received an intracorporeal device (relative risk [RR], 1.8; 95% CI, 1.53 to 2.13). For patients treated with an extracorporeal device, the likelihood of survival did not differ from patients not treated with a VAD (RR=1.08; 95% CI, 0.95 to 1.22). There was no difference in the risk of rejection rates between patients who did and did not receive LVAD treatment.

Deo et al (2014) reported no significant differences in outcomes for 37 bridge to transplant patients with a VAD and 70 patients who underwent a heart transplant directly. Data from the United Network for Organ Sharing Network, reported by Grimm et al (2016), suggested that patients bridged to transplant with an LVAD have better outcomes than those bridged with TAHs or biventricular assist devices. Using the United Network for Organ Sharing database, Davies et al (2008) reported on the use of VADs in pediatric patients undergoing heart transplantation. Their analysis concluded that pediatric patients requiring a pretransplantation VAD have long-term survival similar to those not receiving MCS.

Section Summary: Ventricular Assist Devices as a Bridge to Heart Transplant for End-Stage Heart Failure

Questions remain about defining and identifying the population most likely to experience cardiac recovery with VAD placement. One clearly defined population in which the potential for myocardial recovery exists is in the postcardiotomy setting. The current evidence is insufficient to identify other heart failure patient populations that might benefit from the use of an LVAD as a specific bridge to recovery treatment strategy.
In adults, the evidence on the efficacy of VADs as a bridge to transplant consists of uncontrolled trials, registry studies, and case series. In children, the evidence consists of several uncontrolled trials and a trial with historical controls. Collectively, these studies have reported that substantial numbers of patients have survived to transplant in situations in which survival is historically low. Despite the lack of high-quality controlled trials, this evidence supports a finding that outcomes are improved in patients because they have no other treatment options.

VADS AS DESTINATION THERAPY FOR END-STAGE HEART FAILURE

Clinical Context and Therapy Purpose

The purpose of VADs as destination therapy in patients who have end-stage heart failure is to provide a treatment option that is an alternative to or an improvement on existing therapies.

The question addressed in this evidence review is: Does the use of a VAD as destination therapy improve the net health outcome in individuals with end-stage heart failure?

The following PICOTS were used to select literature to inform this review.

Patients

The relevant population of interest is individuals with end-stage heart failure.

Interventions

The therapy being considered is a VAD as destination therapy.

Comparators

The following therapy is currently being used to make decisions about managing individuals with end-stage heart failure: optimal medical therapy without VADs.

Outcomes

The general outcomes of interest are overall survival, device malfunction, heart failure, respiratory dysfunction, arrhythmias, and infection.

Timing

Time of interest ranges from 6 months to 2 years following implantation of VAD as destination therapy.

Setting

Implantation of a VAD is performed in a hospital setting with specialized staff who are equipped to perform the surgical procedure and manage postsurgical intensive care.

Systematic Reviews

The evaluation of VADs as destination therapy was informed by a TEC Assessment (2002) that offered the following observations and conclusions:

- The available evidence comes from a single, well-designed and rigorously conducted randomized trial, known as the REMATCH study. The trial was a cooperative effort of Thoratec, Columbia University, and the National Institutes of Health.
- The trial found that patients with end-stage heart failure who are not candidates for cardiac transplantation had significantly better survival on a VAD compared with treatment by optimal medical therapy. Median survival was improved by approximately 8.5 months. Serious adverse

events were more common in the VAD group, but they appear to be outweighed by this group's better outcomes on function; New York Heart Association functional class was significantly improved, as was the quality of life among those living to 12 months.

- VAD patients spent a greater relative proportion of time inside the hospital than medical management patients do, but the survival advantage would mean a longer absolute time outside the hospital.

Park et al (2005) published reports on extended 2-year follow-up of patients from the REMATCH trial, which found that survival and quality of life benefits were still apparent. In addition, their reports and other case series have suggested continuing improvement in outcomes related to ongoing improvements in the device and in patient management. However, the durability of the HeartMate device used in the REMATCH trial was a concern (eg, at a participating institution, all 6 long-term survivors required device change-outs).

Nonrandomized Comparative Studies

A prospective observational study called the Risk Assessment and Comparative Effectiveness of Left Ventricular Assist Device and Medical Management in Ambulatory Heart Failure Patients study, reported by Estep et al (2015), compared LVAD support (n=97) with optimal medical therapy (n=103) for patients with heart failure not requiring inotropes also found superior survival and health-related quality of life in LVAD-treated patients. Twelve-month, as-treated, event-free actuarial survival was 80% in the LVAD group and 63% in the best medical therapy group (p=0.022). Two-year results were reported by Starling et al (2017). At the end of 2 years, 35 (34%) medical therapy patients and 60 (62%) LVAD patients were alive on their original therapy; 23 medical management patients received LVADs during the 2 years. The LVAD-treated patients continued to have higher as-treated, event-free actuarial survival (70% vs 41%, p<0.001), although there was no statistical difference in intention-to-treat survival (70% vs 63%, p=0.31).

In an FDA-required postapproval study of the HeartMate II device for destination therapy, which included the first 247 HeartMate II patients identified as eligible for the device as destination therapy, Jorde et al (2014) found that outcomes and adverse events did not differ significantly from those of the original trial, which compared patients who received the HeartMate II with earlier generation devices Survival rates in the postapproval cohort were 82% and 69% at 1 and 2 years postoperatively, respectively.

After the release of the REMATCH trial results, Rogers et al (2007) published results from a prospective, nonrandomized trial comparing LVAD as destination therapy with optimal medical therapy for patients with heart failure who were not candidates for heart transplant. Fifty-five patients who had New York Heart Association functional class IV symptoms and who failed weaning from inotropic support were offered a Novacor LVAD; 18 did not receive a device due to preference or device unavailability and served as a control group. The LVAD-treated patients had superior survival rates at 6 months (46% vs 22%; p=0.03) and 12 months (27% vs 11%; p=0.02), along with fewer adverse events.

Arnold et al (2016) analyzed 1638 patients receiving LVADs as destination therapy between May 2012 and September 2013. Results were selected from the INTERMACS registry and assessed for poor outcomes.

Poor outcome was defined as death or mean Kansas City Cardiomyopathy Questionnaire overall score less than 45 throughout the year after implantation. Analyses included inverse probability weighting to adjust for missing data. About 22.4% of patients died within the first year after implantation, and an additional 7.3% had persistently poor QOL; 29.7% met the definition of poor outcome. Poor outcomes were more common in those patients having higher body mass indices, lower hemoglobin levels, previous cardiac surgery, history of cancer, severe diabetes, and poorer QOL preimplant.

Section Summary: VADs as Destination Therapy for End-Stage Heart Failure
The highest quality evidence on the efficacy of LVADs as destination therapy in patients who are not transplant candidates is the REMATCH trial. This multicenter RCT reported that the use of LVADs led to improvements in survival, quality of life, and functional status. This evidence supports a finding that health outcomes are improved with LVADs in this patient population.

Total Artificial Heart as a bridge to transplant for end-stage heart failure

Clinical Context and Therapy Purpose
The purpose of a total artificial heart (TAH) as a bridge to heart transplant in patients who have end-stage heart failure is to provide a treatment option that is an alternative to or an improvement on existing therapies.

The question addressed in this evidence review is: Does the use of a TAH as a bridge to heart transplant improve the net health outcome in individuals with end-stage heart failure?

The following PICOTS were used to select literature to inform this review.

Patients
The relevant population of interest is individuals with end-stage heart failure.

Interventions
The therapy being considered is a TAH as a bridge to heart transplant.

Comparators
The following therapy is currently being used to make decisions about managing individuals with end-stage heart failure: optimal medical therapy without a TAH.

Outcomes
The general outcomes of interest are overall survival, device malfunction, heart failure, respiratory dysfunction, arrhythmias, and infection.

Timing
Time-to-transplant is of interest, as are short-term outcomes ranging from 30 days to 1 year.

Setting
Implantation of a TAH as a bridge to transplant is performed in a hospital setting with specialized staff who are equipped to perform the surgical procedure and manage postsurgical intensive care.

Nonrandomized Trials
FDA approval of the CardioWest TAH was based on the results of a nonrandomized, prospective study of 81 patients. Patients had failed inotropic therapy, had biventricular failure, and thus were not considered appropriate candidates for an LVAD. The rate of survival to transplant was 79%, which was considered comparable with the experience with LVAD in patients with left ventricular failure. The mean time from entry into the study until transplantation or death was 79.1 days.

Case Series
Case series have been reported on outcomes for the TAH as a bridge to transplant. For example, Copeland et al (2012) reported on 101 patients treated with the SynCardia artificial heart as a bridge to transplant. All patients either met established criteria for MCS or were failing medical therapy on multiple inotropic drugs. Mean support time was 87 days (range, 1-441 days). The rate of survival to transplant was 68.3% (69/101). Of the 32 deaths before the transplant, 13 were due to multiorgan failure, 6 were due to pulmonary failure, and 4 were due to neurologic injury. Survival rates after transplant at 1, 5, and 10 years, respectively, were 76.8%, 60.5%, and 41.2%.

Section Summary: Total Artificial Heart as a Bridge to Transplant for End-Stage Heart Failure
There is less evidence on the use of TAH as a bridge to transplant compared with the use of LVADs. The type of evidence on a bridge to transplant is similar to that for LVADs (ie, case series reporting substantial survival rates in patients without other alternatives). Therefore, similar to LVADs, this evidence is sufficient to conclude that TAH improves outcomes for these patients and TAH is a reasonable alternative for patients who require a bridge to transplantation but who are ineligible for other types of life-prolonging support devices.

TAH AS DESTINATION THERAPY FOR END-STAGE HEART FAILURE

Clinical Context and Therapy Purpose
The purpose of a TAH as destination therapy in patients who have end-stage heart failure is to provide a treatment option that is an alternative to or an improvement on existing therapies.

The question addressed in this evidence review is: Does the use of a TAH as destination therapy improve the net health outcome in individuals with end-stage heart failure?

The following PICOTS were used to select literature to inform this review.

Patients
The relevant population of interest is individuals with end-stage heart failure.

Interventions
The therapy being considered is a TAH as destination therapy.

Comparators
The following therapy is currently being used to make decisions about managing individuals with end-stage heart failure: optimal medical therapy without TAHs.

Outcomes
The general outcomes of interest are overall survival, device malfunction, heart failure, respiratory dysfunction, arrhythmias, and infection.

Timing
Time of interest ranges from 6 months to 2 years following implantation of a TAH as destination therapy.

Setting
Implantation of a TAH as destination therapy is performed in a hospital setting with specialized staff who are equipped to perform the surgical procedure and manage postsurgical intensive care.

Case Series
Data on the artificial heart are available from FDA approval information and from a published article describing results for the first 7 patients. FDA indicated that its decision on the AbioCor implantable heart was based on the manufacturer's (Abiomed) laboratory and animal testing and on a small clinical study of 14 patients conducted by Abiomed. Study participants had a 1-month survival prognosis of not more than 30%, were ineligible for cardiac transplants and were not projected to benefit from VAD therapy. The study showed that the device was safe and likely to benefit for people with severe heart failure whose death was imminent and for whom no alternative treatments were available. Of the 14 patients studied, 12 survived the surgery. Mean duration of support for the patients was 5.3 months. In some cases, the device extended survival by several months (survival was 17 months in 1 patient). Six patients were ambulatory; 1 patient was discharged home. Complications included postoperative bleeding and neurologic events. No device-related infections were reported.

Torregrossa et al (2014) reported on 47 patients who received a TAH at 10 worldwide centers and had the device implanted for more than 1 year. Patients were implanted for dilated cardiomyopathy (n=23), ischemic cardiomyopathy (n=15), and "other" reasons (n=9). Over a median support time of 554 days (range, 365-1373 days), 34 (72%) patients were successfully transplanted, 12 (24%) patients died while on device support, and 1 (2%) patient was still supported. Device failure occurred in 5 (10%) patients. Major complications were common, including systemic infection in 25 (53%) patients, driveline infections in 13 (27%) patients, thromboembolic events in 9 (19%) patients, and hemorrhagic events in 7 (14%) patients. Two of the deaths occurred secondary to device failure.

Section Summary: TAH as Destination Therapy for End-Stage Heart Failure
There is a less evidence on the use of TAH as destination therapy compared with the use of LVADs. Although TAHs show promise as destination therapy in patients who have no other treatment options, the available data on their use is extremely limited. Currently, the evidence base is insufficient to support conclusions about TAH efficacy in this setting.

PERCUTANEOUS VADS FOR CARDIOGENIC SHOCK

Clinical Context and Therapy Purpose
The purpose of pVADs in patients who have cardiogenic shock is to provide a treatment option that is an alternative to or an improvement on existing therapies.

The question addressed in this evidence review is: Does the use of a pVAD as a bridge to heart transplant improve the net health outcome in individuals with end-stage heart failure?

The following PICOTS were used to select literature to inform this review.

Patients
The relevant population of interest is individuals with cardiogenic shock.

Interventions
The therapy being considered is a pVADs.

Comparators
The following therapy is currently being used to make decisions about managing individuals with cardiogenic shock: intra-aortic balloon pump (IABP).

Outcomes
The general outcomes of interest are overall survival, device malfunction, heart failure, respiratory dysfunction, arrhythmias, and infection.

Timing
Timing of interest ranges from perioperative events to 30-day mortality outcomes.

Setting
Implantation of a pVAD is performed in a hospital setting with specialized staff equipped to perform the surgical procedure and manage postsurgical intensive care.

Systematic Reviews
Romeo et al (2016) reported on a systematic review and meta-analysis that evaluated various percutaneous mechanical support methods, including pVADs, for patients with cardiogenic shock due to

acute myocardial infarction (AMI) who were undergoing revascularization. Reviewers included the three RCTs (described below) comparing pVADs with IABPs, along with three observational studies. In the comparison of pVADs with IABP, reviewers found that in-hospital mortality (the primary outcome of the analysis) was nonsignificantly increased in the pVAD group.

A meta-analysis by Cheng et al (2009) included the same 3 trials as Romeo (2016). None of the 3 trials reported a reduction in mortality associated with pVAD use. The combined analysis estimated the RR for death in pVAD patients as 1.06 (95% CI, 0.68 to 1.66; p=0.80). All 3 trials reported an improvement in left ventricle hemodynamics in the pVAD group. On combined analysis, there was a mean increase in cardiac index of 0.35 L/min/m^2 for the pVAD group, an increase in mean arterial pressure of 12.8 mm Hg (95% CI, 3.6 to 22.0 mm Hg; p<0.001), and a decrease in pulmonary capillary wedge pressure of 5.3 mm Hg (95% CI, 1.2 to 9.4 mm Hg; p<0.05). Complications were more common in the pVAD group. In combined analysis, patients in the pVAD group had a significantly increased likelihood of bleeding events (RR=2.35; 95% CI, 1.40 to 3.93). While leg ischemia was more common in the pVAD group, this difference was not statistically significant (RR=2.59; 95% CI, 0.75 to 8.97; p=0.13).

Table 3 provides a crosswalk of studies in the systematic reviews. Tables 4 and 5 summarize the characteristics and results of the systematic reviews.

Table 3. Comparison of Systematic Reviews Evaluating pVADs and IABPs for Cardiogenic Shock

Studies	Romeo et al (2016)	Cheng et al (2016)
Burkhoff et al (2006)	●	●
Seyfarth et al (2008)	●	●
Thiele et al (2005)	●	●
Schwartz et al (2012)	●	
Shah et al (2012)	●	
Manzo-Silberman (2013)	●	

IABP: intra-aortic balloon pump; pVAD: percutaneous ventricular assist device.

Table 4. Characteristics of Systematic Reviews Evaluating pVADs and IABPs for Cardiogenic Shock

Study	Dates	Trials	Participants	N	Design
Romeo et al (2016)	2000-2010	6	Patients receiving IABP or pVADs	271	RCT and observational
Cheng et al (2016)	2000-2015	3	Patients receiving IABP or pVADs	100	RCT

IABP: intra-aortic balloon pump; pVAD: percutaneous ventricular assist device.

Table 5. Results of Systematic Reviews Evaluating pVADs and IABPs for Cardiogenic Shock

Study	Overall In-Hospital Mortality Events		Incidence of Bleeding Events	Incidence of Leg Ischemia
	RCTs	OBS Studies		
Romeo et al (2016)				

pVAD	24	42		
IABP	20	53		
p	0.80	0.20		
Cheng et al (2016)				
pVAD	24		Increased likelihood	Increased likelihood
IABP	20			
RR (95% CI)	1.06 (0.68 to 1.66)		2.35 (1.40 to 3.93)	2.59 (0.75 to 8.97)

CI: confidence interval; IABP: intra-aortic balloon pump; OBS: observational; pVAD: percutaneous ventricular assist device; RR: relative risk.

Randomized Controlled Trials

Four RCTs have compared pVADs with IABPs for patients who had cardiogenic shock; three were included in both systematic reviews described above and one was published after the reviews. The 4 RCTs enrolled a total of 148 patients, 77 treated with a pVAD and 71 treated with an IABP. All 4 trial populations included patients with AMI and cardiovascular shock; 1 trial restricted its population to patients who were postrevascularization in the AMI setting. The primary outcomes reported were 30-day mortality, hemodynamic measures of left ventricle pump function, and adverse events. The trials are summarized in Tables 6 and 7. Some trials reported improvements in hemodynamic and metabolic parameters, but none found any reductions in 30-day mortality. The IMPRESS trial reported 6-month mortality outcomes and also found no difference between groups. Bleeding events and leg ischemia were more common in the pVAD groups.

Table 6. Characteristics of RCTs Evaluating pVADs and IABPs for Cardiogenic Shock

Study	Trial (Registration)	Countries	Sites	Dates	pVAD	Key Eligibility Criteria
Ouweneel et al (2017)	IMPRESS (NTR3450)	Netherlands, Norway	2	2012-2015	Impella CP	AMI and severe CS in the setting of immediate PCI; receiving mechanical ventilation
Seyfarth et al (2008)	ISAR-SHOCK (NCT00417378)	Germany	2	2004-2007	Impella LP 2.5	AMI <48 h and CS
Burkhoff et al (2006)	TandemHeart (NR)	U.S.	12	2002-2004	TandemHeart	CS <24 h due to MI or heart failure
Thiele et al (2005)	NR	Germany	1	2000-2003	TandemHeart	AMI with CS and intent to revascularize with PCI

AMI: acute myocardial infarction; CS: cardiogenic shock; IABP: intra-aortic balloon counterpulsation; IMPRESS: IMPella versus IABP Reduces mortality in STEMI patients treated with primary PCI in Severe cardiogenic SHOCK; ISAR-SHOCK: Efficacy Study of LV Assist Device to Treat Patients With Cardiogenic Shock; MI: myocardial infarction; NR: not reported; PCI: percutaneous coronary intervention; pVAD: percutaneous ventricular assist device; RCT; randomized controlled trial.

Table 7. Results of RCTs Evaluating pVADs and IABPs for Cardiogenic Shock

Study	Numbers Randomized		pVAD vs IABP			Other Outcomes
	pVAD	IABP	30-Day Mortality	Bleeding	Leg Ischemia	
IMPRESS	24	24	• 46% vs 50% • HR=0.96 (0.42 to 2.18)[a] 60-day: • 50% vs 50% HR=1.04 (0.47 to 2.32)[a]	33% vs 8%[b]	NR	Rehospitalization: 21% vs 4%
ISAR-SHOCK	13	13	46% vs 46%	NR	8% vs 0%	Increase in cardiac index (L/min/m^2): 0.49 vs 0.11
TandemHeart	19	14	47% vs 36%	42% vs 14%	21% vs 14%	At least 1 adverse event: 95% vs 71%
Thiele et al (2005)	21	20	43% vs 45%	90% vs 40%	33% vs 0%	Final cardiac index (W/m^2): 0.37 vs 0.28

AMI: acute myocardial infarction; HR: hazard ratio; IABP: intra-aortic balloon counterpulsation; IMPRESS: IMPella versus IABP Reduces mortality in STEMI patients treated with primary PCI in Severe cardiogenic SHOCK; ISAR-SHOCK: Efficacy Study of LV Assist Device to Treat Patients With Cardiogenic Shock; NR: not reported; pVAD: percutaneous ventricular assist devices; RCT: randomized controlled trial.
[a] Values are hazard ratio (95% confidence interval).
[b] Major bleeding.

Registry Studies

O'Neill et al (2014) compared outcomes for patients who had AMI complicated by cardiogenic shock who received pVAD support before percutaneous coronary intervention (PCI) with those who received pVAD support after PCI using data from 154 consecutive patients enrolled in a multicenter registry.[62] Patients who received pVAD support pre-PCI had a higher survival to discharge rate (65.1%) than those who received pVAD support post-PCI (40.7%; p=0.003). In multivariable analysis, receiving pVAD support pre-PCI was associated with in-hospital survival (odds ratio, 0.37; 95% CI, 0.17 to 0.79; p=0.01). However, the potential for underlying differences in patient groups other than the use of pVAD support makes the study's implications uncertain.

Basir et al (2017) compared survival in patients with AMI complicated by cardiogenic shock and undergoing PCI who received an Impella device. Exactly 287 consecutive patients from the global cVAD Registry were analyzed. Impella implantation before and after PCI and before initiation of inotropes or vasopressors was independently associated with survival in multivariate analysis. Survival rates were 66% in patients who received the Impella device less than 1.25 hours from shock onset, 37% in those receiving the device within 1.25 to 4.25 hours, and 26% after 4.25 hours (p=0.017).

Case Series
Case series of patients treated with pVADs as an alternative to IABP in cardiogenic shock have reported high success rates as a bridge to alternative therapies. However, given the availability of RCT evidence, these studies add little to the body of evidence on the efficacy of pVADs for the management of cardiogenic shock.

Section Summary: Percutaneous VADs for Cardiogenic Shock
Four RCTs comparing pVAD with IABP in patients with cardiogenic shock and meta-analyses evaluating three of these RCTs failed to demonstrate a mortality benefit for pVAD use and reported higher complication rates associated with pVAD use.

PERCUTANEOUS VADS FOR HIGH-RISK CARDIAC PROCEDURES

Clinical Context and Therapy Purpose
The purpose of pVADs in patients who undergo high-risk cardiac procedures is to provide a treatment option that is an alternative to or an improvement on existing therapies.

The question addressed in this evidence review is: Does the use of a pVAD improve the net health outcome in individuals who undergo high-risk cardiac procedures?

The following PICOTS were used to select literature to inform this review.

Patients
The relevant population of interest is individuals undergoing high-risk cardiac procedures.

Interventions
The therapy being considered is a pVAD.

Comparators
The following therapy is currently being used to make decisions about managing individuals who undergo high-risk cardiac procedures: IABP.

Outcomes
The general outcomes of interest are overall survival, device malfunction, heart failure, respiratory dysfunction, arrhythmias, and infection.

Timing
Timing of interest ranges from perioperative events to 30-day mortality outcomes.

Setting
Implantation of a pVAD is performed in a hospital setting with specialized staff who are equipped to perform the surgical procedure and manage postsurgical intensive care.

Percutaneous VADs as Ancillary Support for High-Risk Percutaneous Coronary Intervention

Systematic Reviews
Briasoulis et al (2016) reported on a meta-analysis of pVAD devices as an adjunct to high-risk PCI. Reviewers included RCTs and cohort studies, identifying 18 nonrandomized observational studies and a single RCT. The RCT identified was the PROTECT II trial detailed below. In the observational studies, the sample sizes ranged from 7 to 637 patients. In a pooled analysis of the observational trial data, the 30-day mortality rate following Impella-assisted high-risk PCI was 3.5% (95% CI, 2.2% to 4.8%; I^2=20%), while that for TandemHeart-assisted high-risk PCI was 8% (95% CI, 2.9% to 13.1%; I^2=55%). The pooled vascular complication rates were 4.9% (95% CI, 2.3% to 7.6%) and 6.5% (95% CI, 3.2% to 9.9%) for the Impella and the TandemHeart, respectively.

Randomized Controlled Trials
The PROTECT II trial, planned as an RCT, compared the Impella system with IABP in patients undergoing high-risk PCI procedures. Enrollment was planned for 654 patients from 50 clinical centers. The primary end point was the composite of 10 different complications occurring within 30 days of the procedure, with the trialists hypothesizing a 10% absolute decrease in the complication rate for patients in the pVAD group. The trial was discontinued prematurely in late 2010 due to futility after an interim analysis of the first 327 patients enrolled revealed that the primary end point could not be reached. When stopped, 452 patients had been enrolled, three of whom withdrew consent and one of whom died. Results were published by O'Neill et al (2012). The trial's primary analysis was intention-to-treat and included all 448 patients randomized to the Impella system (n=225) or IABP (n=223). The primary composite end point of major adverse events at 30 days occurred in 35.1% of Impella patients and in 40.1% of the IABP patients (p=0.277). There was no significant difference in the occurrence of in-hospital death, stroke, or myocardial infarction (MI) between groups.

In a prespecified subgroup analysis of the PROTECT II trial, Kovacic et al (2015) compared outcomes for the Impella system and IABP among 325 patients with 3-vessel disease with a left ventricular ejection fraction of 30% or less. In the 3-vessel disease subgroup, 167 subjects were randomized to PCI with Impella support and 158 to PCI with IABP support. PCI characteristics differed in that rotational atherectomy was more aggressively used in the Impella support group, with more passes per patient (5.6 vs 2.8, p=0.002) and more passes per coronary lesion (3.4 vs 1.7, p=0.001). Acute procedural revascularization results did not differ between groups. At 30 days, the major adverse event rate did not differ significantly between groups (32.9% of Impella patients vs 42.4% of IABP patients, p=0.078). At 90 days, Impella patients (39.5%) had a significantly lower major adverse event rate than IABP patients (51.0%; p=0.039). The 90-day event rates for the individual components of the composite major adverse event score differed

only for severe hypotension requiring treatment, which was more common in patients treated with IABP (7.6% vs 2.4%, p=0.029).

In a post hoc analysis, results of the PROTECT II trial were reanalyzed by Dangas et al (2014), using a revised definition of MI in the determination of patients with major adverse events and major adverse cardiac and cerebral events. Unlike the original trial, which used a cutoff of 3 times the upper limit of normal for biomarker elevation to define periprocedural MI, the authors used a cutoff of 8 times the upper limit of normal for biomarker elevation or the presence of Q waves to define periprocedural MI. In multivariable analysis, compared with IABP, treatment with the Impella system was associated with freedom from 90-day major adverse events (odds ratio, 0.75; 95% CI, 0.61 to 0.92; p=0.007) and major adverse cardiac and cerebral events (odds ratio, 0.76; 95% CI, 0.61 to 0.96; p=0.020).

Nonrandomized Studies
Kovacic et al (2013) retrospectively compared outcomes for the TandemHeart and Impella devices in 68 patients undergoing high-risk PCI from 2005 to 2010 from a single-center database. There were no reported in-hospital deaths or strokes. There was 1 periprocedural MI in the TandemHeart group and 2 in the Impella group. For 63 patients with available intermediate- and long-term data, there was no statistically significant difference in time to death.

The PROTECT trial evaluated whether the Impella 2.5 system would improve outcomes for patients undergoing high-risk PCI procedures. PROTECT I was a feasibility study of 20 patients who had left main disease or last patent coronary conduit that required revascularization but who were not candidates for coronary artery bypass graft surgery. High-risk PCI was performed using the Impella system for circulatory support. All procedures were successfully completed without any hemodynamic compromise in-procedure. Two (10%) patient died within 30 days, and 2 (10%) patients had a periprocedural MI. Two other patients had evidence of hemolysis, which was transient and resolved without sequelae.

Registry Studies
Schreiber et al (2017) reported outcomes for 127 consecutive patients from the USpella Registry not in cardiogenic shock who underwent unprotected left main PCI supported with an Impella LV device between 2008 and 2015. The in-hospital and 30-day mortality rates were 1.6% and 2.4%, respectively. The 30-day major adverse cardiovascular event rate was 2.4%. One patient had vascular complications requiring surgery. Three (2.4%) patients had a hematoma, and 5 (3.9%) patients had bleeding requiring transfusion.

Maini et al (2012) retrospectively analyzed 175 patients with data in the USpella Registry undergoing high-risk PCI with pVAD support using the Impella 2.5 circulatory support system. The primary safety end point was the incidence of major adverse cardiac events at 30 days. Secondary end points included device safety and efficacy and patient outcomes at 30 days and 12 months. Angiographic revascularization was successful in 99% of patients. At 30-day follow-up, the major adverse cardiac event rate was 8%; survival rates were 96%, 91%, and 88% at 30 days, 6 months, and 12 months, respectively. Secondary safety end points included acute renal dysfunction (2.8%), hypotension on support (3.4%), ventricular tachycardia (VT),

or cardiopulmonary resuscitation (2.8%); other vascular complications included vessel dissection and arteriovenous fistula (3.4%), hematomas ipsi- or contralateral to the device insertion site (8.6%), infection (5.1%), and blood transfusion (9.7%).

Sjauw et al (2009) retrospectively analyzed 144 consecutive patients undergoing high-risk PCI with pVAD support (Impella) from a European registry. End points included successful device function and incidence of adverse events at 30 days. The device was successfully implanted in all 144 patients. There were a periprocedural death and 8 deaths at 30 days for a mortality rate of 5.5%. Bleeding requiring transfusion or surgery occurred in 6.2% of patients, and vascular access site complications occurred in 4.0%. There was 1 (0.7%) stroke, and no MIs were reported.

Section Summary: Percutaneous VADs for High-Risk PCI
Percutaneous VADs have been assessed in 1 RCT (PROTECT II) and subsequent trial data analyses and in uncontrolled studies of high-risk patients undergoing high-risk cardiac interventions such as PCI. The RCT and other nonrandomized studies and accompanying post hoc analyses have not consistently reported a benefit for the use of pVADs. Registry studies have described pVAD use in high-risk patients undergoing an invasive cardiac procedure, but given trial design lacking comparators, these studies add little to suggest the efficacy of pVAD use in this population.

Percutaneous VADs for High-Risk VT Ablation
Reddy et al (2014) reported on outcomes for a series of 66 patients enrolled in a prospective, multicenter registry who underwent VT ablation with a pVAD or IABP. Twenty-two patients underwent ablation with IABP assistance, while 44 underwent ablation with the TandemHeart or Impella pVAD device (non-IABP group). Compared with patients who received support with an IABP, those who received support with a pVAD had more unstable VTs that could be mapped and ablated (1.05 vs 0.32, p<0.001), more VTs than could be terminated by ablation (1.59 vs 0.91, p=0.001), and fewer VTs terminated with rescue shocks (1.9 vs 3.0, p=0.049). More pVAD-supported patients could undergo entrainment/activation mapping (82% vs 59%, p=0.046). Mortality and VT recurrence did not differ over the study follow-up (average, 12 months).

In a retrospective study, Aryana et al (2014) reported procedural and clinical outcomes for 68 consecutive unstable patients with scar-mediated epicardial or endocardial VT who underwent ablation with or without pVAD support. Thirty-four patients had hemodynamic support periprocedurally with a pVAD. Percutaneous VAD- and non-pVAD-supported patients had similar procedural success rates. Compared with non-pVAD-supported patients, patients in the pVAD group had a longer maximum time in unstable VT (27.4 minutes vs 5.3 minutes, p<0.001), more VT ablations per procedure (1.2 vs 0.4, p<0.001), shorter radiofrequency ablation time (53 seconds vs 68 seconds, p=0.022), and a shorter hospital length of stay (4.1 days vs 5.4 days, p=0.013). Over a follow-up of 19 months, rates of VT recurrence did not differ between groups.

Section Summary: Percutaneous VADs for High-Risk VT Ablation
Two nonrandomized studies have compared VT ablation with pVAD or IABP. In both studies, patients who had pVAD support spent less time in unstable VT than patients without pVAD support. Rates of recurrence

of VT was comparable between groups for both studies. The current evidence based does not support conclusions about the use of pVAD for VT ablation.

PERCUTANEOUS VADS FOR CARDIOGENIC SHOCK REFRACTORY TO IABP THERAPY

Clinical Context and Therapy Purpose

The purpose of pVADs in patients who have cardiogenic shock refractory to IABP therapy is to provide a treatment option that is an alternative to or an improvement on existing therapies.

The question addressed in this evidence review is: Does the use of a pVAD improve the net health outcome in individuals with cardiogenic shock refractory to IABP?

The following PICOTS were used to select literature to inform this review.

Patients

The relevant population of interest is individuals with cardiogenic shock refractory to IABP therapy.

Interventions

The therapy being considered is the use of a pVAD.

Comparators

The following therapies are currently being used to make decisions about managing individuals with cardiogenic shock refractory to IABP: optimal medical therapy without IABP and other MCS.

Outcomes

The general outcomes of interest are overall survival, device malfunction, heart failure, respiratory dysfunction, arrhythmias, and infection.

Timing

Timing of interest ranges from perioperative events to 30-day mortality outcomes.

Setting

Implantation of a pVAD is performed in a hospital setting with specialized staff who are equipped to perform the surgical procedure and manage postsurgical intensive care.

Case Series

Case series of patients with cardiogenic shock refractory to IABP therapy who were treated with pVAD have been published. In a large series, Kar et al (2011) treated 117 patients who had severe, refractory cardiogenic shock with the TandemHeart System. Eighty patients had ischemic cardiomyopathy and 37 had nonischemic cardiomyopathy. There were significant improvements in all hemodynamic measures following LVAD placement. For example, the cardiac index increased from 0.52 L/min/m^2 to 3.0 L/min/m^2 ($p<0.001$), and systolic blood pressure increased from 75 mm Hg to 100 mm Hg ($p<0.001$). Complications were

common after LVAD implantation. Thirty-four (29.1%) patients had bleeding around the cannula site, and 35 (29.9%) developed sepsis during hospitalization. Groin hematoma occurred in 6 (5.1%) patients; limb ischemia in 4 (3.4%) patients; femoral artery dissection or perforation in 2 (1.7%) patients; stroke in 8 (6.8%) patients; and coagulopathy in 13 (11.0%) patients.

Section Summary: Percutaneous VADs for Cardiogenic Shock Refractory to IABP Therapy
Percutaneous VADs have been assessed in uncontrolled studies of patients with cardiogenic shock including those refractory to IABP therapy. The case series have reported high rates of adverse events that may outweigh any potential benefits. As a result, the evidence on pVADs does not demonstrate that the use of pVADs is associated with improvements in health outcomes for patients with cardiogenic shock refractory to IABP therapy.

SUMMARY OF EVIDENCE

Ventricular Assist Device
For individuals who have end-stage heart failure who receive a VAD as a bridge to transplant, the evidence includes single-arm trials and observational studies. Relevant outcomes are overall survival, symptoms, functional outcomes, quality of life, and treatment-related mortality and morbidity. There is a substantial body of evidence from clinical trials and observational studies supporting implantable VADs as a bridge to transplant in patients with end-stage heart failure, possibly reducing mortality as well as improving quality of life. These studies have reported that substantial numbers of patients have survived to transplant in situations in which survival would not be otherwise expected. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

For individuals who have end-stage heart failure who receive a VAD as destination therapy, the evidence includes a trial and multiple single-arm studies. Relevant outcomes are overall survival, symptoms, functional outcomes, quality of life, and treatment-related mortality and morbidity. A well-designed trial, with 2 years of follow-up data, has demonstrated an advantage of implantable VADs as destination therapy for patients ineligible for heart transplant. Despite an increase in adverse events, both mortality and quality of life appear to be improved for these patients. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

Total Artificial Heart
For individuals who have end-stage heart failure who receive a TAH as a bridge to transplant, the evidence includes case series. Relevant outcomes are overall survival, symptoms, functional outcomes, quality of life, and treatment-related mortality and morbidity. Compared with VADs, the evidence for TAHs in these settings is less robust. However, given the lack of medical or surgical options for these patients and the evidence case series provide, TAH is likely to improve outcomes for a carefully selected population with end-stage biventricular heart failure awaiting transplant who are not appropriate candidates for a left VAD. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

For individuals who have end-stage heart failure who receive a TAH as destination therapy, the evidence includes 2 case series. Relevant outcomes are overall survival, symptoms, functional outcomes, quality of life, and treatment-related mortality and morbidity. The body of evidence for TAHs as destination therapy is too limited to draw conclusions. The evidence is insufficient to determine the effects of the technology on health outcomes.

Percutaneous Ventricular Assist Device
For individuals with cardiogenic shock or who undergo high-risk cardiac procedures who receive a pVAD, the evidence includes randomized controlled trials. Relevant outcomes are overall survival, symptoms, morbid events, functional outcomes, quality of life, and treatment-related mortality and morbidity. Four randomized controlled trials of pVAD vs IABP for patients in cardiogenic shock failed to demonstrate a mortality benefit and reported higher complication rates with pVAD use. Another randomized controlled trial comparing pVAD with IABP as an adjunct to high-risk percutaneous coronary interventions was terminated early due to futility; analysis of enrolled subjects did not demonstrate significant improvements in the pVAD group. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals with cardiogenic shock refractory to IABP therapy who receive a pVAD, the evidence includes case series. Relevant outcomes are overall survival, symptoms, morbid events, functional outcomes, quality of life, and treatment-related mortality and morbidity. Case series of patients with cardiogenic shock refractory to IABP have reported improved hemodynamic parameters following pVAD placement. However, these uncontrolled series do not provide evidence that pVADs improve mortality, and high rates of complications have been reported with pVAD use. The evidence is insufficient to determine the effects of the technology on health outcomes.

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Policy History

Original Effective Date: 01/20/2010
Current Effective Date: 11/21/2018

01/07/2010	Medical Policy Committee approval
01/20/2010	Medical Policy Implementation Committee approval. New policy.
01/06/2011	Medical Policy Committee approval
01/19/2011	Medical Policy Implementation Committee approval. Title changed. Policy statements revised to address only implantable VADs and total artificial hearts.
04/12/2012	Medical Policy Committee approval
04/25/2012	Medical Policy Implementation Committee approval. Percutaneous VADs added to policy investigational statement and rationale.
04/04/2013	Medical Policy Committee review
04/24/2013	Medical Policy Implementation Committee approval. Added "Implantable" to the beginning of the 2nd coverage statement under Bridge to Transplant to make it consistent with the other coverage statements and the focus of the policy. Coverage statement on children amended; age range changed from 5-16 to 0-16, reflecting the approval of the BERLIN heart EXCOR device for pediatric patients aged 0-16. Clause added to coverage statement on total artificial hearts that says "…or are undergoing evaluation to determine candidacy for heart transplantation…".
08/07/2014	Medical Policy Committee review
08/20/2014	Medical Policy Implementation Committee approval. Coverage statement unchanged.
08/03/2015	Coding update: ICD10 Diagnosis code section added; ICD9 Procedure code section removed.
10/29/2015	Medical Policy Committee review
11/16/2015	Medical Policy Implementation Committee approval. Coverage statement unchanged.
11/03/2016	Medical Policy Committee review
11/16/2016	Medical Policy Implementation Committee approval. No change to coverage.
01/01/2017	Coding update: Removing ICD-9 Diagnosis Codes
11/02/2017	Medical Policy Committee review
11/15/2017	Medical Policy Implementation Committee approval. No change to coverage. Added new FDA information.
01/01/2018	Coding update
11/08/2018	Medical Policy Committee review
11/21/2018	Medical Policy Implementation Committee approval. No change to coverage.

Next Scheduled Review Date: 11/2019

Coding

The five character codes included in the Blue Cross Blue Shield of Louisiana Medical Policy Coverage Guidelines are obtained from Current Procedural Terminology (CPT®)‡, copyright 2017 by the American Medical Association (AMA).

Total Artificial Hearts and Implantable Ventricular Assist Devices

Policy # 00246
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CPT is developed by the AMA as a listing of descriptive terms and five character identifying codes and modifiers for reporting medical services and procedures performed by physician.

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Codes used to identify services associated with this policy may include (but may not be limited to) the following:

Code Type	Code
CPT	33975, 33976, 33977, 33978, 33979, 33980, 33981, 33982, 33983, 33990, 33991, 33992, 33993, 93750 Codes added eff 1/1/18: 33927, 33928, 33929
HCPCS	Q0478, Q0479, Q0480, Q0481, Q0482, Q0483, Q0484, Q0485, Q0486, Q0487, Q0488, Q0489, Q0490, Q0491, Q0492, Q0493, Q0494, Q0495, Q0496, Q0497, Q0498, Q0499, Q0500, Q0501, Q0502, Q0503, Q0504, Q0506, Q0507, Q0508, Q0509 Code added eff 1/1/18: Q0477
ICD-10 Diagnosis	I09.81, I11.0, I13.0, I13.2, I50.20-I50.23, I50.30-I50.33, I50.40-I50.43, I50.9

*****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:

A. Whether the medical treatment, procedure, drug, device, or biological product can be lawfully marketed without approval of the U.S. FDA and whether such approval has been granted at the time the medical treatment, procedure, drug, device, or biological product is sought to be furnished; or
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 technology assessment program (TEC) or other nonaffiliated technology evaluation center(s);
    2. Credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community; or
    3. Reference to federal regulations.

**Medically Necessary (or "Medical Necessity") - Health care services, treatment, procedures, equipment, drugs, devices, items or supplies that a Provider, exercising prudent clinical judgment, would provide to a patient for the purpose of preventing, evaluating, diagnosing or treating an illness, injury, disease or its symptoms, and that are:

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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