I. POLICY

Patent Foramen Ovale
Closure of patent foramen ovale (PFO) using a transcatheter approach is considered investigational. (There are currently no transcatheter devices with FDA approval or clearance for this indication.) There is insufficient evidence to support a conclusion concerning the health outcomes or benefits associated with this procedure.

Atrial Septal Defects
Transcatheter closure of secundum atrial septal defects (ASD) may be considered medically necessary when using a device that has been FDA approved for that purpose and used according to the labeled indications.

Policy Guidelines
At present, no PFO closure devices are FDA approved for patients with cryptogenic stroke. All uses of these PFO closure devices are currently off-label.

There are 2 FDA-approved devices for ASD closure: the AMPLATZER™ Septal Occluder and the GORE HELEX™ Septal Occluder.

The labeled indications for these devices are similar and include:

- Those with echocardiographic evidence of ostium secundum atrial septal defect; AND
- Clinical evidence of right ventricular volume overload (i.e., 1.5:1 degree of left-to-right shunt or right ventricular enlargement).

Generally recognized indications for closure include a pulmonary-to-systemic flow ratio of greater than 1.5, right atrial and right ventricular enlargement, and paradoxical embolism.

Cross-reference: NA
II. PRODUCT VARIATIONS

This policy is applicable to all programs and products administered by Capital BlueCross unless otherwise indicated below.

FEP PPO*

*Refer to FEP Medical Policy Manual MP-2.02.09, Closure Devices for Patient Foramen Ovale and Atrial Septal Defects. The FEP Medical Policy Manual can be found at: www.fepblue.org

III. DESCRIPTION/BACKGROUND

Patent foramen ovale (PFO) and atrial septal defects (ASDs) are relatively common congenital heart defects associated with a range of symptoms. Depending on their size, ASDs may lead to left-to-right shunting and signs and symptoms of pulmonary overload. Repair of ASDs is indicated for patients with a significant degree of left-to-right shunting. PFOs may be asymptomatic but have been associated with higher rates of cryptogenic stroke. PFOs have also been investigated for a variety of other conditions, such as migraine. Transcatheter “closure” devices are intended as less invasive, catheter-based approaches of repairing PFO or ASDs. These devices are alternatives to open surgical repair for ASDs or treatment with antiplatelet and/or anticoagulant medications in patients with cryptogenic stroke and PFO.

**Patent Foramen Ovale**

The foramen ovale, a component of fetal cardiovascular circulation, consists of a communication between the right and left atrium that functions as a vascular bypass of the uninflated lungs. The ductus arteriosus is another feature of the fetal cardiovascular circulation, consisting of a connection between the pulmonary artery and the distal aorta. Before birth, the foramen ovale is held open by the large flow of blood into the left atrium from the inferior vena cava. Over a course of months after birth, an increase in left atrial pressure and a decrease in right atrial pressure result in the permanent closure of the foramen ovale in most individuals. However, a PFO is a common finding in normal adults, detected in up to 25% of adults. In some epidemiologic studies, PFO has been associated with cryptogenic stroke, a type of stroke defined as an ischemic stroke occurring in the absence of potential cardiac, pulmonary, vascular, or neurologic sources. Studies also show an association of PFO and migraine headache. There has been interest in either open surgery or transcatheter approaches to close the PFO in patients with a history of cryptogenic stroke to prevent recurrent stroke.
Atrial Septal Defects

Unlike PFO, which represents the postnatal persistence of normal fetal cardiovascular physiology, atrial septal defects (ASDs) represent an abnormality in the development of the heart that results in free communication between the atria. ASDs are categorized by their anatomy. Ostium secundum describes defects located midseptally and are typically near the fossa ovalis. Ostium primum defects lie immediately adjacent to the atrioventricular valves and are within the spectrum of atrioventricular septal defects. Primum defects occur commonly in patients with Down syndrome. Sinus venous defects occur high in the atrial septum and are frequently associated with anomalies of the pulmonary veins.

Ostium secundum ASDs are the third most common form of congenital heart disorder and one of the most common congenital cardiac malformations in adults, accounting for 30% to 40% of these patients older than age 40 years. The ASD often goes unnoticed for decades because the physical signs are subtle and the clinical sequelae are mild. However, virtually all patients who survive into their sixth decade are symptomatic; fewer than 50% of patients survive beyond age 40 to 50 years due to heart failure or pulmonary hypertension related to the left-to-right shunt. Symptoms related to ASD depend on the size of the defect and the relative diastolic filling properties of the left and right ventricles. Reduced left ventricular compliance and mitral stenosis will increase left-to-right shunting across the defect. Conditions that reduce right ventricular compliance and tricuspid stenosis will reduce left-to-right shunting or cause a right-to-left shunt. Symptoms of an ASD include exercise intolerance and dyspnea, atrial fibrillation, and, less commonly, signs of right heart failure. Patients with ASDs are also at risk for paradoxical emboli.

Repair of ASDs is recommended for those with a pulmonary to systemic flow ratio (Qp:Qs) exceeding 1.5:1.0. Despite the success of operative repair, there has been interest in developing a transcatheter-based approach to ASD repair to avoid the risks and morbidity of open heart surgery. A variety of devices have been researched. Technical challenges include minimizing the size of device so that smaller catheters can be used, developing techniques to properly center the device across the ASD, and ensuring that the device can be easily retrieved or repositioned, if necessary.

Several devices have been developed to treat PFO via a transcatheter approach, including the CardioSEAL® STARFlex™ Septal Occlusion System (NMT Medical), the Amplatzer® PFO Occluder (Amplatzer Inc., now St. Jude Medical, St. Paul, MN), the Figulla® ASD Occluder (Occlutech GmbH, Jena, Germany), and the CeraFlex™ ASD Occluder (Lifetech Scientific, Shenzhen, China). The STARFlex system is no longer manufactured. Transcatheter PFO occluders consist of a single or paired wire mesh discs that are covered or filled with polyester or polymer fabric that are placed over the septal defect. Over time, the occlusion system is epithelialized.

ASD occluder devices consist of flexible mesh disks that are delivered via catheter to cover the ASD.
Regulatory Status

**Patent Foramen Ovale Closure Devices**

In 2002, 2 transcatheter devices were cleared for marketing through a humanitarian device exemption (HDE) by the U.S. Food and Drug Administration (FDA) as a treatment for patients with cryptogenic stroke and patent foramen ovale (PFO): the CardioSEAL® Septal Occlusion System (no longer commercially available) and the Amplatzer® PFO Occluder. HDE approval is applicable to devices designed to treat a patient population of fewer than 4000 patients per year. This approval process requires the manufacturer to submit data on the safety and the probable clinical benefit. Clinical trials validating the device effectiveness are not required. The labeled indications of both limited the use of these devices to closure of PFO in patients with recurrent cryptogenic stroke due to presumed paradoxical embolism through a PFO and who have failed conventional drug therapy.

Following this limited FDA approval, use of PFO closure devices increased by more than 50-fold, well in excess of the 4000 per year threshold intended under the HDE. As a result, in 2006, FDA withdrew the HDE approval for these devices. At this time, FDA also reiterated the importance of randomized controlled trials (RCTs) of PFO closure devices versus medical therapy but noted that ongoing trials were hampered by slow enrollment. Withdrawal of the HDE approval was, in part, intended to spur greater enrollment in ongoing RCTs of these devices.

Currently, all uses of closure devices to treat PFO are off-label uses.

**Atrial Septal Defect Closure Devices**

At present, 2 devices have been approved by FDA through the premarket approval process for atrial septal defect (ASD) closure: the Amplatzer™ Septal Occluder (St. Jude Medical, Minneapolis, MN) and the GORE HELEX™ Septal Occluder (W.L. Gore & Associates, Newark, DE). In 2002, the Amplatzer Septal Occluder was approved for the occlusion of ASDs in the secundum position or in patients who have undergone a fenestrated Fontan procedure who required closure of the fenestration. Patients indicated for ASD closure have echocardiographic evidence of ostium secundum ASD and clinical evidence of right ventricular volume overload.

In August 2006, the GORE HELEX Septal Occluder was approved through the premarket approval process for the percutaneous, transcatheter closure of ostium secundum ASDs.

FDA product code: MLV.

**IV. RATIONALE**

**Transcatheter Device Closure of Patent Foramen Ovale**

**Transcatheter Patent Foramen Ovale Closure for Stroke Prevention**

Conventional therapy for cryptogenic stroke consists of either antiplatelet therapy (aspirin, clopidogrel, or dipyridamole given alone or in combination) or oral anticoagulation with warfarin. In general, patients with a known clotting disorder or evidence of preexisting
thromboembolism are treated with warfarin, and patients without these risk factors are treated with antiplatelet agents. Closure devices are nonpharmacologic alternatives to medical therapy for cryptogenic stroke in patients with a patent foramen ovale (PFO).

Evidence on the efficacy of PFO closure devices consists of 3 randomized controlled trials (RCTs), a few nonrandomized, comparative studies, and numerous case series. Meta-analyses of the published studies have also been performed.

**Randomized Controlled Trials**

**CLOSURE I Trial**
The Evaluation of the STARFlex Septal Closure System in Patients with a Stroke and/or Transient Ischemic Attack due to Presumed Paradoxical Embolism through a Patent Foramen Ovale (CLOSURE I) study was a multicenter, randomized, open-label trial of percutaneous closure versus medical therapy. A total of 909 patients, between the ages of 18 and 60 years, with cryptogenic stroke or transient ischemic attack (TIA) and a PFO were enrolled. Patients in the closure group received treatment with the STARFlex device and antiplatelet therapy. Patients in the medical therapy group took aspirin, warfarin, or both at the discretion of the treating physician. The primary end point was a composite of stroke/TIA at 2 years, death from any cause during the first 30 days after treatment, and death from neurologic causes at 2 years.

Of 405 patients in the closure group, 362 (89.4%) had successful implantation without procedural complications. At 6 months, echocardiography revealed effective closure in 315 (86.1%) of 366 patients. The composite primary outcome was reached by 5.5% of patients in the closure group and 6.8% of patients in the medical therapy group (adjusted hazard ratio [HR], 0.78; 95% confidence interval [CI], 0.45 to 1.35; p=0.37). Kaplan-Meier estimates of the 2-year rate of stroke were 2.9% in the closure group and 3.1% in the medical therapy group (adjusted HR=0.90; 95% CI, 0.41 to 1.98). Serious adverse events were reported by 16.9% of patients in the closure group versus 16.6% in the medical group. Adverse events that were increased in the closure group included vascular procedural complications (3.2% vs 0, p<0.001) and atrial fibrillation (5.7% vs 0.7%, p<0.001).

**RESPECT Trial**
The RESPECT trial was a multicenter RCT comparing PFO closure with medical therapy in 980 patients between the ages of 18 and 60 years with a previous cryptogenic stroke and documented PFO. Patients were randomly assigned to PFO closure with the Amplatzer Occluder, or to medical therapy. Medical therapy consisted of 1 of 4 regimens prescribed at the discretion of the treating physician: aspirin, aspirin plus dipyridamole, clopidogrel, or warfarin. The primary end point was a composite of fatal ischemic stroke, nonfatal ischemic stroke, or early death within 30 days of randomization. Mean follow-up for the entire group was 2.6±2.0 years.

A total of 9 events occurred in 499 patients assigned to closure, and 16 events occurred in 464 patients assigned to medical therapy. All events were nonfatal strokes. The HR for this outcome was 0.49, but this result was not statistically significant on the intention-to-treat (ITT) analysis.
(95% CI, 0.22 to 1.11; p=0.08). On per-protocol analysis, there was a statistically significant effect (HR=0.37; 95% CI, 0.14 to 0.96; p=0.03). On subgroup analyses, there were no statistically significant differences in outcomes, although there were trends for better outcomes in the closure group for patients with a substantial right-to-left shunt (p=0.07) and for patients with an atrial septal aneurysm (p=0.10). The rate of serious adverse events did not differ between the closure and medical therapy groups (23.0% vs 21.6%, p=0.65). Major bleeding (n=2) and cardiac tamponade (n=2) were the most frequent procedure-related adverse events.

**PC Trial**

The PC trial was a multicenter RCT comparing PFO closure with medical therapy in 414 patients younger than 60 years of age with a prior cryptogenic stroke or peripheral embolization and a documented PFO.5 Patients were recruited from 29 centers worldwide and randomly assigned to PFO closure with the Amplatzer device or to medical therapy. Recommended antiplatelet therapy in the closure group was aspirin plus ticlopidine or clopidogrel alone. Medical therapy in the control group was at the discretion of the treating physician, with the requirement that patients receive at least 1 appropriate medication. The primary end point was a composite of death, nonfatal stroke, TIA, or peripheral embolism. Median duration of follow-up was 4.1 years in the closure group and 4.0 years in the medical therapy group.

The primary outcome, after independent adjudication, occurred in 9 (3.4%) of 204 patients in the closure group compared with 11 (5.7%) of 210 patients in the medical group. The HR for this outcome was 0.63 (95% CI, 0.24 to 1.62; p=0.34) on ITT analysis. On per-protocol analysis, results were similar (HR=0.70; 95% CI, 0.27 to 1.85; p=0.48). There were no significant differences in rates of the individual components of the primary outcome, and there were no significant differences in outcome on subgroup analyses. The adverse event rate was 34.8% in the closure group and 29.5% in the medical therapy group.

**Systematic Reviews**

**Systematic Reviews of RCTs**

A large number of systematic reviews with meta-analyses of the 3 available RCTs have been published; several representative studies are summarized here. Rengifo-Moreno et al performed a combined analysis of the 3 RCTs previously discussed.6 The analysis included a total of 1150 patients randomized to PFO closure and 1153 patients randomized to medical therapy followed for a mean of 3.5 years. Two end points were included, recurrent vascular events and a combined end point of death plus recurrent vascular events. On combined analysis, there was a statistically significant reduction in recurrent vascular events with a pooled HR of 0.59 (95% CI, 0.36 to 0.97; p=0.04). For the composite outcome of death plus recurrent vascular events, combined analysis revealed a reduction for the closure group of borderline statistical significance (HR=0.67; 95% CI, 0.12 to 1.03; p=0.05). On subgroup analysis, there was a trend for greater benefit in patients with a substantial right-to-left shunt, although this result was not statistically significant (HR=0.35; 95% CI, 0.12 to 1.03; p=0.06).
Another meta-analysis of the same 3 RCTs was reported by Kitsios et al. This study used recurrent stroke as the primary outcome. The authors noted that the rates of recurrent stroke varied widely across the studies, thereby raising the possibility of ascertainment bias for this outcome. On combined analysis, the difference between groups was not statistically significant (HR=0.55; 95% CI, 0.26 to 1.18). Combined analysis was also performed for the composite outcomes reported in the trials, even though the composite outcomes were not defined in the same way. The combined result for the composite outcome was of borderline statistical significance (HR=0.67; 95% CI, 0.44 to 1.00). No significant differences were found on combined subgroup analyses from the trials.

Meta-analyses of the same 3 RCTs have also been reported by Chen et al, Hakeem et al, Khan et al, Kwong et al, Nagaraja et al, Ntaios et al, Pandit et al, Pineda et al, Udell et al, and Pickett et al. Results from these meta-analyses generally supported findings from previous meta-analyses. For the primary outcome of recurrent stroke or TIA, Chen et al found a pooled risk ratio with PFO device closure for recurrent stroke or TIA of 0.70 (95% CI, 0.47 to 1.04; p=0.08). Hakeem et al reported a pooled risk ratio for a composite outcome of death or recurrent stroke or TIA of 0.71 (95% CI, 0.48 to 1.06; p=0.09). Neither the Chen nor the Hakeem meta-analyses found significant differences between PFO device closure and medical management for the risk of death or adverse events. Similarly, the Udell and Pickett meta-analysis reported no significant association between overall risk of recurrent stroke or TIA and PFO device closure. However, after stratifying by device type, Pickett reported lower stroke risk after Amplatzer PFO device closure (HR=0.44; 95% CI, 0.21 to 0.95; p=0.037). Khan et al reported pooled analyses for the primary outcome of recurrent stroke, with a pooled effect-estimated HR for the primary outcome of recurrent stroke in patients treated with PFO device closure compared with medical management of 0.67 (95% CI, 0.44 to 1.00). In analysis only of the RESPECT and PC trials, which used the Amplatzer PFO occluder device, the HR for recurrent stroke in patients treated with PFO device closure was 0.54 (95% CI, 0.29 to 1.01). Similarly, Pandit et al reported sensitivity analyses including only the RESPECT and PC trials, and found that patients who received the Amplatzer PFO occluder device had a lower risk of recurrent strokes compared with medical therapy (HR=0.44; 95% CI, 0.21 to 0.94; p=0.03). In addition to pooled estimates for the risk of the primary outcomes of recurrent stroke, TIA, or death, Kwong et al reported pooled outcomes for risk of new-onset atrial fibrillation and found that PFO closure was associated with a significantly higher incidence of new-onset atrial fibrillation compared with medical therapy (OR=3.77; 95% CI, 1.44 to 9.87; p=0.007). In the analysis by Ntaios et al, the risk of new-onset atrial fibrillation with device closure compared with medical therapy was higher in patients who received the STARFlex device (5.14% vs 0.64%; odd ratio [OR], 8.30; 95% CI, 1.44 to 9.87) than the Amplatzer PFO Occluder device (1.28% vs 0.72%; OR=1.81; 95% CI, 0.60 to 5.42).

Stortecky et al reported results of a network meta-analysis comparing percutaneous PFO closure with medical therapy among patients with cryptogenic stroke. The authors included 10 publications on 4 RCTs: the PC and RESPECT trials comparing the Amplatzer PFO occluder with medical therapy, the CLOSURE I trial comparing the STARFlex PFO occluder with...
medical therapy, and an additional trial that compared head-to-head the Amplatzer, STARFlex, and Helix PFO occluder devices. Overall, patients randomized to PFO closure with the Amplatzer PFO occluder device were less likely to experience a stroke than those randomized to medical therapy (rate ratio, 0.39; 95% CI, 0.17 to 0.84). No significant differences were found between PFO closure with the STARFlex device in stroke risk or in TIA risk across treatment strategies.

Systematic Reviews of RCTs and Observational Studies
In 2015, Patti et al published a meta-analysis of randomized and observational studies comparing outcomes between 3 management strategies for patients with cryptogenic stroke and PFO: percutaneous closure, antiplatelet therapy, and anticoagulant therapy. The meta-analysis included 21 studies (total N=3311 patients). In an evaluation of the long-term efficacy and safety of PFO closure compared with “conservative therapy” (either antiplatelet or anticoagulant therapy), 11 observational studies were included, with a mean follow-up of 36 months. The incidence of recurrent stroke and/or TIA was significantly lower in patients undergoing percutaneous PFO closure (4.3%) than in those receiving antiplatelet therapy (9.2%; OR=0.50; 95% CI, 0.35 to 0.71; p<0.001), with no increased bleeding risk. The incidence of recurrent stroke and/or TIA did not differ significantly between those undergoing percutaneous PFO closure (4.3%) and those receiving anticoagulant therapy (6.3%; OR=0.66; 95% CI, 0.42 to 1.04; p=0.07); however, patients treated with PFO closure (1%) had a lower incidence of major bleeding (7.1%; OR=0.18; 95% CI, 0.09 to 0.36; p<0.001).

Cappodano et al published an updated systematic review and meta-analysis of studies that compared outcomes associated with medical management or PFO closure among patients with cryptogenic stroke. This analysis included the 3 RCTs previously described, along with 11 observational studies. In the randomized trials, PFO closure was not associated with significantly lower rates of stroke than medical therapy (HR=0.62; 95% CI, 0.34 to 1.11; p=0.10) or with lower rates of TIA (HR=0.77; 95% CI, 0.46 to 1.32; p=0.34). When the analysis was restricted to the RESPECT and PC trials, which used the Amplatzer PFO occluder device, PFO closure was significantly associated with lower recurrent stroke risk (HR=0.44; 95% CI, 0.20 to 0.95; p=0.04). In the observational studies, which included 2231 patients, PFO closure was significantly associated with lower rates of stroke than medical therapy (HR=0.23; 95% CI, 0.11 to 0.49; p<0.01).

Similarly, Wolfrum et al conducted a systematic review and meta-analysis of controlled trials that compared outcomes for PFO closure with medical management among patients with cryptogenic stroke, including 3 RCTs and 11 nonrandomized studies. Again, among the RCTs, there was no significant improvement in stroke risk with PFO closure compared with medical management. However, among the non-RCT studies, PFO closure was associated with a reduced risk of stroke (relative risk, 0.37; 95% CI, 0.20 to 0.67; p<0.001). In a time-to-stroke analysis that included 3 RCTs and 2 non-RCTs that had multivariable adjustments, PFO closure was associated with a borderline significant stroke risk reduction compared with medical therapy (HR=0.58; 95% CI, 0.33 to 0.99; p=0.047).
Systematic reviews of the observational studies have also been published comparing outcomes of PFO closure with medical therapy. Similar to the findings reported by Cappodano et al, these reviews are consistent in reporting that the combined rate of recurrent stroke is lower for patients treated with a closure device than with medical therapy.

Kitsios et al published a systematic review of observational studies and the single RCT in 2012. This review included 52 single-arm studies, 7 nonrandomized comparative studies, and 1 RCT. The combined incident rate for recurrent stroke was lower for patients treated with PFO (0.36 events/100 patient-years; 95% CI, 0.24 to 0.56) than for patients treated medically (2.53 events/100 patient-years; 95% CI, 1.91 to 3.35). The incident rate ratio was 0.19 (95% CI, 0.18 to 0.98), which indicated an approximately 80% reduction in the rate of strokes for the closure group. This systematic review noted that the incident rate for recurrent strokes in patients treated with closure devices was much lower in the RCT than in the observational studies, while the incident rate for recurrent stroke in patients treated medically was only slightly lower in the RCT than in the observational studies. This finding raises the possibility that ascertainment bias in the observational studies may have led to a spuriously low rate of recurrent stroke reported for patients treated with PFO closure.

Wohrle compared the results of 12 series of PFO closure (n=2016) with 8 series (n=998 patients) of medical therapy. At 2-year follow-up, the range of recurrent stroke was 0% to 1.6% for PFO closure and 1.8% to 9.0% for medical therapy. The combined annual incidence of stroke or TIA was 1.3% (95% CI, 1.0% to 1.8%) following PFO closure compared with 5.2% (95% CI, 4.4% to 6.2%) after medical therapy. In an earlier review, Khairy et al analyzed 6 series of medical therapy (n=895 patients) and 10 series of PFO closure (n=1355 patients). They noted differences in key clinical characteristics among patients in the 2 treatment groups. Patients treated with medical therapy were older, had a greater proportion of men, and had higher rates of smoking and diabetes. Patients treated with PFO closure were more likely to have had more than 1 cerebrovascular event. The recurrence rate at 1 year ranged from 0% to 4.9% in the PFO closure groups compared with 3.8% to 12.0% in the medical therapy groups. There was an estimated major complication rate (death, hemorrhage requiring transfusion, tamponade, need for surgical intervention, pulmonary embolus) for PFO closure of 1.5%, and a minor complication rate of 7.9%.

Abaci et al conducted a meta-analysis of studies of both PFO and ASD device closure procedures. The authors reviewed 203 articles, 111 of which reported ASD closure, 61 of which reported PFO closure, and 31 of which reported both closures. Among patients undergoing PFO closure, the pooled rate of major complications was 1.1% (95% CI, 0.9% to 1.3%), most commonly device embolization requiring surgery.
Nonrandomized Comparative Studies

Nonrandomized comparative studies of closure devices versus medical therapy vary in patient populations and how patients were selected for percutaneous closure. Representative nonrandomized comparative studies are discussed next.

Wahl et al performed a nonrandomized comparative study using propensity matching in 308 consecutive patients with stroke or TIA that was presumed due to a PFO. A total of 103 pairs of matched patients were compared on the primary composite outcome of stroke, TIA, or peripheral embolism. After a mean of 9 years of follow-up, the primary end point was reached by 11% of patients in the closure group and 21% in the medical therapy group (HR=0.43; 95% CI, 0.20 to 0.94; p=0.039). The main difference in the outcome measure seemed to be driven by differences in TIA, which occurred in 5% of closure patients compared with 14% of medical therapy patients.

Windecker et al compared 150 patients who underwent PFO closure between 1994 and 2000 with 158 medically treated patients over the same time period. The choice of therapy was based on clinician and/or patient preference. The patients who received closure differed from the medically treated patients on key clinical variables, including percentage with more than 1 cerebrovascular event and PFO size. At the 4-year follow-up, there was a nonstatistically significant trend toward lower recurrence of stroke or TIA in the PFO group (7.8% vs 22.2%, p=0.08).

Harrer et al reported on 124 patients with cryptogenic stroke and PFO treated over a 10-year period. Eighty-three patients were treated with medical therapy, 34 with percutaneous PFO closure, and 7 with surgical closure. After a mean follow-up of 52±32 months, annual recurrence rates of stroke did not differ between medical therapy and PFO closure (2.1% vs 2.9%, respectively, p=NS).

Paciaroni et al performed a prospective observational study on 238 consecutive patients with cryptogenic stroke and PFO treated at 13 Italian centers. A total of 117 patients were treated with antithrombotic therapy, and 121 patients were treated with a closure device, with the treatment decision made according to patient and physician preference. Procedure-related adverse events were reported in 8 (6.8%) of 121 patients treated with a closure device (4 patients with tachycardia, 2 patients with allergic reaction, 1 patient with atrial fibrillation, 1 patient with sepsis). After a 2-year follow-up, 10 (8.5%) of 117 patients in the medical therapy group had a recurrent neurologic event (stroke or TIA) compared with 7 (5.8%) of 121 patients in the closure device group (p=0.28). For recurrent stroke, the difference between the groups was statistically significant (8/117 [6.8%] in the medical therapy group vs 1/121 [0.8%] in the closure device group; p=0.018). On multivariate analysis, treatment with a closure device was a significant predictor of a reduced stroke rate (OR=0.1; 95% CI, 0.0 to 1.0; p=0.05) but not a significant predictor of the combined outcome of stroke or TIA (OR=0.1; 95% CI, 0.02 to 1.5; p=0.10).

Alushi et al reported results from a prospective, single-center study comparing outcomes after PFO device closure or medical management in 418 patients presenting with PFO and
cryptogenic stroke or TIA. Two hundred sixty-two patients underwent percutaneous PFO closure, while 156 were treated medically. The choice of medical intervention versus device closure was determined by the treating physician and patient. Percutaneous device closure was advised for patients younger than age 55 years, with recurrent cerebrovascular events, large interatrial right-to-left shunt, and nonlacunar ischemic events on neuroimaging. Patients undergoing percutaneous closure were younger and more frequently presented with a larger interatrial right-to-left shunt, previous venous thromboembolism, and hypercoagulability state. Patients treated medically presented more frequently with multiple cerebrovascular accident risk factors. In a multivariable model to predict the composite outcome of TIA, stroke, or all-cause mortality, treatment strategy (percutaneous closure vs medical management) was not significantly associated with the outcome (adjusted OR=1.1; 95% CI, 0.44 to 2.74; p=0.81), after controlling for age, multiple prior cerebrovascular events, and the presence of aspirin.

**Single-Arm Case Series**

Many case series have reported outcomes of PFO closure in an uncontrolled fashion; some examples follow. Cifarelli et al reported on 202 consecutive patients treated with a closure device for secondary prevention of thromboembolism. They reported no periprocedural deaths or strokes, and 1 case of device migration 24 hours after placement. Recurrence-free survival was reported in 99% of patients 55 years of age or younger, and 84% in patients older than age 55 years. Recurrence of thromboembolism was associated with a septal aneurysm, with all patients who experienced recurrence of thromboembolism having a septal aneurysm. Onorato et al reported on 256 patients with paradoxical embolism who received transcatheter closure of PFO. They reported a 98.1% full closure rate of the PFO and no neurologic events at a mean follow-up of 19 months. Martin et al also reported on a study of 110 patients with paradoxical embolism who received transcatheter closure of PFO. While the full closure rate of PFO was 71% at 2 years, only 2 patients had experienced a recurrent neurologic event. Windecker et al reported on a case series of 80 patients with a history of at least 1 paradoxical embolic event and who underwent closure of a PFO with various transcatheter devices. Patients were followed for a mean of 1.6 years. During 5 years of follow-up, the risk of an embolic event (TIA, stroke, peripheral embolism) was 3.4%, considered comparable to either medical therapy with anticoagulation or open surgical approaches. The presence of a postprocedural shunt was a predictor of recurrent thromboembolic events, emphasizing the importance of complete closure. Butera et al reported results from a registry that included 122 consecutive patients who underwent PFO closure with the Gore Septal Occluder device, 110 due to previous stroke or TIA and 12 due to history of migraines. During a median follow-up of 9 months (range, 1-18 months), 7 patients experienced atrial arrhythmias, 4 of whom required medical treatment. Chest radiographs showed 2 patients with evidence of wire fractures in the device; the devices were not removed and the patients experienced no problems from the wire fractures at 12 months of follow-up. Three patients experienced neurologic problems, 1 of which was recurrent migraines. None of these patients had residual shunt or intracardiac or device thrombi.
Other single-arm studies of transcatheter PFO closure in patients presenting with stroke or TIA and PFO have generally reported high rates of freedom from embolic events.36-41

No clinical trials have focused specifically on patients who failed medical therapy, as defined by recurrent stroke or TIA while on therapy. Many published studies include patients with first cryptogenic stroke patients with recurrent stroke or TIA, and generally do not analyze these patient populations separately. As a result, it is not possible to determine from the evidence whether PFO closure in patients who have failed medical therapy reduces the risk of subsequent recurrences.

Section Summary: Transcatheter Patent Foramen Ovale Closure for Stroke Prevention
The results of 3 RCTs do not support the conclusion that closure devices improve outcomes for patients with cryptogenic stroke and PFO. These trials, which included 1108 patients who underwent PFO closure and 1178 patients who received medical management, did not report significant improvement in outcomes with PFO closure. These results contrast with the results of nonrandomized, comparative studies and systematic reviews of observational studies, which have reported lower rates of recurrent events following closure of PFO. The discrepancy may arise from selection bias, because selection for closure devices or medical therapy may vary, resulting in populations that may have unequal distribution of confounders. Also, the rate of recurrent stroke for patients treated with closure devices in the RCT was much higher than combined estimates from observational studies. This raises the possibility that ascertainment bias in the observational studies may have resulted in a spuriously low stroke rate for patients treated with a closure device. Multiple meta-analyses of the 3 RCTs, with or without the addition of nonrandomized studies, reached varied conclusions, with some reporting a statistically significant reductions in recurrent events on pooled analysis and others reporting trends for benefit that were not statistically significant. While these results suggest that a benefit might be present, the evidence is inconclusive and the risk-benefit ratio not well-defined.

Transcatheter PFO Closure for Migraine
Migraine headache is another condition associated with PFO in epidemiologic studies. Noncontrolled observational studies have reported improvement in migraine headaches after PFO closure.

A sham-controlled randomized trial of PFO closure for refractory migraine headache was published in 2008.42 In this study, there was no significant difference observed in the primary end point of migraine headache cessation (3/74 in the implant group, 3 /73 in the sham group, p=0.51). The results of this study cast some doubt on the causal relationship between PFO and migraine.

In 2014, Lip and Lip published a primarily descriptive systematic review that included 20 studies of the prevalence of PFO in patients with migraines and 21 studies of the effects of PFO closure.43 In case series and cohort studies of patients with migraines, the prevalence of PFO in patients with migraines ranged from 14.6% to 66.5%. In case control studies, the prevalence of PFO in control patients ranged from 16.0% to 25.7%, while the prevalence of PFO in patients
who had migraine with aura or migraine without aura ranged from 26.8 to 96.0% and 22.6% to 72.4%, respectively. In the 18 case series that reported migraine outcomes after PFO closure, rates of resolution for migraine with aura and migraine without aura ranged from 28.6% to 92.3% and 13.6% to 82.9%, respectively. In 2 case-control studies that compared PFO closure and medication for migraines with intervention, improvement in migraine symptoms occurred in 83% to 87% compared with 0% to 21% of those managed medically. The single RCT identified (Dowson et al42) did not identify significant improvements in migraine symptoms in the PFO closure group.

In a study not included in the Lip and Lip systematic review, Biasco et al retrospectively compared transcatheter PFO closure with medical therapy in terms of impact on daily activities.44 The study included 217 patients with migraine and echocardiographic evidence of PFO, 89 of whom were managed with percutaneous PFO closure and 128 medically managed. PFO device closure was recommended for patients with migraine associated with previous suspected paradoxical embolic events, or for those without a history of suspected embolic events only in the case of severely disabling symptoms not controlled by multiple therapies. At a mean follow-up of 1299 days, both groups demonstrated significant improvements in scores on the Migraine Disability Assessment Questionnaire (MIDAS). However, there were no significant differences in MIDAS score between groups (p=0.204). The degree of residual right-to-left shunt was not associated with symptom perception.

**Section Summary: Transcatheter PFO Closure for Migraine**

Although observational studies have shown a possible association between PFO closure and reduction in migraine symptoms, 1 sham-controlled RCT did not demonstrate significant improvements in migraine symptoms after PFO closure. Nonrandomized studies have shown highly variable rates of migraine improvement after PFO closure.

**Transcatheter PFO Closure for Other Indications**

Several other medical conditions have been reported to occur more frequently in patients with PFOs, including platypnea-orthodeoxia syndrome, myocardial infarction with normal coronary arteries, decompression illness in response to change in environmental pressure, high altitude pulmonary edema, and obstructive sleep apnea.45 Evidence about clinical outcomes related to these conditions after PFO closure is limited to case reports and case series. For example, Mojadidi et al reported on a series of 17 patients who underwent transcatheter PFO closure for platypnea-orthodeoxia syndrome at a single institution, among whom 64.8% were classified as having improved oxygen saturation postprocedure.46

**Transcatheter Device Closure for ASDs**

At present, the Food and Drug Administration (FDA) has approved 2 devices for ASD closure: the Amplatzer Septal Occluder and the GORE HELEX Septal Occluder.
Overview of the Evidence

The evidence supporting the efficacy of devices for closure of ASD consists of nonrandomized comparative studies and case series. However, unlike PFO and cryptogenic stroke, the relation between closure of the ASD and improved clinical outcomes is direct and convincing, because the accepted alternative is open surgery. Results have generally shown a high success rate in achieving closure and low complication rates. FDA approval of the Amplatzer Septal Occluder was based on the results of a multicenter, nonrandomized study comparing the device with surgical closure of ASDs in which 423 patients received 433 devices. This study was subsequently published with slightly different numbers but similar quantitative findings. All patients had an ostium secundum ASD and clinical evidence of right ventricular volume overload. The results for the septal occluder group showed comparably high success rates with surgery; the 24-month closure success rate was 96.7% in the septal occluder group and 100% in the surgical group. While the pattern of adverse events was different in the 2 groups, overall, those receiving a septal occluder had a significantly lower incidence of major adverse events (p=0.03). Similarly, there was a significantly lower incidence of minor adverse events in the septal occluder group (p<0.001). It should be noted that the mean age of patients of the 2 groups differed significantly; in the septal occluder group, the mean age was 18 years while in the surgically treated group it was 6 years.

Systematic Reviews

A systematic review of percutaneous closure versus surgical closure was published by Butera et al in 2011. Thirteen nonrandomized comparative studies that enrolled at least 20 patients were included (total N=3082 patients). The rate of procedural complications was higher in the surgical group (31%; 95% CI, 21% to 41%) than in the percutaneous group (6.6%; 95% CI, 3.9% to 9.2%), with an OR for total procedural complications of 5.4 (95% CI, 2.96 to 9.84; p<0.000). There was also an increased rate of major complications for the surgical group (6.8%; 95% CI, 4% to 9.5%) compared with the percutaneous group (1.9%; 95% CI, 0.9% to 2.9%), for an OR of 3.81 (95% CI, 2.7 to 5.36; p=0.006).

In the Abaci et al meta-analysis of periprocedural complications after ASD/PFO device closures referenced earlier, for ASD closure, the pooled rate of major complications after ASD closures was 1.6% (95% CI, 1.4% to 1.8%).

Nonrandomized Comparative Studies

Other nonrandomized studies comparing transcatheter closure with surgery have shown similar success rates. Suchon et al, in a study of 100 patients, had a 94% success rate in the transcatheter closure group compared with a 100% success rate in the surgical group. A study by Berger et al showed identical 98% success rates in both treatment groups. A nonrandomized comparative analysis by Kotowycz et al reported that mortality rates at 5-year follow-up did not differ between transcatheter and surgical closure (5.3% vs 6.35% respectively, p=1.00), but that reintervention rates were higher for patients undergoing transcatheter closure (7.9% vs 0.3% respectively, p<0.004). Xu et al reported a retrospective analysis of transcatheter (n=35) and surgical (n=43) closure of ASD in patients with ASD and pulmonary stenosis.
rates did not differ significantly between groups, and all patients in both groups had complete correction of their ASD.

**Single-Arm Studies**

Single-arm studies have shown high success rates of ASD closure. The FDA study discussed previously was the largest series, with an enrollment of 442 patients.48 Fischer et al reported on use of the Amplatzer device in 236 patients with secundum ASD.54 In this evaluation study, closure was achieved in 84.7% of patients, and intermediate results were reported as excellent.

Javois et al reported outcomes up to 5 years for patients enrolled in the FDA Continued Access trial of the GORE HELIX Septal Occluder, which included 137 patients who underwent device implantation.55 Of 122 patients who completed follow-up at 1 year, 96.7% were defined as having clinical success, which was a composite of safety and efficacy. During follow-up, 5 adverse events considered major were seen: 2 device embolizations, both on day 1; 1 wire frame fracture incidentally discovered at 61 days postimplantation; 1 wire frame fracture associated with echocardiographic abnormalities and requiring surgical removal; and 1 unrelated death.

In another relatively large series including 336 patients with large secundum ASDs (balloon-stretched diameter ≥34 mm in adults or echocardiographic diameter >15 mm/m² in children) managed with the Amplatzer closure device, Baruteau et al reported closure rates of 92.6%.56 Other smaller studies have reported favorable results for transcatheter closure of ASD. In Du et al, transcatheter closure of ASD in 23 patients with deficient ASD rims was compared to transcatheter closure of 48 patients with sufficient ASD rims.57 The authors reported no significant differences in closure rates between the groups (91% for deficient rims, 94% for sufficient rims) along with no major complications at 24 hours and 6-month follow-up. Oho et al also reported a successful closure rate of 97% at 1-year follow-up in 35 patients receiving transcatheter closure of ASD, with only 1 patient complication of second-degree atrioventricular block noted.58 Brochu et al evaluated 37 patients with New York Heart Association (NYHA) functional class I or II physical capacity who underwent transcatheter closure of ASD.59 At 6-month follow-up, maximal oxygen uptake improved significantly, and the dimensions of the right ventricle decreased significantly. Twenty patients moved from NYHA class II to class I and improved exercise capacity. Numerous other small, single-arm studies have reported similar results, with procedural success approaching 100% and successful closure on follow-up reported in the 90% to 100% range.35

**Single-Arm Studies in Pediatrics**

Several single-arm studies have reported outcomes from transcatheter ASD closure in children and adolescents. Grohmann et al reported outcomes from a single-center series of children aged 3 to 17 years (median, 6 years) who were treated with the GORE Septal Occluder, with technical success in 41 (91%) of 45 patients in whom closure was attempted.60 Nyboe et al reported outcomes from 22 patients with secundum ASD who underwent ASD closure with the GORE Septal Occluder, 10 of whom were children younger than age 15, with technical success in all patients.61 Yilmazer et al reported improvements in echocardiographic parameters in a series of
25 pediatric patients (mean age, 9.02 years) who underwent successful transcatheter closure of secundum ASD.

**Section Summary: Transcatheter Device Closure of ASDs**

For patients with an ASD, nonrandomized comparative studies and single-arm case series have shown rates of closure using catheter-based devices approaching the high success rates of surgery. The percutaneous approach has a low complication rate and avoids the morbidity and complications of open surgery. If the percutaneous approach is unsuccessful, ASD closure can be achieved using surgery. Because of the benefits of percutaneous closure over open surgery, this evidence is considered sufficient to determine that transcatheter ASD closure improves outcomes in patients with an indication for ASD closure.

**Ongoing and Unpublished Clinical Trials**

Some currently unpublished trials that might influence this review are listed in Table 1.

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NCT: national clinical trial.  
\(^a\) Denotes industry-sponsored or cosponsored trial.

**Summary of Evidence**

The evidence for patent foramen ovale (PFO) closure with a transcatheter device in individuals who have PFO and cryptogenic stroke includes 3 randomized controlled trials (RCTs) comparing device-based PFO closure with medical therapy, multiple nonrandomized comparative studies, and multiple systematic reviews and meta-analyses of these studies. Relevant outcomes include overall survival, morbid events, and treatment-related morbidity and mortality. None of the 3 trials reported statistically significant improvements on their main outcome using intention-to-treat analysis. In all 3 trials, low numbers of outcome events in both groups limited the power to detect differences between groups. One trial showed a significant benefit for the closure group.
on per protocol analysis and another showed significant benefit on secondary outcomes. Meta-
analyses of these trials have also come to different conclusions, with some reporting a
statistically significant reduction in recurrent events on pooled analysis and others reporting a
trend for benefit that is not statistically significant. While these results suggest that a benefit
might be present, the evidence is not definitive and the risk-benefit ratio of transcatheter PFO
closure as an alternative to medical therapy is not well-defined. The evidence is insufficient to
determine the effects of the technology on health outcomes.

Given the conflicting findings from multiple systematic reviews related to the use of PFO closure
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determine qualitatively that the technology results in a meaningful improvement in the net health outcome.

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

In response to requests, input was received from 2 academic medical centers (1 of which provided 2 responses) and no specialty societies while this policy was under review in 2016. Input was mixed about the medical necessity of closure devices for PFO in patients with cryptogenic stroke or transient ischemic attack due to presumed paradoxical embolism through the PFO. There was consensus that closure devices for PFO in patients with other conditions (eg, migraine, platypnea-orthodeoxia syndrome) is not medically necessary.

**Practice Guidelines and Position Statements**

**American College of Chest Physicians**
The American College of Chest Physicians (ACCP) published guidelines on antiplatelet and antithrombotic therapy in 2012, which updated 2008 guidelines. The 2012 guidelines contained the following statements about the treatment of patients with PFO:

- “In patients with asymptomatic patent foramen ovale (PFO) or atrial septal aneurysm, we suggest against antithrombotic therapy (Grade 2C).”
- “In patients with cryptogenic stroke and PFO or atrial septal aneurysm, we recommend aspirin (50-100 mg/d) over no aspirin (Grade 1A).”
- “In patients with cryptogenic stroke and PFO or atrial septal aneurysm, who experience recurrent events despite aspirin therapy, we suggest treatment with (VKA [vitamin K antagonists] therapy) (target INR [international normalized ratio], 2.5; range, 2.0-3.0) and consideration of device closure over aspirin therapy (Grade 2C).”
- “In patients with cryptogenic stroke and PFO, with evidence of DVT [deep vein thrombosis], we recommend VKA therapy for 3 months (target INR, 2.5; range, 2.0-3.0) (Grade 1B) and consideration of device closure over no VKA therapy or aspirin therapy (Grade 2C).”

The 2008 ACCP guidelines compared outcomes from medical management and percutaneous closure in patients with PFO and cryptogenic stroke. ACCP concluded that there was no differences in risk of death or between major adverse clinical events between patients with cryptogenic stroke who underwent medical management and those who underwent percutaneous closure procedures.

**American Academy of Neurology**
The American Academy of Neurology published guidelines in 2004 stating the evidence was inconclusive on the comparative efficacy of PFO closure devices and medical therapy.
guidelines did not offer specific recommendations as to when PFO closure devices should be used.

**American Heart Association and American Stroke Association**

In 2014, the American Heart Association (AHA) and American Stroke Association published updated guidelines on the prevention of stroke in patients with ischemic stroke or transient ischemic attack (TIA). The guidelines list the following recommendations for device-based closure for PFO:

“For patients with a cryptogenic ischemic stroke or TIA and a PFO without evidence for DVT, available data do not support a benefit for PFO closure (Class III; Level of Evidence A).”

“In the setting of PFO and DVT, PFO closure by a transcatheter device might be considered, depending on the risk of recurrent DVT (Class IIb; Level of Evidence C).”

**American College of Cardiology and American Heart Association**

Guidelines issued by the American College of Cardiology and AHA in 2008 on the management of congenital heart disease recommended closure of an ASD by either percutaneous or surgical methods for several indications. For sinus venosus, coronary sinus, or primum ASD, however, surgery rather than percutaneous closure was recommended.

**U.S. Preventive Services Task Force Recommendations**

Not applicable.

**Medicare National Coverage**

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

### V. Definitions

**Anticoagulant** is an agent that delays or prevents blood coagulation.

**Atria** are the upper chambers of the heart.

### VI. Benefit Variations

The existence of this medical policy does not mean that this service is a covered benefit under the member’s contract. Benefit determinations should be based in all cases on the applicable contract language. Medical policies do not constitute a description of benefits. A member’s individual or group customer benefits govern which services are covered, which are excluded, and which are subject to benefit limits and which require preauthorization. Members and providers should consult the member’s benefit information or contact Capital for benefit information.
VII. DISCLAIMER

Capital’s medical policies are developed to assist in administering a member’s benefits, do not constitute medical advice and are subject to change. Treating providers are solely responsible for medical advice and treatment of members. Members should discuss any medical policy related to their coverage or condition with their provider and consult their benefit information to determine if the service is covered. If there is a discrepancy between this medical policy and a member’s benefit information, the benefit information will govern. Capital considers the information contained in this medical policy to be proprietary and it may only be disseminated as permitted by law.

VIII. CODING INFORMATION

Note: This list of codes may not be all-inclusive, and codes are subject to change at any time. The identification of a code in this section does not denote coverage as coverage is determined by the terms of member benefit information. In addition, not all covered services are eligible for separate reimbursement.

Investigational: therefore not covered when used for closure of patent foramen ovale

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<td>CAC 7/26/11 Adopted BCBA for PFO and ASD. Added list of labeled indications for Amplatzer Septal Occluder and GoreHelex Septal Occluder. Deleted information related to closure for PDA since it appears this procedure is a standard medical practice using an FDA approved device. Changed title to Closure Devices for Patent Foramen Ovale, and Atrial Septal Defects (ASD) (Formerly Closure Devices for Patent Foramen Ovale, Patent Ductus Arteriosus and Atrial Septal Defects). Minor wording changes to policy statements but intent is unchanged.</td>
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# Medical Policy

**Policy Title**

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<th>Policy Title</th>
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<tr>
<td>CLOSURE DEVICES FOR PATENT FORAMEN OVALE, AND ATRIAL SEPTAL DEFECTS (ASD)</td>
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**Policy Number**

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<td>MP-1.039</td>
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**CAC 8/28/12** Consensus review. References updated. No changes to policy statements. FEP variation added. 
Codes reviewed klr

**CAC 7/30/13** Consensus review. References updated. No changes to the policy statements. Policy guidelines added. Admin code review complete.


**CAC 3/24/15** Consensus review. No change to policy statements. References and rationale updated. Policy coded.

**CAC 3/29/16** Consensus review. No change to policy statements. References and rationale updated. Removed the Medicare variation referencing IOM 100-02 Chapter 14 Medical Devices. No mention of coverage criteria for these devices. Coding reviewed.

**Admin Update 11/9/16**– Variation Reformatting.

**Administrative update 11/18/16.** Reference section update.

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