## Title

SCAI expert consensus statement on operator and institutional requirements for PFO closure for secondary prevention of paradoxical embolic stroke



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CLINICAL DECISION MAKING

# SCAI expert consensus statement on operator and institutional requirements for PFO closure for secondary prevention of paradoxical embolic stroke

## The American Academy of Neurology affirms the value of this statement as an educational tool for neurologists.

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## Abstract

Until recently, evidence to support Patent Foramen Ovale (PFO) closure for secondary prevention of recurrent stroke has been controversial. Publication of high-quality evidence from randomized clinical trials and the subsequent FDA approval of two devices for percutaneous PFO closure is expected to increase the volume of PFO closure procedures not only in the United States but worldwide. As this technology is disseminated broadly to the public, ensuring the safe and efficacious performance of PFO closure is essential to mitigate risk and avoid unnecessary procedures. This document, prepared by a multi-disciplinary writing group convened by the Society for Cardiovascular Angiography and Interventions and including representatives from the American Academy of Neurology, makes recommendations for institutional infrastructure and individual skills necessary to initiate and maintain an active PFO/stroke program, with emphasis on shared decision making and patient-centered care.

**KEYWORDS**

ASD/PDA/PFO, comparative effectiveness/patient centered outcomes research, closure, evidence-based medicine, structural heart disease intervention

## 1 | PREAMBLE

Cryptogenic stroke in young to middle-aged individuals represents a significant problem in terms of disability and societal costs. The FDA approval of the Amplatzer Patent Foramen Ovale (PFO) Occluder in October 2016, and the Gore Cardioform device in March 2018, represents an important nonpharmacologic treatment to reduce the risk of recurrent stroke. These approvals cap an almost two-decade journey in

  

the United States in which several devices have been used off-label, some under a humanitarian device exemption (HDE) and others as part of randomized clinical trials. Since PFO closure using FDA approved devices with clearly stated indications for use are now available in general clinical practice, it is essential that physician stakeholders ensure the safe promulgation of this technology and establish criteria for the performance of these procedures that will be used in granting initial and ongoing privileges. These criteria are offered to support The Joint Commission mandate that medical staff privileges be granted based on professional criteria specified in the medical staff bylaws to ensure safe and effective patient-centered care. As an extension of this concept, the Society for Cardiovascular Angiography and Interventions (SCAI) and representatives from the American Academy of Neurology (AAN) agreed to provide recommendations to institutions and interested physicians for the establishment and maintenance of PFO closure programs. Since PFO closure is considered a nascent technology the recommendations contained herein initially rely on expert consensus and the lessons learned from clinical trials. As experience with PFO closure grows, these recommendations will be revised and updated based on expanded expertise and published data. However, the recent FDA approval of two percutaneous PFO occluder devices underscores the need to make initial recommendations now to provide a starting point for future modifications. The recommendations that follow were reviewed by the entire writing committee, with a majority required in order to be incorporated.

In accordance with SCAI policies on relationships with industry and other entities (RWI), relevant author disclosures are included in Supporting Information Table S1. To avoid actual, potential, or perceived conflicts of interest because of industry relationships or other personal conflicts, members of the writing committee and the peer reviewers of this document were asked to disclose all present or prior (within 12 months before the initiation of this clinical document) potential conflicts. The writing committee includes a majority of members without relevant RWI. Authors with relevant RWI were not permitted to draft or vote on content or recommendations pertaining to their RWI. RWI were reviewed during conference calls and updated as changes occurred. The work of the writing committee was supported exclusively by SCAI without commercial support. Writing committee members donated their time for the preparation of this document. Conference calls of the writing committee were closed and attended only by committee members and society staff. The respective executive boards of the two professional societies provided final review and approval of the document.

SCAI and AAN hope that adherence to the recommendations in this document will ensure safe and effective PFO closure technology dissemination for prevention of recurrent PFO mediated stroke in the United States and other countries to reduce the risk of recurrent ischemic stroke in patients with stroke due to a presumed paradoxical embolism.

## 2 | INTRODUCTION

Stroke is the fifth most common cause of death and the leading cause of preventable disability in the United States. There are approximately 795,000 strokes that occur each year of which 87% are considered ischemic.[1] The societal cost in terms of healthcare, medications and missed work days is estimated to be in excess of $34 billion dollars. Cryptogenic stroke, defined as brain infarction that is not attributed to definite large vessel atherosclerosis, small artery disease, or embolism from cardiac abnormalities despite extensive vascular, serologic, and cardiac evaluation, represents from 10–40% of ischemic strokes.[1] PFO is present in 25% of the general population and generally thought to be a benign persistence of a remnant of the fetal circulation.[2] Paradoxical embolism, defined as a systemic thrombotic embolism of venous or right atrial origin is presumed to pass through a right-to-left cardiac shunt, usually a PFO, but rarely a pulmonary arterio-venous malformation or other right to left shunt, and is thought to be the etiologic mechanism in some patients with cryptogenic stroke. Such patients tend to be younger and have a paucity of traditional stroke risk factors.

Cryptogenic stroke patients have traditionally been treated with a variety of oral anti-platelet agents and anticoagulants alone or in combination to reduce the risk of recurrent stroke. Despite this, there is a lingering 4.5% risk of recurrent stroke over 4 years of follow-up in an updated meta-analysis of randomized trials.[3] Such events in young patients can lead to devastating lifelong consequences and long term disability. Optimal medical therapy to prevent recurrent stroke in this patient population has not been studied in a randomized clinical trial. Since oral anti-coagulants have not been proven to confer additional protection over anti-platelet therapy but have been associated with increased bleeding complications the AAN has recommended anti-platelet therapy for these patients.[4]

There has been interest in seeking an alternative, nonpharmacologic therapy that may, more effectively, reduce recurrent stroke risk in these patients without adverse consequences. Several approaches to PFO closure have evolved over the years including surgical suturing and endovascular closure most often using devices with a double disc design and a connecting waist. The appositional forces applied by the two discs on either side of the septum exert pressure on the septum primum and septum secundum closing the PFO.

The evolution of approval for device-mediated PFO closure has spanned two decades. Prior to 2006, PFO closure in the United States was only permitted under an FDA humanitarian device exemption (HDE). In 2006, the number of patients exceeded the regulatory mandated limit of 4,000 patients and the HDE was voluntarily withdrawn. Over the ensuing years randomized controlled trials (RCTs) were initiated using several different devices. Early trials were hampered by poor device design, poor enrollment, off label PFO closure, selection bias, and excessively liberal enrollment criteria. Initial PFO closure device designs were hampered by high residual shunt rates and thrombosis. As a result, the early RCTs for PFO closure versus medical therapy did not meet the primary endpoints. Despite this a patient-level meta-analysis of the early trials demonstrated superiority of PFO device closure over medical therapy.[5] Four contemporary RCTs of PFO closure using more advanced device designs and more stringent enrollment criteria have recently been completed and published.[6–9] Each of these trials has consistently shown a statistically significant advantage of PFO device closure over medical therapy in preventing recurrent ischemic events in young to middle aged patients with unexplained stroke and a PFO. Interestingly, the most recently published of the RCTs, the DEFENSE-PFO trial, from South Korea studied only patients with large shunts or atrial septal aneurysms

**TABLE 1** Contemporary randomized trials on percutaneous Closure of patent foramen Ovale

| Trial name | Year published | PFO device used | Control arm(s) | *N* | Mean follow-up (years) | Primary endpoint | Results | | | Conclusions |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | Closure | Control | *p* value | |
| CLOSURE I | 2012 | STARFlex (NMT medical) | Aspirin and/or warfarin (INR 2–3) | 909 | 2 | Composite of stroke/TIA, all-cause mortality, death from neurologic causes | 5.5% | 6.8% | HR 0.78<br>95% CI 0.45–1.35<br>*p* = 0.37 | Closure is not superior to medical therapy |
| PC trial | 2013 | Amplatzer PFO Occluder (Abbott structural) | Antiplatelet therapy or oral anticoagulation | 414 | 4.1 | Composite of death, nonfatal stroke, TIA, or peripheral embolism | 3.4% | 5.2% | HR 0.63<br>95% CI 0.24–1.72<br>*p* = 0.34 | Closure is not superior to medical therapy |
| RESPECT | 2013 | Amplatzer PFO Occluder (Abbott structural) | Aspirin or warfarin or Clopidogrel, or aspirin with extended release dipyridamole | 980 | 2.6 | Composite of recurrent nonfatal ischemic stroke, fatal ischemic stroke, or early death after randomization | Intention-to-treat:<br>0.66 events per 100 pts/year<br><br>As-treated<br>0.39 events per 100 pts/year | Intention-to-treat:<br>1.38 events per 100 patients/year<br><br>As treated<br>1.45 events per 100 patients/year | HR 0.49<br>95% CI 0.22–1.11<br>*p* = 0.08<br><br>HR, 0.27<br>95% CI 0.10–0.75<br>*p* = 0.007 | No significant benefit for closure (intention-to treat-analysis)<br>Closure is superior to medical therapy (as-treated analysis) |
| RESPECT (long-term follow-up) | 2017 | Amplatzer PFO Occluder (Abbott structural) | Aspirin or warfarin or Clopidogrel, or aspirin with extended release dipyridamole | 980 | 5.9[a] | Composite of recurrent nonfatal ischemic stroke, fatal ischemic stroke, or early death after randomization | Intention-to-treat:<br>0.58 events per 100 pts/year<br><br>New stroke of unknown mechanism:<br>0.31 events per 100 pts/year | Intention-to-treat:<br>1.07 events per 100 pts/year<br><br>New stroke of unknown mechanism:<br>0.86 events per 100 pts/year | HR 0.55<br>95% CI 0.31–1.0<br>*p* = 0.046<br><br>HR 0.38<br>95% C, 0.18–0.79<br>*p* = 0.007 | Closure is superior to medical therapy on extended follow-up in intention-to-treat analysis |
| CLOSE | 2017 | Any CE marked PFO device | (1) *Antiplatelet arm*: Aspirin or Clopidogrel or aspirin with extended release dipyridamole<br>(2) *Oral anticoagulant arm*: Vitamin K antagonists or NOACs | 663 | 5.3 | Recurrent fatal or nonfatal stroke | Closure vs. antiplatelet therapy: 0 | Closure vs. antiplatelet therapy:<br>4.9% 5-year estimate<br><br>Anticoagulant vs. antiplatelet therapy:<br>1.5% vs. 3.8%, respectively, 5-year estimate | Closure vs. antiplatelet therapy:<br>HR 0.03<br>95% CI 0–0.26<br>*p* < 0.001<br><br>Anticoagulant vs. antiplatelet therapy:<br>HR 0.43<br>95% CI 0.1–1.5<br>*p* = 0.17 | Closure is superior to antiplatelet in patients with ASA or PFO with large shunt<br><br>Anticoagulant is equivalent to antiplatelet therapy |
| REDUCE | 2017 | Helex Septal Occluder and Cardioform Septal Occluder (W.L. Gore and Associates) | Aspirin or Clopidogrel or aspirin with dipyridamole | 664 | 3.2[a] | (1) recurrent stroke<br>(2) new brain infarct inclusive of silent brain infarct (SBI) | Ischemic stroke:<br>0.39 strokes per 100 patient years<br><br>[b]New brain infarct:<br>5.7% | Ischemic stroke:<br>1.71 strokes per 100 patient years<br><br>New brain infarct:<br>11.3% | HR 0.23<br>95% CI 0.09–0.62<br>*p* = 0.002<br><br>RR0.51<br>95% CI 0.29–0.91<br>*p* = 0.04 | Closure is superior to antiplatelet therapy |

*(Continues)*

**TABLE 1** (Continued)

| Trial name | Year published | PFO device used | Control arm(s) | *N* | Mean follow-up (years) | Primary endpoint | Results | | | Conclusions |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | Closure | Control | *p* value | |
| DEFENSE-PFO | 2018 | Amplatzer PFO Occluder (Abbott structural) | Aspirin or aspirin and Clopidogrel, or aspirin and Cilostazol, or warfarin | 120 | 2.8[a] | Stroke, vascular death or TIMI-defined major bleeding | Ischemic stroke: 0<br>2 year event rate 0<br>New ischemic lesion on MRI: 8.8% | Ischemic stroke: 10.5%<br>2 year event rate 12.9%<br>New ischemic lesion on MRI: 18.4% | $p = 0.023$<br>Log-rank $p = 0.013$<br>$p = 0.24$ | Closure in patients with high risk PFO characteristics resulted in lower rate of ischemic stroke versus medical therapy |

N: Number of patients.
CLOSURE I: 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.
PC: Percutaneous closure of patent foramen ovale using the AMPLATZER® PFO occluder with medical treatment in patients with cryptogenic embolism.
RESPECT: Randomized evaluation of recurrent stroke comparing PFO closure to established current standard of care treatment.
CLOSE: Closure of patent foramen ovale or anticoagulants versus antiplatelet therapy to prevent stroke recurrence.
REDUCE: GORE® HELEX® Septal Occluder/GORE® CARDIOFORM septal occluder and antiplatelet medical management for reduction of recurrent stroke or imaging-confirmed TIA in patients with patent foramen ovale (PFO).
INR: International normalized ratio.
TIA: Transient ischemic attack.
PFO: Patent foramen ovale.
ASA: Atrial septal aneurysm.
HR: Hazard ratio.
RR: Relative risk.
CI: Confidence interval.
Pts: Patients.
Yr: Year.
NOACs: Novel oral anticoagulants.
TIMI: Thrombolysis in myocardial infarction.
[a] Median follow-up reported.
[b] New brain infarction defined as clinical ischemic stroke or silent brain infarction.

was prematurely terminated after publication of the other recent RCTs due to safety concerns.[11] There have now been six RCTs completed comparing PFO closure to best medical therapy Table 1) and a meta-analysis of these trials encompassing 3,440 patients with a mean follow-up of 4 years demonstrated a recurrent stroke rate of 2% for PFO closure versus 4.5% for medical therapy.[5]

The landmark study, *Randomized Evaluation of Recurrent Stroke Comparing PFO Closure to Established Current Standard of Care Treatment (RESPECT)* trial compared medical therapy with one or more antiplatelet medications or warfarin alone with PFO closure using the Amplatzer PFO Occluder (Abbott Structural) in 980 patients with cryptogenic stroke was initially reported in 2013 after 25 primary end-points had occurred.[10] The primary efficacy endpoint was nonfatal ischemic stroke, fatal ischemic stroke or early death after randomization. With a mean follow-up of 2.6 years, the intention-to-treat cohort did not reach significance, although both the prespecified per-protocol and the as-treated analyses suggested superiority of closure over medical therapy. In May 2016 the FDA convened an expert advisory panel to review longer term follow-up results from RESPECT and the panel voted in favor of approval.[11] The FDA also requested supplemental long-term analysis of the RESPECT patient cohort before finalizing device approval in October 2016 (Approval announcement). Long-term follow-up with a mean of 5.9 years now demonstrated a significant reduction in recurrent ischemic stroke in the closure arm as compared to medical therapy (18 vs. 29 had events HR, 0.55; 95% CI, 0.305–1.0; $p = 0.046$). The reduction in new stroke of unknown mechanism was significant in the closure arm and superior to medical therapy (10 vs. 23 had events, HR, 0.38; 95% CI, 0.18–0.79; $p = 0.007$). Based upon extended follow-up results of the RESPECT trial, the FDA approved the Amplatzer PFO Occluder for use as the first device for PFO closure in the United States *to reduce the risk of recurrent ischemic stroke in patients, predominantly between the ages of 18 and 60 years, who have had a cryptogenic stroke due to a presumed paradoxical embolism, as determined by a neurologist and a cardiologist following an evaluation to exclude known causes of ischemic stroke.*[12]More recently, on March 30, 2018, the FDA approved a second device, the Gore Cardioform™ Septal Occluder for PFO Closure, based on the results of the REDUCE trial.[8] The REDUCE trial randomized 664 patients with cryptogenic stroke to PFO closure versus treatment with antiplatelet therapy. At a median follow-up of 3.2 years of follow-up the study demonstrated a significant reduction in the rate of ischemic stroke (1.4 vs. 5.4% HR, 0.23; 95% [CI], 0.09 to 0.62; $p = 0.002$) and the incidence of a composite of new brain infarction on MRI and clinical events (5.7 vs. 11.3% relative risk, 0.51; 95% CI, 0.29 to 0.91; $p = 0.04$) favoring device closure.

Percutaneous PFO closure techniques have the potential to have a major, positive impact on treatment of patients with paradoxical embolic stroke and fulfills an important unmet clinical need. PFO occlusion techniques are relatively safe when carried out by experienced operators. This expert consensus document statement outlines our proposed institutional and operator requirements to assist with the implementation of credentialing standards and help providers to participate responsibly, safely, and effectively in this new and important clinical field. The safe application of PFO closure requires specific cognitive and technical skillsets and respect for the potential for serious procedure and device-related complications of these interventions. Procedural specialists performing PFO closure will come from a variety of backgrounds, including interventional, structural, and pediatric cardiology. It is expected that physicians will operate in the context of a multidisciplinary team (MDT) to optimize patient selection and clinical benefit. A PFO closure program should be institutional in nature, with assessments and therapy delivered across multiple disciplines. Patient centered care defined by the Institute of Medicine as "health care that establishes a partnership among practitioners, patients, and their families to ensure that decisions respect patients' wants, needs, and preferences and that patients have the education and support to make decisions and participate in their own care". Patient-centered care will be a guiding principle in the implementation of these novel interventional therapies. Physicians participating in PFO closure programs must work together in the context of a larger system of health that includes stakeholders from multiple disciplines. The notion of MDT s was first validated in the surgical arena and has gained traction more recently with the evolution of percutaneous valve therapies.[13] It is therefore expected that recurrent stroke prevention in the cryptogenic stroke patient population will be a collaborative effort of physician and nonphysician experts that may include vascular neurologists, interventional cardiologists, hematologists, imaging experts, primary care providers, and others.

## 3 | BACKGROUND

Historically, societal guideline documents regarding management of patients with cryptogenic stroke and a PFO have not supported device closure except in highly restricted patient subsets such as patients with deep vein thrombosis.[14] This was the result of a lack of RCT data supporting this procedure related to poorly designed early trials, which included patients with TIA, and using devices with high rates of device associated thrombus, atrial fibrillation, and residual shunt.[15] Recently published contemporary RCTs comparing device closure of PFO to best medical therapy using contemporary devices with longer follow-up demonstrate the superiority of PFO closure over medical therapy in this patient population. Based on the totality of evidence from RCT data, the FDA has now approved two devices for PFO closure for patients with paradoxical embolic stroke. While there are a variety of devices for PFO closure available in other countries through their regulatory pathways, the Amplatzer PFO Occluder and the Gore Cardioform device are currently the only devices approved in the US for this indication. We can anticipate that PFO closure in the management of patients with unexplained stroke will assume a greater role as the guideline documents regarding management of these patients are revised. This has already begun as evidenced by the recently published Canadian Stroke Best Practice Recommendations stating that PFO closure is suitable for patients in alignment with the FDA labeling with level of evidence A.[16] As the penetration of percutaneous PFO closure increases, physicians have a fiduciary responsibility to ensure the safe and effective application of these technologies. Therefore, it is essential that stakeholders have a thorough understanding of the cognitive and technical skillsets surrounding PFO closure.

As this procedure spreads into the wider public domain, training of new proceduralists needs to be carried out in a controlled, systematic fashion to ensure optimal results with respect to efficacy and safety. A PFO closure program must be established in the context of a larger stroke program that includes all stakeholders such as cardiologists, stroke neurologists, hematologists, and imaging specialists. In addition, there are specific cognitive and technical skillsets essential for proceduralists to master when performing PFO closure. Physicians performing PFO closure should have knowledge of principles surrounding ischemic stroke, including:

1. Etiologies of ischemic stroke.
2. Clinical syndromes that mimic stroke.
3. Stroke phenotype classification systems such as ASCOD.[17]
4. Stroke risk scoring systems including (CHA2DS2-VASC) and risk of paradoxical embolus (RoPE) scores.[18,19]
5. Interpretation of invasive and noninvasive stroke neuroimaging results.
6. RCTs comparing PFO closure to medical therapy.
7. Medical therapies for prevention of recurrent stroke including anti-platelet and anti-coagulants
8. Diagnostic evaluation of patients with ischemic stroke
9. Cardiac imaging techniques in patients with ischemic stroke potentially related to a cardiac source of embolism including transthoracic, transesophageal, intracardiac, and contrast echocardiography and transcranial Doppler (TCD).[20]
10. Indications and contraindications for PFO closure.
11. Knowledge and understanding of shared decision making and working in the context of a MDT.[21]

Proceduralists planning on developing a PFO closure program must understand ischemic stroke in terms of how it presents clinically, predisposing risk factors, and how recurrent stroke is prevented using traditional pharmacologic therapy. The proper application of adjunctive diagnostic testing in stroke patients is important. Certain stroke syndromes are more likely to be cardio-embolic. Appropriate use and interpretation of noninvasive brain imaging modalities including CT, MRI, and ultrasound is vital for establishing the cause of stroke and screening patients for possible PFO closure. Multiple cortical strokes in different vascular distributions of different ages are more likely to be embolic than a lacunar stroke. These differences must be recognized since their treatments to prevent recurrent events are different. This highlights the importance of close collaboration between cardiovascular specialists and stroke neurologists for any patient presenting with a possible unexplained ischemic stroke and being considered for PFO closure. Establishing the diagnosis of unexplained, or cryptogenic stroke, implies that an exhaustive search for secondary causes has been carried out and should focus on excluding all forms of congenital and acquired cardiovascular disease. Searching for disorders of coagulation is also important in select patients and may involve hematologists as part of the MDT. Detection of occult atrial fibrillation using long-term monitoring (see below) is also essential due to the strong association of nonvalvular atrial fibrillation and ischemic stroke in certain patient subsets. Scoring systems have been validated which predict the probability that an unexplained stroke was due to a PFO-mediated paradoxical embolism and relies on young age, absence of traditional stroke risk factors and infarct location on neuroimaging to establish attributable risk.[19] Such scoring systems may be useful in assessing the likelihood that a stroke was caused by a PFO and in assessing the risk–benefit ratio of PFO closure.

Evaluation of patients with suspected cryptogenic stroke should include echocardiography, either transthoracic and/or transesophageal.[22] A nuanced understanding of image interpretation of these modalities as well as intra-cardiac echocardiography is required for proper patient selection as well as procedural guidance (Table 2). Echocardiography should include echo contrast, usually in the form of agitated saline microbubbles. Transesophageal echocardiography (TEE) provides more detailed morphological data on the interatrial septum with regards to tunnel length, thickness of the septum secundum, the presence of a Eustachian valve or Chari network, and the magnitude of the atrial shunt, all of which is essential for procedural planning.[23,24] The presence of a large sized-PFO associated with a large shunt or an atrial septal aneurysm is important to recognize and increases the risk of recurrent stroke.[25] TCD can also aid in detecting CNS-directed PFO-mediated shunting.[26]

Proper patient selection for PFO closure is critical in order to treat the patients who will benefit the most and avoid unnecessary procedures. The risk/benefit ratio of performing PFO closure should be weighed carefully especially in patients with a low RoPE, for example, those with a RoPE score of less than 7.[27] The RoPE score was derived form a large database of patients with cryptogenic stroke and PFO and incorporates six variables (hypertension, diabetes, history of stroke, smoking, cortical infarct on imaging, and age) to assist in determining the likelihood that a stroke is related to paradoxical embolism.[28] The RoPE score should not be used in isolation since it does not take into consideration a recent history of DVT, stroke shortly after straining, or echocardiographic features suggestive of a PFO favorable for transmitting emboli (i.e., large size, atrial septal aneurysm). The FDA approval of both PFO Occluders clearly mandates that patients be evaluated by both a cardiologist and a neurologist prior to consideration of PFO closure. The "Heart-Brain Team" fosters shared decision making between the patient and a MDT of providers, promotes proper patient selection, serves to select only appropriate candidates for PFO closure while mitigating unnecessary risks.[29]

## 4 | PROCEDURAL AND OPERATOR REQUIREMENTS

Proceduralists performing PFO closure will come from a variety of different backgrounds including interventional cardiology, structural heart disease (SHD), and pediatric interventional cardiology. Regardless of background all operators must possess the same technical skillsets that would include:

1. Use of various imaging modalities for procedural guidance including fluoroscopy, TEE and/or intracardiac echocardiography (ICE)
2. Manipulation of intracardiac catheters, wires and sheaths, and balloons in the left and right atrium and pulmonary veins
3. Techniques for vascular access management

4. Use of all forms of endovascular retrieval devices including snares and forceps
5. Ability to recognize and treat complications including percutaneous pericardiocentesis

Experience with specific percutaneous procedures requiring access to the left atrium is helpful in forming a foundation of technical expertise for PFO closure. These would include:

- Closure of secundum atrial septal defect
- Left atrial appendage (LAA) occlusion
- Techniques for transseptal puncture
- Closure of prosthetic mitral paravalvular leaks
- Mitral valve repair using techniques involving transseptal puncture
- Balloon mitral valvuloplasty
- Left ventricular assist device placement when such devices involve a transseptal approach (i.e., Tandem Heart)
- Pulmonary vein interventions
- Balloon atrial septosomy or septoplasty

### 4.1 | Imaging guidance

Operators performing PFO closure should have a mastery of imaging modalities used for procedural guidance. These modalities include fluoroscopy, angiography, TEE interpretation, and/or ICE. Operators should also be familiar with the anatomy of the atrial septum and its surrounding structures including the aorta, the vena cava, and adjacent valve structures. Fluoroscopic landmarks provide invaluable information to understand the precise location of wires, sheaths catheters, and devices which are not always visible on echocardiographic imaging. Integrating fluoroscopic and echocardiographic data is important for successful PFO closure. Fluoroscopy, either single or biplane, should be used for visualization of the relational anatomy in the posterior anterior or left anterior oblique views (with or without cranial angulation) to define the atrio-septal plane.

Imaging for PFO device closure typically requires TEE or ICE guidance (Table 2). The implanter needs to understand echocardiographic imaging interpretation to inform proper device selection. Skill in echocardiographic guidance for PFO closure aids in identifying anatomic variants which would make PFO closure more difficult and guides proper positioning of the closure device. Wide tunnels, Long tunnel length, the presence of an ASA, eustachian valves, Chiari network, thick septum secundum and pacemaker leads can lead to difficulties when performing PFO closure and be associated with inadequate disc apposition, residual shunts or device embolization. The writing committee strongly recommends that proceduralists rely on procedural TEE or ICE guidance for imaging of the interatrial septum in multiple planes. TEE provides excellent image quality of the entire IAS (interatrial septum), as well as adjacent cardiac and extra-cardiac structures. TEE can effectively image left atrial and LAA thrombi, prominent Eustachian valves and Chiari networks. With the echocardiographer as the main TEE operator, the proceduralist is freed from additional tasks during device closure. However, TEE may require general anesthesia (GA) which exposes the patient to risks of GA, esophageal trauma, and patient discomfort. Relying on TEE for PFO closure requires the presence of an additional physician to manipulate the TEE probe and acquire necessary images. Alternatively, ICE imaging quality has been shown to be comparable to TEE and allows for a better visualization of the septal rims prior to closure.[23,30]ICE also obviates the need for GA. In addition, the operator has complete control over image acquisition, eliminating the need for an additional physician for the procedure. The choice of imaging modalities used for PFO closure will differ among sites and depend on local factors including the availability of technologies, local expertise, and patient-specific factors. The preprocedural echocardiographic imaging is essential to the initial diagnosis and characterization of the PFO, assessment of additional potential causes of paradoxical embolism, and clarifying the image guidance needs of the PFO closure procedure. While some very experienced proceduralists may be able to perform PFO closure using fluoroscopy and angiography alone, it is recommended for less experienced proceduralists to incorporate some form of ultrasound guidance.[31] Even for experienced proceduralists the addition of soft tissue imaging is essential for many anatomic variants.

### 4.2 | Venous access and manipulation of sheaths and catheters into the left atrium

Current PFO devices require a medium to large bore outer diameter sheath or delivery system (8Fr–12Fr). Fundamental aspects of obtaining vascular access using large venous sheaths, achieving hemostasis at the end of the procedure, working with long wires and sheaths, and closed loop hemodynamic monitoring systems would be expected to be part of the foundational knowledge base of the PFO proceduralist. It is the usual practice for stroke related PFO device closure to perform sheath exchanges over a stiff 0.035″ guidewire positioned in the left upper pulmonary vein. Physicians must also be familiar with advancement of PFO delivery systems safely into the left atrium as well as a nuanced understanding of device size selection accounting for all the anatomic issues described above. Meticulous attention must be given to safe catheter techniques to avoid emboli (air or thrombus). Once catheters and delivery sheaths are in the left atrium, operators need to understand the relationship between the sheath and the left atrial roof, LAA, pulmonary veins and posterior wall at all times, since these are thin walled structures prone to perforation that would lead to pericardial effusion and tamponade.[32]

### 4.3 | Management and best practice recommendations to avoid/manage adverse events

Physicians must be familiar with potential adverse events that can arise related to the procedure and the techniques required to promptly treat them. Physicians must have knowledge of the different types of sheaths, catheters, snares or forceps that can be used for device retrieval in case of device embolization. It is important to know the limitations of transcatheter device retrieval, especially if the device is caught in chordae or subvalvar apparati of the mitral or tricuspid valves. Further, physicians must be well trained in managing vascular access and performing pericardiocentesis. As was seen with percutaneous ASD closure, the success

**TABLE 2** Stroke-related PFO closure peri-procedural imaging modality knowledge

| Image modality | Indication | PFO shunt | Advantages | Disadvantages |
|---|---|---|---|---|
| Transthoracic echocardiography | Assess left ventricular function and screen for valvular disease | Positive for right to left shunt at the atrial level when contrast enters the left atrium within the first three cardiac cycles.<br><br>Trace <5 bubbles<br><br>*-moderate:*<br>*6–20 particles*<br><br>*Severe:*<br>*>20 particles* | Easily available preliminary evaluation for sources of emboli and left to right shunting<br><br>In most cases, allows for a better Valsalva maneuver with agitated saline contrast | Limited anatomic assessment of intraatrial septum<br><br>Inability to resolve the nature of a septal defect<br><br>Often limited by technical factors such as body habitus |
| Transesophageal echocardiography With contrast (microbubbles) | Morphological characterization of interatrial septum, atrial structures<br>Evaluation of ascending aorta<br>Anatomical details of PFO indicated for intervention | Positive for right to left shunt at the atrial level when contrast enters the left atrium within the first 3 cardiac cycles.<br><br>*Trace ≤ 5 bubbles*<br>*Moderate 6–20 particles*<br><br>*Severe:*<br>*>20 particles* | Gold standard for visualization of the foramen ovale and associated anatomy. | More invasive as a technique and usually requires general anesthesia if used procedurally<br><br>Can result in local pharyngeal and esophageal trauma<br><br>Not universally possible in all patients (previous esophageal surgery, dysphagia, musculoskeletal problems with neck, esophageal varices)<br><br>Requires the presence of a dedicated physician operator |
| Intra cardiac echocardiography | Intra procedural assessment of intraatrial septum and device position | Positive for right to left shunt at the atrial level when contrast enters the left atrium within the first three cardiac cycles.<br><br>Trace ≤ 5 bubbles<br>*Moderate:*<br>*6–20 particles*<br><br>*Severe:*<br>*>20 particles* | Excellent resolution of septum and intracardiac structures<br><br>Obviates the need for intraprocedural TEE and general anesthesia<br><br>Provides a critical skill that can be translated to other procedures | Requires another venous access<br><br>Cost of the probe<br><br>Can be difficult to use if there is no access to the heart from the IVC (chronic thromboembolic disease with collateralized IVC, Azygous continuation of inferior vena cava) |
| Transcranial Doppler (TCD) | Diagnosing right-to-left shunts at rest and after a Valsalva maneuver | Presence of right to left shunt but not location of the shunt.<br><br>*Mild–moderate*<br>*Spencer grade I, II*<br>*Moderate–severe*<br>*Spencer grade III–V*[50] | Highly sensitive for identifying presence of a right-to-left shunt, determination of shunt magnitude, and predictor of post device residual shunting during follow-up | Not useful intraprocedurally for anatomic evaluation<br><br>Baseline positivity in patients with no anatomic shunt |

rate of PFO closure improves with increasing experience, leading to reduced procedural complications such as air-embolization, stroke, atrial arrhythmias, LAA perforation and high radiation dose.[33,34]

Among the most serious adverse events associated with PFO device closure include device malposition and device embolization. The proceduralist should be skilled in retrieval techniques including the use of various forms of bioptomes and snares. A strong understanding of the above imaging modalities will improve recognition of device malposition. Embolization events can be categorized by location as either intracardiac or intravascular. Current experience in device retrieval suggest that intracardiac location should be approached with extreme caution due to risk of perforation or valve injury. Most intravascular embolization events occur to the descending aorta and can be removed early and some limited reports suggesting mid-term follow-up removal using a snare technique and covered stent angioplasty if deeded necessary after removal. The most concerning serious adverse event involves cardiovascular perforation, pericardial effusion, and tamponade. This can occur acutely (early), during the midterm (weeks) or occasionally late following implant due to erosion.[32] Erosion has been reported with the Amplatzer PFO device at a rate of 0.018%, no erosions have been reported with the Gore device. It is critical, particularly in the acute presentation, that operators recognize early signs of an effusion so that it can be managed quickly and safely. Continuous hemodynamic monitoring during an implant is essential. There are multiple modalities that can allow a rapid determination of a new effusion, including fluoroscopy (decreased excursion of the left side of the cardiac silhouette in the LAO projection often precedes hemodynamic changes), echo imaging, and hemodynamic monitoring.[35] The implanting physician must be well trained in the basic principles and equipment required to safely access and drain the pericardial space. The patient must be monitored for other adverse events including procedure-related stroke, air embolus, and device thrombus, all of which are mitigated by sophisticated handling of the sheath delivery system and the anticoagulation status of the patient during the procedure. Sudden ST segment elevation, which is usually transient, can signify air introduced into the left atrium that has embolized into the more anterior right coronary artery. Air embolism can result in severe bradycardia, cardiac arrest, and stroke. The implanting team should continuously monitor ultrasound images for the presence of thrombus on the PFO device or sheath/delivery system during the case. Having access to an interventional stroke team is advisable to minimize embolic stroke severity should a stroke occur during or after the procedure. Postprocedure patients should be monitored in a suitable recovery area until they have recovered from the effects of anesthesia. Unexplained hypotension or instability should prompt immediate echocardiography to assess for device embolization, tamponade or other mechanical complication. A new pericardial effusion postprocedure should be monitored and determined to be stable prior to discharge.

There should be a structured program for postdischarge follow-up and evaluation by a cardiovascular specialist. That evaluation will likely include an ECG, an echocardiogram as well as a clinical visit. Further ambulatory ECG monitoring should be carried out if atrial arrhythmias are suspected post device closure.

It is important to be knowledgeable of the long-term medical therapy required postprocedure including anti-platelet therapy, anticoagulation therapy, when indicated, and endocarditis prophylaxis. In addition, appropriate timing of clinical follow-up and serial echocardiography imaging should be established according to the device's approved labeling. A physician must also be aware of the symptoms and signs of potential long-term adverse events including late device erosion, infection, endocarditis, nickel allergy, atrial fibrillation, and others.

### 4.4 | Operator-specific requirements

Currently, no data are published on the average number of procedures performed by various individual operators. Furthermore, there are no data in the literature to indicate the total number of stroke-related PFO closure procedures required to achieve proficiency as a procedural specialist. There is published survey data garnered from experts in the field suggesting initial procedure volumes of 7–50 cases to achieve a basic level of proficiency.[36–38] Such data will be important to collect going forward. Given the limitations of the available data regarding PFO specific device closure, the writing committee arrived at consensus recommendations for operator requirements for stroke-related PFO device closure which includes >50 life-time structural or congenital catheter based interventions which includes a minimum of 25 procedures involving atrial septal interventions or 12 specific to PFO closure (Table 3). Qualifying life-time procedures would include those listed above and in Table 3. As mentioned earlier, each device has unique characteristics that necessitate a consistent, organized training approach provided by the manufacturer that complies with FDA requirements. Before undergoing formal training for a specific device or technique, there are skillsets fundamental to transcatheter PFO device closure in which all operators must demonstrate a high level of training, competence, and continued experience. Therefore, our recommendations are purely based on current guidelines regarding secundum ASD device closure requirements and consensus opinion of the writing group.[39] This is similar to other documents addressing operators and institutional requirements for interventional catheterization procedures.[40–43] Recommendation categories include the experienced operator and the novice operator. On an ongoing basis, an experienced operator should perform >30 procedures that involve atrial septal interventions or > 15 PFO device closures over a 2 years period (Table 3).

### 4.5 | Additional requirements for the novice operator

The writing group supports the standards of the 2007 multi-society guidance document[36] suggesting that an interventional cardiologist with no experience in PFO device closure should have a physician proctor or mentor during interventional training, for the initial 10 cases and have a physician proctor present for 3–5 cases for each new device system used. Novice operators should also attend an FDA recommended mandatory peer-to-peer training course. Such courses should include:

- Patient selection process and establishment of neurological relationship.
- Clinical baseline assessment and category of stroke determination.

**TABLE 3** PFO closure requirements—Procedural specialist and medical facility

| | |
|---|---|
| Procedural specialist[a] | *Initial qualification*<br>• Clinical knowledge-base that includes a comprehensive understanding of stroke-related PFO closure and appropriate treatment strategies for this unique patient population.<br>• Suitable training on the PFO closure device(s) approved by the FDA.<br>• Understanding of atrial anatomy and imaging<br>• >50 life-time structural/congenital[b] catheter interventions with either a minimum of 25 involving septal interventions[c] or 12 specific to PFO device placement.<br>• Experience with catheter-based management of potential complications, including pericardiocentesis, recognition of device malposition, and embolized device retrieval.<br><br>*Novice operators*<br>• Mandatory peer-to-peer training course.<br>• Physician proctor or mentor during interventional training––10 cases total.<br>• Physician proctor present for 3–5 cases for each new device system.<br><br>*Ongoing*<br>• Over a 2-year period, >30 procedures that involve septal interventions[c] or >15 specific to PFO device placement.<br>• Process for identifying whether additional training is required on the basis of technological or clinical changes. |
| Medical facility | • >100 structural/congenital[b] catheter interventions in the 2 years leading to PFO program initiation.<br>• Yearly and thereafter, 50 structural/congenital[b] interventions, at least 25 of which involved septal interventions[c] and/or 12 specific to PFO device placement.<br>• Continuous intraprocedure availability of a physician (interventional cardiologist, imaging cardiologist, or cardiac anesthesiologist certified in echocardiography and with experience in guiding structural/congenital heart interventions) with experience at transesophageal echocardiography or intracardiac echocardiography in structural/congenital heart disease.<br>• Multidisciplinary team that includes necessary staff and expertise for preoperative evaluation, performing the PFO closure procedure, and acute and long-term postprocedure follow-up<br>• Ready access to an active cardiothoracic surgery program with cardiac surgeons and perfusionists.<br>• Cardiac catheterization laboratory, or hybrid room with hemodynamic monitoring and high-resolution imaging. |
| Data collection and quality | • Internal collection of data on all cases with a structure process for analysis of the program with quality assessment and quality improvement process. Data should include patient characteristics, indication for procedure, procedure performance, and up to 30 day outcomes.<br>• Submission of all cases to a national or multicenter registry (if and when available) for benchmarking.<br>• Institutional multi-stakeholder process for evaluation of patient selection, outcomes, and quality of care |

[a] Procedures for stroke-related PFO device closure are typically performed either by interventional adult or pediatric cardiologists. This document uses the term "procedural specialist" to apply to members of any subspecialty who perform stroke-related PFO closure procedures. In some cases, a physician team will be composed of two operators; therefore, the procedural volume criteria and ongoing proficiency requirements apply to at least one member of the team.

[b] Structural/congenital procedures include cardiac catheterization procedures for cardiovascular structure or congenital heart defect interventions.

[c] Septal interventions included transseptal puncture, PFO and ASD placement, mitral valve interventions, mitral paravalvar leak closure, LAA occluder placement, pulmonary vein interventions, and other trans atrial procedures.

- Transcatheter stroke-related PFO device closure procedural technique.
- Anticipated potential serious adverse events and their management.
- Perform three simulated PFO device placement scenario cases *(if available.)*
- Perform first 2–3 PFO device placement cases under the supervision of a proctor and at the end of these cases, the trainee should be certified by the proctor to perform PFO closure procedures independently.

### 4.5.1 | Patient selection

A successful PFO program must have a rigorous process for selection in order to offer the procedure to only the patients with unexplained stroke who will benefit the most in order to mitigate risk and avoid unnecessary procedures. As mandated by the FDA, patient selection should involve close collaboration between the PFO proceduralist and a neurologist (preferably a stroke neurologist). Discussions with the patient regarding the risks and benefits of the procedure should be carried out in the spirit of patient centered care. Patient selection should adhere closely to the FDA labeling which coincides with the inclusion criteria for the major RCTs. The contemporary randomized trials of PFO closure only included patients with documented stroke 60 years of age or less and this is the subset of patients primarily included in the FDA labeling. Patients with transient ischemic attack (TIA) were not included. Operationally, stroke is defined as an acute neurologic deficit, presumably due to ischemia, that either resulted in clinical symptoms lasting 24 hr or longer, or symptoms lasting less than 24 hr but associated with a new, neuro-anatomically relevant, cerebral infarction on noninvasive imaging. Prior to considering PFO closure, a careful evaluation should be done to rule out other causes of stroke including hypercoagulable states, atherosclerotic lesions, small vessel disease other cardioembolic sources and arterial dissection which would obviate the need for PFO closure. It is also important to exclude atrial fibrillation due to its association with cardioembolic stroke. A period of extended cardiac monitoring should be performed for approximately 4 weeks in patients over the age of 40 with a presumed cryptogenic stroke prior to considering PFO closure.[44,45] A shorter period of monitoring of 1–2 weeks may be appropriate for patients under 40 unless there are superimposed atrial fibrillation risk factors such as hypertension, hyperthyroidism, valvular disorders or alcohol use. Unmasking a significant burden of occult atrial fibrillation or flutter would suggest an etiologic association and mandate guideline-directed chronic anticoagulation as opposed to PFO closure. The RoPE score can also be helpful in determining the probability that a given stroke event was PFO mediated and is based

on age, cortical location of stroke and an absence of traditional stroke risk factors.[19] Other factors such as a history of deep vein thrombosis, recent travel, pulmonary embolus, or Valsalva maneuver prior to the stroke event tend to add to the likelihood of a PFO-mediated stroke and needs to be explored.[46]

## 5 | INSTITUTIONAL REQUIREMENTS AND COLLABORATIVE CARE MODELS

PFO closure should not be carried out by a single individual in isolation but rather as an institutionally supported program for the comprehensive evaluation and treatment of all forms of stroke. The medical facility should have an established SHD and/or Adult Congenital Heart Disease (ACHD) Program, as well as physical space and ancillary services to execute the procedure effectively and safely. Specifically, the writing committee considered the following aspects to be key institutional requirements:

### 5.1 | Institutional requirements

The institutional requirements to embark on a stroke-related PFO closure program are summarized in Table 3. Specifically, the institution should have performed >100 structural/congenital catheter-based interventions in the year leading to program initiation. On an ongoing annual basis, the institution should perform at least 50 structural/congenital procedures at least 25 of which involve atrial septal interventions and/or 12 specific to PFO device closure. There should be ready access to an active cardiothoracic surgical program. While it is preferred that this program exist on-site, rapid transfer to a nearby facility which offers cardiothoracic surgery may be acceptable in some carefully considered circumstances.

### 5.2 | Procedural area

1. Stroke-related PFO closures should be performed in the interventional cardiac catheterization laboratory or hybrid OR with continuous hemodynamic monitoring.
2. Fixed single plane or biplane radiographic imaging systems with fluoroscopy, offering catheterization laboratory-quality imaging are required.
3. The capability to acquire and record cineangiograms.
4. A mobile C-Arm for fluoroscopic imaging is currently not considered acceptable.
5. The room should have adequate dimensions to accommodate, in the event of urgent or concomitant situations, standard echocardiographic and anesthesia equipment, in addition to the regular cardiac catheterization radiographic imaging system.
6. The interventional cardiac catheterization laboratory or hybrid suite should be stocked with equipment for safe procedures and for handling adverse events such as device stabilization or retrieval and managing pericardial effusions. This equipment includes a variety of endovascular sheaths, diagnostic catheters, transseptal kits, wires, various vascular snare types and sizes, bioptomes, vascular occluders, and pericardiocentesis equipment.

### 5.3 | Imaging specific requirements

1. Preprocedural and procedural Imaging:
   - An echocardiography laboratory with the full array of on-site transthoracic echocardiography (TTE) and TEE capabilities with sonographers and physician echocardiographers experienced in atrial anatomy and/or congenital heart disease as well as placement of TEE probes.
   - Intracardiac echocardiography (ICE) is an alternative to TEE but not required.
   - Either a TEE or ICE capable console and probe should be available in the procedure room.
   - Three-dimensional echocardiography capability is helpful but not required.
   - Appropriate staff should be present during the procedure, which may include a noninvasive cardiologist or cardiac anesthesiologist familiar with the procedural steps and subtleties of invasive echocardiography and TEE probe placement.
   - If a general anesthetic is used, an appropriately staffed area to recover patients safely
2. Radiologic imaging
   - Neuro CT capabilities.
   - Neuro MRI capabilities.
3. Cardiovascular catheterization laboratory equipped with a fixed X-ray system with fluoroscopy offering high-resolution imaging, hemodynamic recording, and archiving capabilities.

## 6 | SHARED DECISION MAKING AND THE MDT

The benefits of a patient-centered, MDT evaluation for SHD procedures has convincingly been demonstrated and mandated for transcatheter aortic valve replacement, percutaneous mitral valve repair, and LAA closure. It is the opinion of the writing committee that an analogous concept be extended to programs engaged in PFO closure for prevention of recurrent ischemic stroke and that it be embedded in centers which have stroke and structural/congenital heart disease programs. The FDA-approved indications for use for the currently approved PFO occluder devices clearly mandate that patients be evaluated by both a cardiologist and a neurologist to determine that the patient had a cryptogenic stroke due to a presumed paradoxical embolism and that other known causes of ischemic stroke have been excluded. This *Heart-Brain* MDT fosters a shared decision making process between the patient and a MDT of stakeholders which ensures appropriate patient selection and follow-up care The outpatient setting is where most patients are seen and evaluated. A MDT of a cardiologist and a neurologist jointly seeing the patient is efficient, allows the team to learn from one another, and eliminates the possibility of patients receiving contradictory recommendations.[47,48] The composition of the MDT will vary from site to site but will include an interventional cardiologist skilled in PFO closure and other structural/congenital heart disease catheter-based procedures who may function as the leader. A stroke neurologist with expertise in the diagnosis and management of stroke syndromes particularly in the younger age groups is

also critical. It is understood that many patients being considered for PFO closure will be referred from the community after evaluation by a local neurologist. In cases of diagnostic uncertainty, the stroke neurologist will provide a second opinion regarding the appropriateness of PFO closure. Neurologists participating in assessment of patients with PFO should have a minimum of 8 hr of continuing medical education per year in keeping with the recommendations of the Brain attack coalition for neurologists participating in care of stroke patients at primary stroke centers.[49] In addition to the stroke neurologist, a noninvasive cardiologist with expertise in imaging and a neurovascular radiologist would also be required as essential components of the MDT. Other physician and nonphysician personnel are required for a successful PFO closure program and may include nurses, mid-level providers, cardiac anesthesiologists, coordinators, and hematologists. It is expected that the MDT will meet on a regular basis to discuss the best approach for each patient. The MDT will also discuss issues related to quality metrics, complications, and future opportunities for quality improvement and education. The composition of the implanting team will also vary from center to center. In some institutions, physician teams, consisting of a primary operator along with an assistant or co-operator, may jointly perform the procedure to offer the greatest expertise and to optimize procedural success and safety. In other highly experienced centers, a single procedural specialist may be adequate for PFO device closure procedures. Specific components and services required for a successful PFO closure program will include:

### 6.1 | Stroke neurologist

- A neurologist with expertise in stroke, preferably a neurologist with subspecialty certification in vascular neurology.
- The stroke neurologist will serve as both a primary consultant and as a second opinion, when necessary, for patients referred for PFO closure.
- The stroke neurologist should have:
    - Expert level understanding of the differential diagnosis of transient or permanent central neurologic dysfunction.
    - Expert level skills in the investigation of stroke syndromes in the young.
    - Detailed understanding of neuroimaging and its role in determining stroke etiology.
    - Expertise in the management of medical therapy in the treatment of stroke.

### 6.2 | Structural and/or adult congenital interventional cardiologist

- Board certified or board eligible
    - Adult interventional cardiologist
    - Pediatric cardiologist with expertise (including advanced training) in interventional cardiology
- Consultative and cognitive skills to assess completeness and adequacy of investigations for stroke in the young
- Cognitive and technical skillsets as described in the sections above
- Procedural volumes in accordance with consensus recommendations (Table 3).

### 6.3 | Hematologist

- The institution where PFO closure is carried out should have access to a hematologist with experience in coagulation disorders

### 6.4 | Noninvasive imaging physicians

- Neuroradiologists skilled in the interpretation of invasive angiography and noninvasive MRI and CT imaging should be readily available

  The institution where PFO closure is carried out should have a board certified/board eligible cardiologist with expertise in echocardiography with skillsets necessary to:
- Carryout and interpret transthoracic and transesophageal echocardiograms as well as use of contrast echo
- Evaluate atrial level defects and anatomic variations along the spectrum of congenital heart disease
- Assess device placement and stability and residual shunts

### 6.5 | Anesthesia

- An anesthesiologist should be available if necessary at the time of PFO closure
- The anesthesiologist should be able to support a procedure with conscious sedation or GA
- If TEE is being used for imaging an anesthesiologist should be on site and available as dictated by local policies

### 6.6 | Cardiac surgery

- A cardiac surgeon, anesthesiologist, perfusionist, and cardiothoracic operating room staff should be available for surgical backup. Cardiac surgery operating rooms should be available in the rare event of a severe adverse event requiring surgical intervention.

### 6.7 | Ancillary services

- After undergoing PFO closure, patients can be managed in a post-anesthesia care unit or telemetry unit. Personnel experienced in managing patients undergoing complex cardiac procedures must be present.
- An outpatient clinic should be present and staffed by members of the MDT who engage in patient follow-up and gather data for quality assessment.

## 7 | TRAINING MODELS

Effective and efficient acquisition of the technical skills for transcatheter device PFO closure is variable. These skills are dependent on prior experience with complex structural and/or congenital heart

procedures in general, and across the atrial septum in particular, as well as a detailed understanding of the associated imaging techniques. The writing committee recommends an educational program that will provide the background necessary for proceduralists as well as imaging specialists to develop skills for a successful, consistent, and safe technology delivery. Education may be in the form of a formal didactic course focused on basic principles of the field of PFO device technology. Training should also consist of hands-on experience with procedure equipment, viewing live cases performed by experienced physicians in an interactive format, and the use of simulation. Finally, proctors who are experienced in PFO device closure with a specific device should be available to monitor the initial implants performed by the procedural specialist.

### 7.1 | Technical skill development

During the run-in phase of technology dissemination, interventional physicians who took part in the pivotal trials will likely serve as teachers and proctors. Training should entail a review of clinical issues surrounding PFO related stroke and adverse event risks of the procedure, the relevant atrial anatomy, and imaging of the atrial septum, as well as the delivery system and the devices available under FDA approval. Training should also highlight techniques to maximize the likelihood of successful device placement while minimizing the risk of periprocedural adverse events by acknowledging potential pitfalls and techniques to avoid them. Bailout techniques including retrieval of embolized devices should be included.

The process should include manipulation of the delivery system into the left atrium and device placement using simulations and three-dimensional models for appropriate tactile learning. While theoretical knowledge is requisite when establishing a program, practical experience is desired. Until new physician specialists become proficient, proctoring by physicians or clinical specialists with extensive experience should be considered. Over time, implantation techniques will likely change as the field evolves and new devices emerge. Therefore, continuing medical education will be necessary. Simulation-based education has been shown to be an effective method for learning and for safe implementation of new technology, and the development of simulators for PFO device closure techniques will likely become an integral part of a comprehensive training program.

## 8 | QUALITY OF CARE ASSESSMENT

A rigorous approach to the assessment of the quality of care is becoming commonplace in medicine and should be applied to the care of patients undergoing PFO closure.[50] This assessment should include not only the procedure itself, but also the pre- and post-procedure evaluation and care (Table 4).

### 8.1 | National Registry

Professional societies have a responsibility to consider how to collect and analyze data to enable setting national standards so that individual sites and physicians can evaluate their program's performance with national benchmarks. Presently, no system exists for the evaluation of the quality of programs offering patients an evaluation and treatment that may include a PFO closure procedure. There is no national coverage decision mandating a national registry that would include data from all patients undergoing PFO closure. The National Cardiovascular Data Registry (NCDR) IMPACT Registry[51] captures some data elements relevant for this procedure but does not capture many pre-, intra-, and post-procedure data elements relevant to the care of patients who have suffered a cryptogenic stroke after a comprehensive evaluation, have had their PFO characterized by anatomic and physiologic criteria, and have undergone a PFO closure. In addition, there is currently no neurology professional society registry for cryptogenic stroke in the United States. Tracking procedural outcomes and long term follow-up data is of particular importance with regard to patients undergoing PFO closure since such patients tend to be younger (mean age in the RESPECT and REDUCE device cohorts were 48 and 45) and looking forward to many more years of quality life. It is the hope of the writing committee that a registry is formed to track immediate and long term outcomes of patients undergoing PFO closure. This registry should consider standardized follow-up, such as is done with the TVT registry. There are industry-sponsored ongoing FDA mandated postapproval studies that will follow patients out to 5 years. However, even 5-year follow-up may not be adequate for these young patients with many years of life ahead of them.

### 8.2 | Establishing and maintenance certification criteria

Presently, the focus of quality of care assessment in the area of PFO closure is on local site performance, that is, hospitals offering services to evaluate and treat patients who are being considered for PFO closure to prevent recurrent ischemic strokes. This document proposes a quality assessment program for individual sites. Quality measurements are essential for quality assessment and quality improvement processes but are also potentially used in pay-for-performance programs, public reporting, and site performance rankings.

As a template for a site's quality assessment program it is important to consider:

1. A framework for quality measurements.
2. Specific aspects of care of patients undergoing PFO closure that would be germane to assessment of quality of care.
3. A proposed quality assessment process that is practical for use by individual sites.

Accepted and relevant frameworks for the assessment of quality of care are useful for application to a newly approved therapy such as PFO closure. The Donabedian triad of structure, process, and outcomes measures of quality of care is one reasonable framework[52].

The *structure measures of quality* include the requirement of operators and institutions to have the skills, experience, on-going procedure volume, and facilities that are fundamental to delivering the multidisciplinary initial evaluation and the performance of PFO closure. These operator and institutional requirements have been previously covered in this document.

**TABLE 4** Proposed quality assessment measures

| Metric | Target performance |
|---|---|
| Operator and institutional requirements met | 100% |
| Percentage of patients who were seen by both a cardiologist and neurologist prior to PFO closure | 100% |
| Procedure-related major adverse outcomes:<br>• Mortality<br>• Intraprocedure stroke<br>• Air embolism<br>• Device embolization<br>• Major vascular complications | <1% or below the 10th percentile if registry benchmarking data becomes available |
| • Major bleeding complications<br>• Atrial fibrillation, transient or sustained, if treatment required, and if oral anticoagulation initiated<br>• Myocardial infarction<br>• Pericardial effusion with and without tamponade<br>• Emergency surgery | <5% |
| Postprocedure major adverse outcome<br>• Stroke<br>• Mortality<br>• Deep vein thrombosis or pulmonary embolism if occurring within 6 months of the procedure<br>• Atrial fibrillation, atrial flutter, ventricular tachyarrhythmias, or complete heart block requiring pharmacologic therapy or cardioversion<br>• Thrombus on device detected<br>• Pericardial effusion with and without tamponade<br>• Device erosion<br>• Device explantation<br>• Residual moderate or severe shunting if persistent after 6–12 months | <1% or below the 10th percentile if registry benchmarking data becomes available |
| Discharge with dual antiplatelet therapy or anticoagulant and aspirin<br>• Provide rational for deviation in individual patients | 100% |
| Freedom from recurrent ischemic stroke at 1 year | 100% |

*The process measures of quality* defined as best practices and standardized processes that are accepted and incorporated into programs, have not been identified in any professional society expert consensus statements regarding PFO closure.

- The multidisciplinary approach to patient evaluation involving those with both cardiology and neurology expertise is a process measure of quality that can be assessed at the site level. It is expected that all potential PFO closure patients will receive evaluation by a MDT consisting of a cardiologist and neurologist.
- Other process measures used in other areas of medicine are appropriate use criteria (AUC) that categorize different patient scenarios with the assignment of levels of appropriateness of a treatment based on the current understanding of procedure outcomes plus the potential patient benefits and risks. The new terms "appropriate care," "may be appropriate care," and "rarely appropriate care," are assigned in this AUC process. Currently AUC do not exist for patients with cryptogenic stroke and PFO but such an effort can be considered for the future.
- Another process measure of quality is the use of shared decision-making and the development of educational material for patients and families. Best practices may include directing patients and family to an objective, noncommercial website for education. Decision aids could also be development to assist decision-making for patients facing the decision of whether or not to undergo PFO closure. These educational and decision-aids are not currently available but should be considered for future efforts by professional societies, individual site, and other stakeholders.

The *outcome measures of quality* are of critical importance since they address the quality domain of safety. From the clinical trials in PFO closure there are data on rates of complications that may serve as the first set of standards. The frequency of adverse events related to the procedure or the closure device should be very low. Individual serious adverse events in the RESPECT and REDUCE trials were very low, often <1%. One-year assessment of outcomes is important but has been challenging for centers due to many patients who are often not followed by the site performing the procedure but by referring clinicians who may or may not be part of the same medical system and, as a consequence, the medical records may not be readily available. Therefore, the outcome measures recommended in this first document of operator and institutional requirements will focus predominantly on 30-day outcomes.

Outcome measures, especially those related to complications, ideally should be adjusted to patient characteristics that are separate determinants of outcomes from that due to the quality of procedure performance. Bleeding and vascular complications are typically risk-adjusted. Given the lack of a comprehensive national registry gathering data on all patients undergoing PFO closure it is currently not feasible to have the large database necessary to develop, validate, and report risk adjusted outcomes for PFO closure. Therefore, absolute rates of complications will need to be reported as a quality metric for PFO closure.

The proposed assessment of quality of care at the site level is outlined in Table 4. This can serve as a blueprint for PFO closure programs to gather the appropriate data and review their findings on a regular basis. Through this process of quality assessment, it is key that the following steps be taken after data collection: (1) identification of

problematic areas, (2) analysis of potential causes of these problems, (3) identification and implementation of opportunities for improvement involving specific action items, and (4) re-evaluation of outcomes after an improvement process has been implemented.

In addition to Table 4, a program should have a running assessment of patient characteristics that were evaluated, the reasons that PFO closure was not recommended, and overview statistics of those who underwent PFO closure in terms of patient and procedure characteristics.

## 9 | LONG-TERM FOLLOW-UP

Although participation in a registry is currently not mandatory for use of the currently approved devices, it is important for individual institutions to have aggregate and operator-specific quality analysis processes. Within institutions, a regular quality analysis process reviewing key metrics, including number of implants, complications, and outcomes, should be a standard part of any stroke-related PFO program.

After PFO device closure procedures, results from continued follow-up and the post approval studies, along with an analysis of national databases, would be beneficial for measuring initial and long-term clinical outcomes. However, individual institutions should have protocols in place for follow-up that include echocardiographic and other imaging data that identify the presence and severity of persistent leaks; medication use (particularly anticoagulants); and clinical outcomes, including bleeding, neurologic events, and device complications. Clinicians and institutions performing PFO closure procedures should consider by what means they gather longer-term data on their patients. This process needs to be individualized to the health care system, the individual PFO closure program, the ability to capture long-term data from the electronic medical record, and the ability of the program to have patients return for follow-up. Follow-up is particularly important given the enhanced clinical benefits of PFO closure found in the long term follow-up in the recent RCTs.[6–8]

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## SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

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