MANAGEMENT IN CONFIDENCE

CLINICAL PRIORITIES ADVISORY GROUP
29 05 2019 and 30 05 2019

Agenda Item No	03.4
National Programme	Internal Medicine
Clinical Reference Group	Cardiac
URN	1770

Title
Percutaneous patent foramen ovale closure for the prevention of recurrent cerebral embolic stroke (adults aged around 60 years and under).

Actions Requested	1. Support the policy proposition.
	2. Recommend its relative priority.

Proposition
NHS England currently has a 'not for routine commissioning' policy in place for adults on percutaneous patent foramen ovale (PFO) closure for the prevention of recurrent cerebral embolic stroke (2013). A Commissioning through Evaluation (CtE) scheme was then established and designed to collect additional data on outcomes and safety and to consider later evidence. On behalf of NHS England NICE produced an Evaluation Report including clinical and cost effectiveness in March 2018. In parallel NHS England followed its agreed Methods to review the latest published evidence and to develop this revised proposition for people referred to adult cardiac services.

Clinical Panel recommendation
The Clinical Panel recommended that the policy progress as a routine commissioning policy.

The committee is asked to receive the following assurance:	
1.	The Head of Clinical Effectiveness confirms the proposal has completed the appropriate sequence of governance steps and includes an: Evidence Review; and Clinical Panel Report.
2.	The Head of Acute Programme confirms the proposal is supported by an: Impact Assessment; Stakeholder Engagement Report; Consultation Report; Equality Impact and Assessment Report; Clinical Policy Proposition. The relevant National Programme of Care Board has approved these reports.

3.	The Director of Finance (Specialised Commissioning) confirms that the impact assessment has reasonably estimated a) the incremental cost and b) the budget impact of the proposal.
4.	The Clinical Programmes Director (Specialised Commissioning) confirms that the service and operational impacts have been completed.

The following documents are included (others available on request):	
1.	Clinical Policy Proposition
2.	Consultation Report
3.	Evidence Summary and CtE Evaluation Report
4.	Clinical Panel Report
5.	Equality Impact and Assessment Report

The Benefits of the Proposition – Percutaneous Patent Foramen Ovale (PFO) Closure Vs. Medical Therapy Alone (MTA) for secondary prevention of cryptogenic stroke.		
No	Metric	Summary from evidence review
1.	Survival	For the duration of the RCTs (up to median follow up of 5.3 years (Mas et al 2017)], all-cause mortality (death) was recorded for all subjects regardless of cause. In their systematic review and meta-analysis (SRMA) of RCTs, De Rosa et al 2018 found that there was no statistically significant difference between treatment groups for all-cause mortality (PFO 4 deaths/1382; MTA 0 deaths/1149; risk difference and p value were not reported). This is a very important outcome for patients but the reduction in the relatively low risk of stroke (4.1-4.6% risk of stroke on medical treatment alone (MTA)) did not translate into reduced risk of death within the duration of the RCTs. After receiving a PFO device, no additional patients were alive who would not otherwise have been compared to medical therapy alone. The follow up period in the RCTs may have been too short (range mean of 2.6 to 5.3 years), and the incidence of death too low to be able to assess if the risk of all-cause mortality was significantly different in patients receiving PFO compared to MTA.
2.	Progression free survival	
3.	Mobility	
4.	Self-care	

5.	Usual activities	
6.	Pain	
7.	Anxiety / Depression	
8.	Replacement of more toxic treatment	
9.	Dependency on care giver / supporting independence	
10.	Safety	Serious adverse events (SAEs) were not clearly defined in the SRMA by De Rosa et al (2018) They are usually considered to include any untoward clinical event that results in death, is life-threatening, requires inpatient hospitalization or causes prolongation of existing hospitalization, results in persistent or significant disability/incapacity, requires intervention to prevent permanent impairment or damage. During the follow up period of the 4 RCTs included in this SRMA (mean 2.6-5.3 years), there was no significant difference in SAEs between those having PFO closure and MTA: 25% vs 24% (RD: -0.006(95%CI: -0.036 to -0.048), p=0.781) (De Rosa et al 2018). This indicates that PFO closure is not more harmful for SAEs compared to MTA, although the SAE rate is not insignificant for either the MTA or the PFO closure groups. The study duration was relatively short (2.6 – 5.3 yrs). There was heterogeneity among the four RCTs for this outcome (different devices used, differences in medication, as well as variation in baseline characteristics of subjects including existing risk factors for stroke (diabetes, hypertension), PFO morphology and presence of an ASA).
11.	Delivery of intervention	

Other health metrics determined by the evidence review - Percutaneous Patent Foramen Ovale (PFO) Closure Vs. Medical Therapy Alone (MTA) for secondary prevention of cryptogenic stroke.		
No	Metric	Summary from evidence review
1	Recurrent Stroke	This outcome is the risk of a recurrent stroke during the study period (ranging from mean 3.2 to median 5.9 yrs) for

		those people who had PFO closure compared to those who were treated with medication alone (MTA). Shah et al (2018) found that patients who had PFO closure had a 3.3% lower risk of recurrent stroke than those on medication alone [RD: -0.033 (95%CI: -0.062- to -0.004), p=0.037]. This was based on 25/1382 events /patient in the PFO closure group and 59/1149 events/patient in the MTA group. A similar reduction in risk was reported by De Rosa et al 2018 for PFO closure vs MTA: risk of ischaemic stroke 1.2% vs 4.1% (RD: -0.031 (95%CI: -0.051 to -0.010), p=0.003, I^2=61%). The meta-analysis by Piccolo et al 2018 of the same 4 RCTs as Shah et al 2018 (including the extended follow-up results of the RESPECT RCT) also reported a reduced risk of recurrent stroke in patients who had PFO closure (HR 0.14 (95% CI 0.04 to 0.55), p=0.005) up to 5 years follow up. The 3.3% reduction in risk for PFO vs MTA reported by Shah et al 2018 should be considered against the relatively low risk of stroke for patients on MTA (between 4.1% and 4.6%). The absolute benefit is not reported by the authors but reviewer analysis of the event rates indicate that compared to MTA there might be 33 fewer recurrent stroke events per 1000 patients who undergo PFO closure for cryptogenic stroke. This is the equivalent of an NNT of 30 PFO closures to prevent one stroke. These estimates should be treated with caution. There was significant heterogeneity between the four RCTs (different devices used, differences in medication, as well as a range of baseline characteristics of subjects including existing risk factors for stroke (e.g. diabetes, hypertension, size of interatrial shunt, presence of an ASA). Two of the four RCTs did not individually show a statistically significant difference between treatment groups for recurrent stroke.
2	Transient Ischaemic Attacks (TIA)	This outcome is the risk of a TIA during the study period (ranging from mean 3.2 to median 5.9 yrs) for those people who had PFO closure compared to those who were treated with MTA. The SRMA by Shah et al (2018) found that patients who had PFO closure were no more or less likely to have a TIA than those on medication alone [RD: -0.004 (95%CI: -0.017 to 0.010), p=0.46].

		A reduction in risk for TIA would be welcome to patients. Although transient, a TIA is sometimes associated with a non-transient stroke event soon after. This result should be treated with caution. The study results by Shah et al 2018 were amended in June 2018 but the results for TIA do not appear to have been amended to reflect the corrected MTA population from the CLOSE trial. The impact of this on their estimate of reduction of risk is not clear although the authors confirm that the results are 'similar'[1]. In addition, there was significant heterogeneity among the four RCTs (different devices used, differences in medication, as well as variation in baseline characteristics of subjects including existing risk factors for stroke (e.g. diabetes, hypertension, PFO morphology and presence of an ASA).
3	Composite of stroke or TIA	This outcome is the risk of either a stroke or a TIA event occurring during the study period (ranging from 2.6 to 5.3 yrs) for those people who had PFO closure compared to those who were treated with medication alone. The SRMA by De Rosa et al (2018) found that patients who had PFO closure were less likely to have a TIA or stroke than those on medication alone. PFO closure vs MTA: 3.6% vs 6.3% (RD: -0.029 (95%CI: -0.050 to -0.007), p=0.008, I^2=34%). A reduction in risk for TIA or stroke would be welcome to patients. Although transient, a TIA is sometimes associated with a non-transient stroke event soon after. There was heterogeneity among the four RCTs (different devices used, differences in medication, as well as variation in baseline characteristics of subjects including existing risk factors for stroke (diabetes, hypertension, size of interatrial shunt and presence of an ASA).
4	Composite of stroke, vascular death or Thrombolysis in Myocardial Infarction (TIMI)-defined major bleeding	This outcome is the K-M cumulative estimate of risk of either a stroke, vascular death or TIMI-defined major bleeding during the 2 year follow up for those people who had PFO closure compared to those who were treated with medication alone. Lee et al 2018 reported that during the 2 year follow up period, patients were less likely to have a stroke, vascular death or TIMI-defined major bleeding than those on

		medication alone. PFO closure vs MTA: 0/60 vs 6/60 (12.9%), (95%CI 3.2 to 22.6; SE 5.0, p=0.013). A reduction in risk for stroke, vascular death or major bleeding is important outcome for patients. These results are based on one RCT only (n=120) and a short follow up period (2 years). The study was underpowered to detect this primary end point. The study was conducted in only 2 centres, both in South Korea which may have resulted in selection bias. This study did not recruit all patients with a cryptogenic stroke which was presumably due to PFO; rather, the population recruited was considered to have a high risk PFO[2] confirmed by a TEE protocol to assess morphological features. These results may not be generalisable to a wider patient group.
5	Major Bleeding	A major bleed includes bleeding which results in death, bleeding in a critical area or organ, or bleeding causing a fall in haemoglobin level, or leading to transfusion of whole blood or red cells. During the follow up period (mean 3.2 to median 5.9 yrs), the SRMA by Shah et al 2018 reported no difference in risk for major bleeding for PFO closure compared to MTA. (RD -0.021 (95%CI: -0.051 to 0.009), p=0.093). This was consistent with the SRMA by De Rosa et al 2018 (PFO closure vs MTA: 0.9% vs 1.2% (RD: -0.002 (95%CI: -0.012 to 0.007), p=0.605). The avoidance of major bleeding at any time is an important outcome for patients. De Rosa et al 2018 found relatively low heterogeneity between the four RCTs for this outcome (despite different devices used, differences in medication, as well as variation in baseline characteristics of subjects including existing risk factors for stroke (diabetes, hypertension, presence of an ASA). However, the low event rate and limited duration of the RCTs mean that it is not certain if over a longer duration, the difference in risk of bleeding associated with PFO closure might be considered statistically and clinically significant given the potential ongoing annual risk of bleeding associated with exposure to oral anticoagulant (OAC) and antiplatelet therapy (APT) medication in the MTA group.

[2] A high-risk PFO was defined as a PFO with an atrial septal aneurysm (protrusion of the dilated segment of the septum at least 15 mm beyond the level surface of the atrial septum), hypermobility (phasic septal excursion into either atrium $10 mm), or PFO size (maximum separation of the septum primum from the secundum during the Valsalva manoeuvre) ≥2 mm on TEE.

6	Asymptomatic new ischaemic lesion	This outcome is the number of patients who were found to have a new ischaemic brain lesion following an MRI scan 6 months after either PFO closure or starting MTA, but who had experienced no symptoms. Lee et al 2018 reported that at 6 months follow up, there was no difference in risk of having an asymptomatic ischaemic lesion when patients who had received a PFO closure device were compared to those on medication alone. PFO closure vs MTA: 3/34 (8.8%) vs 7/38 (18.4%), p=0. 24 It is not clear from the study what proportion of asymptomatic lesions are likely to develop into a TIA or stroke. It is therefore not clear if this outcome is meaningful to patients. These results are based on one RCT only (n=120) and a short follow up period (2 years). The study was underpowered to detect the primary end point. The study was conducted in only 2 centres, both in South Korea which may have resulted in selection bias. This study did not recruit all patients with a cryptogenic stroke which was presumably due to PFO; rather, the population recruited was considered to have a high risk PFO confirmed by a TEE protocol to assess morphological features. These results may not be generalisable to a wider patient group
7	Non-fatal major procedural complications	At median duration of follow up of 2.8 years, major procedure related complications were observed in patients who had received an Amplatzer PFO Closure device. Lee et al 2018 reported that 2 out of 53 patients who had received the Amplatzer PFO Closure device had a major procedural complication i.e.: Pericardial effusion, n=1 Pseudo aneurysm, n=1 Procedure related adverse events are of importance to patients but if the event is peri-procedural and can be managed successfully prior to discharge without risking explantation of the device or requiring further intervention, then this may be acceptable, compared to the possibility of future stroke prevention. These results are based on one RCT only (n=120) and a short follow up period. Only 53 of the 60 patients randomised to have PFO closure had the procedure (7 declined). The study was underpowered to detect the primary end point. The study was conducted in only 2 centres, both in South Korea which may have resulted in selection bias. This study did not recruit all patients with a cryptogenic stroke which

		was presumably due to PFO; rather, the population recruited was considered to have a high risk PFO confirmed by a TEE protocol to assess morphological features. These results may not be generalisable to a wider patient group
8	New onset AF or Atrial flutter	New onset AF is a chaotic and irregular atrial arrhythmia that may occur following the introduction of the PFO closure device. AF is known to cause significant morbidity and mortality including palpitations, dyspnoea, angina, dizziness or syncope, and features of congestive heart failure, tachycardia-induced cardiomyopathy, stroke, and death. De Rosa et al (2018) reported a statistically significant increased incidence of new onset AF or atrial flutter for PFO closure compared with MTA: 4.4%[3] vs 1.0% (RD: 0.033 (95%CI: 0.012 to 0.054), p=0.002, I^2=66%). Shah et al (2018) also found an increased risk of new onset AF in the PFO group but considered the heterogeneity among the RCTs for new onset AF (I^2=81.98%) to be too high to allow meta-analysis of the pooled results. These findings suggest that the evidence on the magnitude of the increased risk of AF associated with PFO closure is inconclusive. Given that AF is, by itself a known risk factor for stroke, whether or not it is an adverse effect associated with PFO closure device implantation, the rationale for which is to prevent recurrence of stroke, is of great importance to patients. It is also important whether the AF persists or is transient or managed effectively; however the studies did not provide these details. The two SRMAs are of similar quality. De Rosa et al (2018) includes the more complete results of the initial RESPECT study (Carroll et al 2013) whereas Shah et al (2018) included RESPECT extended follow-up (Saver et al 2017) in which missing data and loss to follow-up were much higher (missing data: 13.2% vs 26.9% respectively). This may account for the higher estimate for heterogeneity (I^2) in Shah et al 2018 although the authors' explanation for the heterogeneity is that it is most likely due to the different types of devices used across all the trials. It is not clear why the range of devices used did not therefore result in heterogeneity for other outcomes reported by Shah et al 2018. Given that even the lower estimate of I^2 for this outcome in De Rosa et al (2018) was 66% and may

[3] reported by the authors as 4.1%,but corrected by reviewer after checking absolute number of events in the PFO closure group.

		represent substantial heterogeneity, these results should be treated with great caution.
9.	Cost Effectiveness (Amplatzer device only)	The cost effectiveness of PFO closure compared to MTA was based on the UK and NHS direct costs and clinical outcomes (both benefits and complications) of the Amplatzer PFO device and MTA regimes used in a UK subpopulation of the RESPECT RCT. Tirschwell et al 2018 reported that the estimated time for PFO closure to reach a cost effectiveness threshold of <£20,000 per quality adjusted life year (QALY) was 4.2 yrs (no CI reported) At 4 years post PFO closure procedure, the findings for PFO with Amplatzer compared with MTA were: • Incremental cost per patient: +£6071 (no CI reported) • Incremental QALYS: 0.29 • Incremental Cost Effectiveness Ratio (ICER): £20,951 At 10 years post PFO closure procedure, the findings for PFO with Amplatzer compared with MTA were: • Incremental cost per patient: +£4858 (no CI reported) • Incremental QALYS: 0.71 • ICER: £6887 89% of probabilistic sensitivity analysis (PSA) iterations were cost effective At 20 years post PFO closure procedure, the findings for PFO with Amplatzer compared with MTA were: • Incremental cost per patient: £2848 (no CI reported) • Incremental QALYS: 1.32 • ICER: £2158 Cost effectiveness may not be a priority to individual patients; it is an important outcome for decision makers. It reflects the incremental clinical effectiveness of PFO closure compared to MTA as well as the acquisition cost of the device and related procedure. The cost effectiveness outcomes modelled in this study should be treated with some degree of caution. It reflects the results from a UK sub-population recruited to the extended RESPECT RCT (Saver et al 2017). The sub-population is not clearly defined. The authors state that anatomical features of the PFO were considered but the criteria for PFO closure is not explicit, and it may have been open to local interpretation. The baseline characteristics for the UK sub-population are not clear, so there might be pre-treatment differences between the PFO closure and MTA treatment arms. No confidence intervals were reported..

		However, the costs are all recent UK and NHS based which means that as the ICER estimates are well below the NICE threshold of £20,000 over a lifetime, it is highly likely that the results are reliable and generalisable as long as the patient selection criteria are identical to those used in the assumptions for this modelled UK subpopulation. In addition, indirect costs were not included. This means that the cost effectiveness estimates did not take into account the non-NHS costs of stroke care (social care, personal productivity such as employment etc). Inclusion of these wider costs might reduce the ICER estimate further (i.e. improve cost-effectiveness). **CtE economic analysis** The CtE evaluation team developed their own Markov model, using clinical data from the RESPECT trial. This analysis concluded that for every 1,000 patients undergoing PFO closure there could be 275 fewer strokes over a lifetime (45-year time horizon). The cost-consequences model indicates that each PFO procedure would cost the NHS £5,415 more per patient undergoing the procedure than MTA (over these 45 years); this after taking account of the costs of treatment, the likelihood of sustaining a stroke and the costs of treatment and care for such events. The additional cost above MTA reduced to £3,729 per patient undergoing PFO when taking into account the societal costs of stroke.

The Benefits of the Proposition – Percutaneous Patent Foramen Ovale (PFO) Closure for secondary prevention of cryptogenic stroke (uncontrolled studies).		
No	Metric	Summary from evidence review
1.	Survival	
2.	Progression free survival	
3.	Mobility	
4.	Self-care	
5.	Usual activities	**In the NHS England CtE study:** Quality of Life: Pre-procedure, EQ-5D values were available for 432 patients. At 6 weeks, 241 paired scores were available and these showed a mean gain in utility of 0.03, with 34% of patients reporting improved quality of life, 50% no change and 17% a deterioration. At 6 months, paired data for 207 patients were available. The marginal improvement was maintained, with a similar percentage of

		patients (35%) reporting an improved quality of life, 18% no change and 47% a deterioration. The mean baseline value was 0.87±0.19, however, the median value of 0.91 was adopted as a measure of central tendency.
6.	Pain	
7.	Anxiety / Depression	
8.	Replacement of more toxic treatment	
9.	Dependency on care giver / supporting independence	
10.	Safety	**In the NHS England CtE study:** The adverse events experienced by 417 patients during a median follow up of 212 days (approx. 7 months) were: • 2.2 neurological events per 100 patient years (95% CI 1.2 to 3.6 events) • 2.6 neurological events or deaths per 100 patient years (95% CI 1.5 to 2.4 events) All recent trials of PFO closure- bar one- report that patients undergoing PFO closure experience less than one adverse event per 100 patient years. The outcomes of NHS patients appear more comparable with patients in the control (MTA) arms of trials, where the adverse event rates range from 1.3 to 3.4 per 100 patient years albeit that the trial follow up periods- for both MTA and PFO closure groups- are considerably longer (2 to 6 years). Whilst these estimates give some indication of potential benefits in usual NHS practice, direct comparison between observational studies and protocol-driven RCTs are of course problematic. **Updated information: February 2019** Using the HES / APC / ONS and CtE linked data, the updated information reported in the longer-term a total neurological event rate (using n=33 events over 1693.9 person years (PY) follow up) of 1.9 (95% CI 1.3 to 2.7) per 100 PY follow up, a composite annualised incidence rate of death and neurological event of 2.3 (95% CI 1.6 to 3.1) per 100 PY across a total aggregated follow-up period of 1688 PY (with 7 deaths and 33 neurological events.) Again across the three datasets 25 ischaemic events were reported giving a rate of 1.5 (95% CI 0.9 to 2.2) per 100 PY.
11.	Delivery of intervention	

Other health metrics determined by the evidence review - Percutaneous Patent Foramen Ovale (PFO) Closure for secondary prevention of cryptogenic stroke (uncontrolled studies).		
No	Metric	Summary from evidence review
1.	Immediate procedural success within 30 days	Immediate procedural success was defined as the device remaining in situ and effectively closing the PFO within the first 30 days after the percutaneous procedure. 99.8% devices and device procedures were successful (998 patients of the 1000 consecutive subjects). The device was intraprocedurally removed in 2/1000 patients. The reasons were not explained. The procedural complication rate within 30 days of implantation is low. This is of modest importance given that the endpoint outcome of interest is prevention of recurrent stroke. This outcome is based on one uncontrolled study of 1000 patients who received a PFO device between 1999 and 2012. It is not clear what proportion of subjects had cryptogenic stroke: a high proportion had known risk factors for stroke (e.g. diabetes, hypertension, smoking). There was heterogeneity between subjects (e.g. PFO size, presence of ASA), PFO devices and concomitant medication.
2.	Complications within 30 days	Electrical complications and non-electrical complications that occurred within 30 days of PFO device implantation were reported. 59 (5.9%) of the 1000 PFO closure device recipients experienced electrical complications (Rigatelli et al 2017) comprising • Temporaneous AF: 46 (4.6%) all resolved within procedure • Permanent AF: 1 (0.1%) • Temporaneous AVB I or II grade: 3 (0.3%) all resolved within procedure • Permanent AVB I or II grade: 3(0.3%) • Temporaneous or permanent AVB III: 0 • Supraventricular arrhythmias: 6 (0.6%). 4 required pharmacological cardioversion. 26/1000 (2.6%) experienced non-electrical complications (Rigatelli et al 2016): • device embolization: 2(0.2%)

		• sheath or device entrapment: 3(0.3%) • groin haematomas:10(1.0) • pericardial effusion: 3(0.3%) • air embolism: 4(0.4%) • death:0(0) Complications due to the PFO closure device or procedure, particularly those which are not temporary, are important factors for patients to consider especially given that the PFO closure treatment is a preventative strategy rather than a treatment for a symptomatic condition. These complication rates should be treated with caution. They are based on one uncontrolled study of 1000 patients who received a PFO device between 1999 and 2012. It is not clear what proportion of subjects had cryptogenic stroke: a high proportion had known risk factors for stroke (e.g. diabetes, hypertension, smoking). There was heterogeneity between subjects (e.g. PFO size, presence of ASA), PFO devices and concomitant medication.
3.	Predictors of complications within 30 days	Analysis of the characteristics of patients who experienced complications following PFO closure implantation was reported. Females were more than twice as likely to experience complications within 30 days of PFO closure: electrophysiological complications: OR 2.3 (95%CI 0.5 to 5.1), p<0.001(Rigatelli et al 2017) Non-electrical complications: OR 2.1 (95%CI 0.5 to 4.6), p<0.001 (Rigatelli et al 2016) People who required a PFO device disk larger than 30mm were 4-5 times more likely to experience complications within 30 days electrophysiological complications: OR 5.0 (95%CI 1.2 to 7.2), p<0.001 (Rigatelli et al 2017) Non-electrical complications: OR 4.0 (95%CI 0.8 to 6.1), p<0.001 (Rigatelli et al 2016) Female patients and patients who require a larger PFO closure device would wish to know the absolute risk to which they are exposed, rather than the overall risk to a wider population. Complications due to the PFO closure device or procedure, particularly those which are not temporary, are important factors for patients to consider especially given that the PFO closure treatment is intended as a preventative strategy rather than a treatment for a symptomatic condition.

		These predictors of complications should be treated with caution. They are based on one uncontrolled study of 1000 patients who received a PFO device between 1999 and 2012. It is not clear what proportion of subjects had cryptogenic stroke: a high proportion had known risk factors for stroke (eg diabetes, hypertension, smoking). There was heterogeneity between subjects (eg PFO size, presence of ASA), PFO devices and concomitant medication.
4.	Complication rate at median 10.5 yr f/up	Longer term electrical complications and non-electrical complications that had occurred at the median follow up time of 10.5 years after PFO closure device implant were reported. 14/1000 (1.4%) of the 1000 PFO closure device recipients experienced long-term electrical complications (Rigatelli et al 2017) comprising • permanent AF: 5 (0.5%) • paroxysmal AF: 4 (0.4%) • complete AVBIII: 1 (0.1%) • supraventricular arrhythmias: 4 (0.4%) 22/1000 (2.2%) experienced long-term non-electrical complications (Rigatelli et al 2016): • device thrombosis: 5(0.5%) • erosion: 0(0) • mitral valve regurgitation: 2(0.2) • recurrent stroke (minor/major): 6/2(0.8) • device embolization/removal: 1(0.1%) • device fracture: 0(0) • cardiac related death: 1(0.1%) • non-cardiac related death: 13 (1.3%) (11 neoplastic related, 2 car accident related) Complications due to the PFO closure device or procedure, particularly those which are not temporary, are important factors for patients to consider especially given that the PFO closure treatment is a preventative strategy rather than a treatment for a symptomatic condition. These complication rates should be treated with caution. They are based on one uncontrolled study of 1000 patients who received a PFO device between 1999 and 2012. It is not clear what proportion of subjects had cryptogenic stroke: a high proportion had known risk factors for stroke (e.g. diabetes, hypertension, smoking). There was heterogeneity between subjects (including

		PFO size, presence of ASA), PFO devices and concomitant medication.
5.	Predictors of complications at median 10.5 yr f/up	Analysis of the characteristics of patients who experienced long-term complications following PFO closure implantation was reported. Patients with a large (3-5 grade) ASA as well as PFO were 2 to 3 times more likely to experience complications in the longer term: • electrophysiological complications: HR 2.2 (95%CI 0.4 to 3.9), p<0.001 (Rigatelli et al 2017) • Non-electrical complications: OR 2.9 (95%CI 0.4 to 4.3), p<0.001 (Rigatelli et al 2016) Patients for whom the mean ratio between device size and entire septum length was >0.8 were 2 to 3 times more likely to experience complications: • electrophysiological complications: HR 2.61(95%CI 0.3 to 4.1), p<0.001 (Rigatelli et al 2017) • Non-electrical complications: OR 3.1(95%CI 0.3 to 5.2), p<0.001 (Rigatelli et al 2016) Patients with a large ASA as well as a PFO, as well as those who require a large PFO closure device relative to the length of their septum, would wish to know the absolute risk to which they are exposed, rather than the overall risk to a wider population. Complications due to the PFO closure device or procedure, particularly those which are not temporary, are important factors for patients to consider especially given that the PFO closure treatment is intended as a preventative strategy rather than a treatment for a symptomatic condition. These predictors of complications should be treated with caution. They are based on one uncontrolled study of 1000 patients who received a PFO device between 1999 and 2012. It is not clear what proportion of subjects had cryptogenic stroke: a high proportion had known risk factors for stroke (e.g. diabetes, hypertension, smoking). There was heterogeneity between subjects (including PFO size, presence of ASA), PFO devices and concomitant medication.
6.	Procedure related outcomes	A number of procedural related outcomes were reported. This included the time that it took for the percutaneous PFO closure procedure, the continuous medical imaging time required to implant the PFO device (fluoroscopy time) and the total dose area product which is a measure of radiation risk (defined as the absorbed dose multiplied

		by the area irradiated, expressed in gray - centimetres squared (Gy-cm2). Procedure time: 36.5+/-6.1 minutes Fluoroscopy time: 7.3+/-4.7 minutes Total dose area product: 26.7+/-1.88 Gycm^2 It is not clear what the significance of these outcomes are to patients, although the procedure time and exposure to radiation contribute to both the overall procedure costs and potential safety outcomes. These results are based on one uncontrolled study, the procedure and duration and dose of radiation exposure may vary depending on provider, device used and experience of the interventional cardiologist, patients with PFO wo are treated with medical therapy would not be exposed to the PFO device implant procedure or the radiation associated with the procedure.

Considerations from review by Rare Disease Advisory Group
Not applicable.

Pharmaceutical considerations
Not applicable.

Considerations from review by National Programme of Care
1) The proposal received the full support of the Internal Medicine National Programme of Care Business Meeting on 10th April 2019 and reported to the full Board on 25th April 2019.

Abbreviations:
AF: atrial fibrillation
ASA: atrial septal aneurysm
AVB: atrioventricular block
f/up: follow up
HR: hazard ratio
I^2: measure of heterogeneity
MTA: medical therapy alone
OR: odds ratio
PFO: patent foramen ovale
QALY: quality adjusted life year
RD = risk difference
TIA: transient ischaemic attack;
yrs: years

PC-TRIAL: Clinical Trial Comparing Percutaneous Closure of Patient Foramen Ovale using the Amplatzer PFO Occluder with Medical Treatment in Patients with Cryptogenic Embolism (Meier et al 2013)
RESPECT: Randomised Evaluation of Current Stroke Comparing PFO Closure of established current Standard of Care Treatment (Carroll et al 2013, Saver et al 2017)
CLOSE: Patent Foramen Ovale Closure or Anticoagulants versus Antiplatelet Therapy to Prevent Stroke Recurrence (Mas et al 2017)
REDUCE: GORE HELEX Septal Occluder/GORE CARDIOFORM Septal Occluder for Patent Foramen Ovale Closure in Stroke Patients (Sondergaard et al 2017)