

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Centre for Health Technology Evaluation Observational Data Unit

Commissioning through Evaluation Project Report Percutaneous patent foramen ovale closure (PFOC)

1 Lay summary

- 1.1 The foramen ovale is a hole in the wall that divides the upper two chambers of the heart (the atria). Before birth, it allows blood to enter the left atrium from the right atrium, bypassing the lungs. In most people, the foramen ovale closes naturally after birth. However in as many as one in four individuals, it does not close properly and remains partially 'patent' (open). This is referred to as a patent foramen ovale (PFO). In most people the hole does not cause any problems, but in some people it can lead to cryptogenic strokes (strokes of undetermined origin).
- 1.2 Percutaneous patent foramen ovale closure (PFOC) is a minimally invasive surgical procedure (carried out under local or general anaesthetic without having to make large incisions in the skin). It has been developed to reduce the risk of a subsequent stroke in people with a patent foramen ovale who have had a stroke that was thought to be due to a paradoxical embolism (that is, caused by the passage of material such as a blood clot from the right side to the left side of the heart). Before the procedure, the doctors will assess the hole using a small ultrasound probe that is put down the throat (transoesophageal echocardiography or TEE) or introduced into the heart through a vein in the groin (intra-cardiac echocardiography or ICE). During the procedure, the hole is blocked using a small occlusion device made up of two tiny umbrella-like structures joined at the centre, which is introduced into a vein in the groin and passed into the heart. The device is introduced into the groin on the

opposite side of the body if ICE is used. The two umbrella sections of the device open on opposite sides of the hole, plugging the space. The position of the device is confirmed using TEE and x-ray. Most people stay in hospital for one night after the procedure.

1.3 Although clinical trials have shown that PFOC is safe and reduces the risk of subsequent stroke, there is limited evidence showing how well it works in normal clinical practice, that is, outside a clinical trial. In order to determine the effectiveness and safety of PFOC in general clinical practice in England, NHS England commissioned a time-limited study in which over 900 people had the PFOC procedure at one of 20 specialised hospitals. The study was part of NHS England's Commissioning through Evaluation (CtE) programme which enables valuable new clinical and patient experience data to be collected for treatments that are not currently routinely funded by the NHS, but which nonetheless show significant promise for the future.

1.4 The surgical procedure to fit the occlusion device was successful in nearly every case. About 1 in 100 patients had a major complication (including death, stroke, major bleed and heart attack) while still in hospital. One death was reported. These in-hospital findings were consistent with the published evidence for PFOC. Patients were followed up for a maximum of 2 years with an overall follow up period of almost 700 patient years (the total accumulated number of years that all the patients in the scheme were followed). In about 1 in 10 of the patients measured, there was still some blood flow from the right to the left side of the heart, one year after the PFOC procedure. This suggests that the PFO had not been completely closed. These patients may be at continued risk of paradoxical embolism. Two patients died after discharge from hospital and a further 33 major complications were reported. Some patients had more than one complication. Sixteen patients had a neurological event (caused, for example, by a bleed or a blockage of the blood supply to the brain, or having an undetermined cause) either in-hospital or following discharge, giving a rate of 2.2 events per 100 patient years. For every 100 patient

years there were 2.6 incidents of neurological events or deaths. There were a total of 9 events caused by a blockage of the blood supply to the brain (including stroke) either in-hospital or following discharge, giving a rate of 1.3 events per 100 patient years. One patient had a haemorrhagic neurological event (when a blood vessel that supplies the brain ruptures and bleeds) after discharge from hospital. There were a total of 14 major bleeds and 12 minor bleeds either in-hospital or following discharge. These results were generally not as good as the published results for people who have had PFOC. The results from the registry also showed that 3.5% of patients experienced worsening atrial fibrillation (AF; a heart condition that causes an irregular and often abnormally fast heart rate) after the procedure, or experienced AF for the first time. There was a 57% reduction in the number of people taking anticoagulation medication when discharged from hospital compared with before the PFOC procedure. This was sustained for the 2 year follow-up period. There was an initial increase in the number of people prescribed antiplatelet medication but this had returned to pre-procedure levels at 1 year after the PFOC procedure.

- 1.5 PFOC improved the quality of life of people in the scheme for up to 6 months after the procedure, but this was not sustained at the 1- and 2-year follow-up. The improvement was associated with a reduction in anxiety and depression.
- 1.6 Longer-term findings show that the number of strokes following the PFOC procedure were generally higher in the CtE study compared to the published evidence, however such comparisons are limited because of differences in how the outcomes were measured, the methods used and the populations studied.
- 1.7 The PFOC procedure costs around £8,230 per person.
- 1.8 Data collected during the CtE scheme will be considered alongside published data from research trials to inform the development of NHS

England's clinical commissioning policy for PFOC, that is whether it will be available on the NHS for a specific population.

2 Background

- 2.1 This project report is prepared by NICE for NHS England, based on the work of, and advised by, Newcastle and York External Assessment Centre (EAC), which was commissioned by NICE to collaborate on this CtE scheme. The EAC prepared an evaluation report which contains results of the analysis of evidence compiled during the CtE scheme, alongside relevant evidence published during the scheme and de novo economic modelling where this is carried out by the EAC. The evidence referred to in section 3 is a summary of the full evidence base analysed by the EAC, which appears in the evaluation report. The evaluation report, including detailed references for all of the studies referred to in this project report, is available at Appendix A, and the project report should be read in conjunction with it.
- 2.2 The objective of this CtE scheme was to evaluate the clinical- and cost-effectiveness of percutaneous patent foramen ovale closure (PFOC) in patients who had had a confirmed ischaemic stroke presumed to be due to paradoxical embolism.
- 2.3 The CtE scheme proposals supported in principle by the NHS England Clinical Panel for potential investment were further developed and refined, in partnership with NICE. A set of evaluation questions was agreed between NHS England, NICE and the EAC at the start of the scheme. The questions are set out in a table at section 4 of this project report, with respective answers derived from the CtE work.

3 The evidence

Summary of new CtE evidence

- 3.1 The aim of this CtE scheme was to generate new evidence from real-world settings to enable a judgement on the clinical- and cost-effectiveness of PFOC in the identified population.
- 3.2 In-hospital procedural efficacy data reported from the CtE registry are largely complete and consistent with published data from randomised controlled trials (RCTs) and observational studies. Approximately 95% of PFOC procedures resulted in procedural success (device implanted and no major complications). About 1 in 10 of the patients measured had residual shunt after 1 year follow-up. These patients may be at continued risk of paradoxical embolism.
- 3.3 Comparison of the medium term efficacy results (measured as the rate of neurological events, ischaemic neurological events and/or death) from the CtE registry and the control arms of the RCTs suggest that PFOC plus medical therapy¹ did not result in a clear benefit compared with medical therapy alone. Comparison with the intervention arms of the RCTs (that is, patients who also received PFOC plus medical therapy) suggests that patients in the registry were not achieving the benefit reported in these studies (particularly the more recently published studies). It is important to note, however, that published studies and the CtE registry are not directly comparable because of differences in the definitions of the outcome measures, and issues with generalisability (for example, diagnostic workup including better echocardiography and the use of provocation manoeuvres designed to raise the pressure in the right atrium and improve the detection of PFO). In addition, only 282 (31.3%) of the patients who had a PFOC device implanted, were still alive and reached the second anniversary of their procedure during the data collection phase

¹ Medical therapy consisted of antithrombotic treatment including antiplatelet therapy or oral anticoagulants.

of the CtE scheme. Data was available for 112 (39.7%) of these people at 2 years.

- 3.4 Further assessment of the validity of the CtE registry data will be done using data linkage to Hospital Episode Statistics (HES) and Office for National Statistics (ONS) mortality records. A report analysing findings from data linkage is planned for summer 2018.
- 3.5 A cost consequence analysis compared PFOC plus medical therapy with medical therapy alone. The estimated discounted NHS costs per patient were £12,956 for PFOC plus medical therapy and £7,596 for medical therapy alone. The benefit to the NHS from avoided strokes and transient ischaemic attacks (TIAs) (£2,084) and savings in primary care (£837) with PFOC were insufficient to offset the initial procedure costs of £8,233 per patient. PFOC was cost incurring for the NHS by £5,360 per person.
- 3.6 The current CtE evidence does not appear to suggest a clinical or cost advantage of PFOC plus medical therapy over medical therapy alone for the prevention of strokes in people who have had a confirmed ischaemic stroke presumed to be caused by paradoxical embolism. It may, however, have an advantage over medical therapy for people for whom anticoagulants are contraindicated or not tolerated. NHS England policy review will need to include assessment of the level of risk at which PFOC could be the preferred option. The data linkage will provide helpful information in that discussion. A report analysing findings from data linkage is planned for summer 2018.

Population

- 3.7 People who had had a confirmed ischaemic stroke presumed to be due to paradoxical embolism.

Intervention

- 3.8 Percutaneous patent foramen ovale closure (PFOC).

PFOC CtE registry study

- 3.9 The single-arm PFOC CtE registry study was carried out in 20 NHS centres in England between 1 October 2014 and 10 August 2017. People who had had a confirmed ischaemic stroke presumed to be due to paradoxical embolism were eligible to receive PFOC. Closure of the PFO was measured using contrast echocardiography at rest and with provocative manoeuvres designed to raise the pressure in the right atrium and improve the detection of PFO, at 6 months, 1 year and 2 year after the procedure. Data on patients' baseline characteristics, the PFOC procedure, safety, clinical outcomes, and health-related quality of life were collected in a registry. Data were collected at follow-up appointments at 6 weeks, 6 months, 1 year and 2 years.
- 3.10 A total of 1126 PFOC procedure records were extracted from the CtE registry, of which 940 people with a median age of 45 years (range 17 to 82 years) were included in the analysis. This includes 111 people (11.8%) who met the eligibility criteria for CtE but had the PFOC procedure outside of the CtE scheme, that is, it was conducted by non-CtE commissioned centres or as a private procedure. NHS England accepted the inclusion of these data. The large majority of patients (85.7%) had had an ischaemic stroke diagnosed by cranial imaging (computed tomography [CT] or MRI scanning). All patients had a PFO identified by echocardiography which was thought to be the causal reason for the stroke (through paradoxical embolism). Two year follow up data was available for 39.7% of all eligible patients. Where data was available, data completeness was more than 75% for the minimum data set (an acceptable standard for data submissions to be measured against) at each follow-up date. The image guidance method and type of anaesthesia used was recorded for 910 and 904 procedures, respectively. A total of 663 procedures were conducted with planned intra-operative TOE or transthoracic imaging, 627 of which were under general anaesthesia (94.6%). A total of 206 procedures were conducted with planned intra-operative ICE imaging, 185 of which were under local anaesthesia (89.8%).

Procedural safety

3.11 Device implantation was recorded in 907 of the eligible PFOC procedures. Of these, 901 procedures resulted in an occlusion device being implanted successfully, giving a technical success rate of 99.3% (95% confidence interval [CI] 98.6% to 99.8%). The reasons for technical failure included being unable to position the device correctly or it not being the correct size. Most patients received either a device from the AMPLATZER range (St. Jude Medical; 45.5%) or a GORE CARDIOFORM Septal Occluder (30.1%). A smaller proportion of patients received a device from the Figulla Flex range (Occlutech; 13.1%). The procedural success rate (device implanted and no major complications) was 95.1% (95% CI 93.5% to 96.4%). About 1 in 10 of the patients measured had residual shunt at the 1 year follow-up. These patients may be at continued risk of paradoxical embolism. The in-hospital major complication rate (includes death, neurological event, device embolisation, major bleed and myocardial infarction) was 1.0% (95% CI 0.4% to 1.8%) and included 1 death. Twenty four patients (2.6%, 95% CI 1.6% to 3.8%) had a minor complication in hospital (including new onset or worsening AF, minor vascular injury, minor bleed, device malposition, and migraine or worsening migraine). Nine patients had new onset or worsening AF (1.0%, 95% CI 0.4% to 1.9%). The procedural mortality rate was 0.1% (95% CI 0.0% to 0.6%). Two patients were recorded as having a neurological event (defined as being of ischaemic, haemorrhagic or undetermined origin) in hospital. One of the events was ischaemic in nature. Ischaemic neurological events include stroke, TIA and reversible ischaemic neurological deficiency. The majority of patients required a hospital stay of one night.

Clinical outcome

3.12 Two patients died following discharge from hospital (0.2%, 95% CI 0.0% to 0.9%), and a further 33 major complications were recorded during the follow up period (4.1%). Some patients experienced multiple events. Fourteen patients were recorded as having a neurological event after

discharge from hospital. In eight of these patients the event was ischaemic in nature and in one patient the event was classified as haemorrhagic. For the remaining five patients, the neurological event was of undetermined origin. In addition, thirteen patients had major bleeds (1.6%, 95% CI 0.9% to 2.7%). No patients died as a result of these events. After discharge, 118 patients (14.6%, 95% CI 12.2% to 17.2%) developed minor complications including minor cardiac structural complication, migraine or worsening migraine, minor bleed and minor vascular injury. Twenty eight patients had new onset or worsening AF (3.5%, 95% CI 2.3% to 5.0%). Anticoagulant medication was used by 12.5% of the people before the PFOC procedure. This reduced to 5.2% of people (a reduction of nearly 60%) after discharge from hospital and remained fairly constant throughout the scheme. The number of people taking only antiplatelet medication increased from 671 (78.5%) before the procedure to 783 (89.2%) on discharge from hospital. There was a gradual decrease in the use of antiplatelet therapy during follow-up, with 64.5% of people recorded as having only antiplatelet medication at 2 years.

- 3.13 Overall, three patients (0.3%) died during the study (1 in-hospital and 2 following discharge). The recorded causes of death were 1 fungal endocarditis and multi organ failure with auto-immune sclerosing cholangitis (recorded in-hospital), 1 unknown cause (recorded at 1 year follow up) and 1 multi-organ failure complicated by septicaemia (recorded at 2 year follow up). No fatal strokes were reported. Over a total aggregated follow-up period of almost 700 patient years, the event rate for death was 0.4 (95% CI 0.1 to 1.3) per 100 patient years. The 1 year survival from death was 99.9% (95% CI 99.6% to 100.0%). The overall event rate for neurological events (including events occurring in-hospital and following discharge) using time to event analysis was 1.7% (95% CI 1.0% to 2.8%). In total 21 events were recorded, indicating some patients experienced multiple events. The neurological event rate per 100 patient years was 2.2 (95% CI 1.2 to 3.6). The 1 year probability of being free of neurological events was 97.9% (95% CI 96.5% to 99.3%). In total, nine

patients had an ischaemic neurological event (one of which was in-hospital with eight occurring following discharge), giving a rate of 1.3 events per 100 patient years (95% CI 0.6 to 2.5). The 1 year probability of being free of ischaemic neurological events was 98.5% (95% 97.2% to 99.7%). The overall event rate per 100 patient years for the combined outcome (composite of death and neurological events, both in-hospital and following discharge) was 2.6 (95% CI 1.5 to 4.1). One year survival from death or neurological events was 97.7% (95% CI 96.3% to 99.2%). The rate of neurological events was not significantly different between the types of device implanted (p=0.26).

Health related quality of life

3.14 Health-related quality of life data were collected using EQ-5D-5L health assessment questionnaires before the PFOC procedure and at all subsequent follow-up visits, and converted to utilities. Visual analogue scale (VAS) scores, the overall health status reported by the patient on the day of follow-up, were also recorded. The mean utility value pre-procedure was 0.87. There was a numerical improvement in the utility score during the follow-up period, however this was only statistically significant at 6 weeks and 6 months post-procedure. The domain in which the greatest benefit from the procedure was seen was anxiety and depression. There was also a statistically significant improvement in the median VAS score at 6 weeks and 6 months when compared with the score before the procedure.

Costs and resources

3.15 Data on the resources required to conduct PFOC (pre-operative assessment, peri-operative procedure and post-operative management) were collected from the 20 centres involved in the CtE scheme. The forecast cost for a PFOC procedure was estimated to range from £6,939 to £9,251, with a base case estimate of £8,229. The device accounts for █% of the total cost, with investigations forming the second largest cost component (32%). Consumables (█%), staff (6%), length of stay (3%),

theatre use (■%), and outpatient follow-up (2%) account for the remaining costs.

Published evidence

Clinical evidence

- 3.16 As the registry was single-armed, a parallel literature search was undertaken in order to present the registry findings from real-world NHS practice in the context of published studies in other populations, and to assess whether the procedural outcomes were consistent with previously reported studies. The systematic review of published evidence included 3 RCTs and 6 observational studies.
- 3.17 The principal clinical evidence on the use of PFOC to prevent recurrent ischaemic events is derived from 3 superiority RCTs. These were the CLOSURE-1 trial (Furlan et al. 2012), the RESPECT trial (Carroll et al. 2013), and the PC trial (Meier et al. 2013). The RCTs were of reasonable methodological quality, although all were potentially subject to attrition bias. All of the trials were considered to be highly generalisable to the population covered by the CtE scheme. The primary outcomes of the RCTs were composites of recurrent ischaemic events, and procedural- and post-procedural mortality, using intention to treat (ITT) analysis.
- 3.18 The CLOSURE-1 trial (n=909; Furlan et al. 2012) compared the now discontinued STARFlex device (NMT Medical) plus antiplatelet therapy (clopidogrel and aspirin) with medical therapy alone (either warfarin or aspirin or both). It had a 2 year follow-up period. The procedural success rate (defined as successful implantation of one or more STARFlex devices at the closure site during the index procedure with no procedural complications) was 89.4%. The reported event rate per 100 patient years for the primary composite endpoint (composite of stroke or TIA during 2 years of follow-up, death from any cause during the first 30 days, and death from neurologic causes between 31 days and 2 years) was estimated by the EAC from raw data counts and the follow up period. This

was estimated to be 2.8 for the PFOC arm compared with 3.4 for the medical therapy only arm.

- 3.19 Both the RESPECT trial (n=980; Carroll et al. 2013) and the PC trial (n=414; Meier et al. 2013) used the AMPLATZER PFO Occluder (St. Jude Medical). The RESPECT trial compared PFOC with medical therapy alone (aspirin, warfarin, clopidogrel, or aspirin combined with extended-release dipyridamole. Aspirin with clopidogrel was also permitted at the start of the study until a change in guidelines meant that their combined use was no longer recommended). Patients in the PFOC arm also received aspirin plus clopidogrel for 1 month, followed by aspirin monotherapy for 5 months. Subsequently, antiplatelet therapy was administered at the discretion of the site investigator. The technical success rate (successful implantation) was 99.1% and the procedural success rate (technical success in the absence of in-hospital serious adverse events) was 96.1%. The event rates per 100 patient years for the primary endpoint (a composite of recurrent non-fatal ischaemic stroke, fatal ischaemic stroke, or early death after randomisation) were 0.66 in the PFOC arm and 1.38 in the medical therapy only arm, with a median follow-up period of 2.1 years. All primary events were non-fatal ischaemic strokes (Carroll et al. 2013).
- 3.20 In the PC trial (Meier et al. 2013), PFOC was also compared to medical therapy alone (antithrombotic treatment including antiplatelet therapy or oral anticoagulants at the discretion of the clinician, provided that patients received at least one antithrombotic drug). Patients in the PFOC arm also received antithrombotic treatment (aspirin, and either ticlopidine or clopidogrel). Over 95% of procedures were successful (defined as effective closure with no or minimal shunting). The median follow-up period was about 4 years. In the PFOC arm, the event rate for the combined outcome (composite of death, stroke, TIA or peripheral embolism) was estimated by the EAC to be 0.83 per 100 patient years compared with 1.3 per 100 patient years in the control arm. There were no deaths in the medical therapy only arm.

3.21 All the RCTs reported statistically negative results for the primary outcome, that is, there was no significant benefit associated with PFOC compared with medical therapy alone. On the basis of these results the evidence for the clinical benefit of PFOC is equivocal (but, in contrast, emerging evidence is reporting PFOC to be associated with significant benefits, see sections 3.26-3.28). The EAC considered it likely that the lack of significance reported in the RESPECT trial was due to a type II statistical error. This was because there was a clear trend toward superiority of PFOC, with the point estimate of the hazard ratio (HR) being low but with wide confidence intervals (HR 0.49 [95% CI 0.22 to 1.11; $p=0.08$]). Significance was reached when 'as treated' analysis was employed. Analysis from a patient-level meta-analysis also indicated significant benefits of the AMPLATZER PFO Occluder device in important outcomes such as the prevention of recurrent stroke. Larger trials with more participants, or reporting more outcome events over a longer time period, are required to demonstrate an unequivocal effect. Additionally, any benefits in reduction of ischaemic neurological events should be considered in the context of peri-procedural and longer term adverse events, such as new onset or worsening AF.

3.22 Six observational studies were selected for focussed review (Taggart et al. 2017, Pezzini et al. 2016, Inglessis et al. 2013, Wallenborn et al. 2013, Thomson et al. 2014 and Mirzaali et al. 2015). The latter two studies were based in the UK. The studies were relatively large allowing for a degree of precision in clinical measurements and used a variety of PFOC devices including the AMPLATZER Septal Occluder, the AMPLATZER Cribriform and the GORE HELEX Septal Occluder. The technical and procedural success rates were all above 92%, however the definitions used to describe the success rates varied across the studies. Similarly, the definitions used to describe efficacy and adverse events varied across the studies. Although, they provided useful data on procedural efficacy and safety, and some estimates of the longer-term prognosis of patients receiving PFOC, the studies were limited by the lack of a prospectively defined comparator and evidence of confounding. Taggart et al. (2017)

investigated long-term efficacy of different PFOC devices. Four devices were used (AMPLATZER Septal Occluder, AMPLATZER Cribriform, GORE HELEX and CardioSEAL [NMT Medical]), albeit 82% of the procedures used the AMPLATZER Septal Occluder. The median follow up was 6 years. The proportion of patients with successful implantation and without residual shunt ranged from 92% to 100% for the different devices. The study by Pezzini et al. (2016) compared PFOC using a number of different devices including AMPLATZER Occluders (86.8% of all procedures), CardioSEAL, STARFlex and GORE HELEX Septal Occluder, with medical therapy alone. All patients in the PFOC arm also received antithrombotic treatment. The proportion of patients with complete PFO closure (that is, without residual shunt) was 92.2%.

3.23 Results from the four systematic reviews were not entirely consistent. Kent et al. (2016) reported an individual patient meta-analysis of the 3 controlled RCTs (Furlan et al. 2012, Carroll et al. 2013 and Meier et al. 2013; n=2,303). In the medical therapy arm, the event rate for the primary composite outcome (a composite of ischemic stroke, TIA, or death from any cause) was 2.3 events per 100 patient years, with an ischaemic stroke rate of 1.3 per 100 patient years. In the PFOC arm, there were 1.5 events per 100 patient years for the primary composite outcome and 0.7 events per 100 patient years for ischaemic stroke. However, when data for the AMPLATZER device only was considered (from the RESPECT and PC trials), the event rate per 100 patient years was 1.0 for the primary composite outcome and 0.4 for ischaemic stroke. PFOC significantly reduced recurrent strokes when compared with medical therapy alone, and the AMPLATZER PFO Occluder was associated with a reduction in the composite measure of recurrent stroke, TIA and early death (HR 0.57, 95% CI 0.33 to 1.00, p=0.048). Interestingly, a statistically significant benefit was not reported in a Cochrane review of the same studies (Li et al. 2015). A network analysis of three PFOC devices (AMPLATZER PFO Occluder, STARFlex Septal Occluder and GORE HELEX) reported high estimates of numbers-needed-to-treat (NNT), indicating low absolute benefits from PFOC compared with medical therapy alone (Stortecky et

al. 2015). Another systematic review (n=4,335; Wolfrum et al. 2014) reported no significant treatment benefit with PFOC among the RCTs analysed, however the relative risk of stroke was reduced in the pooled comparative observational studies.

- 3.24 There is evidence that the type of devices employed during the PFOC procedures may not be clinically equivalent. One RCT (n=660; Hornung et al. 2013), of generally poor methodology and reporting, compared the AMPLATZER PFO Occluder device directly with the GORE HELEX device (discontinued in 2011) and the NMT Medical STARFlex device (also since discontinued). Antiplatelet treatment was also given. The aggregated technical success rate for all the devices was 100%. The GORE HELEX device was associated with increased device embolisation, incomplete device closure, and the requirement for an additional device to be used, compared with the AMPLATZER PFO Occluder. It is worth noting that results from the GORE HELEX device may not be generalisable to the GORE CARDIOFORM Septal Occluder used in the CtE scheme. Device equivalence need to be considered when assessing the published evidence on the procedure.

Emerging clinical evidence

- 3.25 The results of 3 important studies that are directly relevant to the CtE registry were published in a single issue of the New England Journal of Medicine after the literature search had been conducted. It has not been possible for the EAC to critique these new studies for this report, however the key results have been used to inform the responses to the CtE questions (see table 1).
- 3.26 The CLOSE trial by Mas et al. (2017) was an investigator-initiated, multicentre, randomised, open-label, superiority trial set in France (32 sites) and Germany (2 sites). Relatively young patients (aged 16 to 60 years, n=663) who had had a prior ischemic stroke suspected to be caused by embolism mediated through PFO were randomised to three arms in a 1:1:1 ratio (PFOC and long-term antiplatelet therapy [several

devices and antiplatelet regimens]: antiplatelet drugs only: oral anticoagulation only). Mean follow up was 5.3 years. Comparisons were made between PFOC and antiplatelet arms, and antiplatelet and oral anticoagulation arms. There was a procedural complication rate of 5.9% associated with PFOC, and PFOC was significantly associated with development of new AF (4.6% compared with 0.9% for the antiplatelet only arm). However, over the course of follow up, no strokes occurred in the PFOC arm (n=238) compared with 14 strokes in the antiplatelet arm (n=235). This difference was significant (HR 0.03; 95% CI 0 to 0.26; $p<0.001$).

- 3.27 The GORE REDUCE study (Sondergaard et al. 2017), was a multinational, prospective, randomised, controlled, open-label trial. Patients (n=664) were randomised in a 2:1 ratio to receive either a GORE PFOC device (either the HELEX Septal Occluder, which was discontinued in 2011, or CARDIOFORM Septal Occluder) with antiplatelet therapy, or antiplatelet therapy alone. Patients were aged 18 to 59 years (mean age 45.2 years), had had a cryptogenic ischemic stroke within 180 days before randomisation, and had a PFO with an identified right-to-left shunt. After a median follow up of 3.2 years, clinical ischemic stroke occurred in 6 of 441 patients (1.4%) in the PFOC arm compared with 12 of 223 patients (5.4%) in the antiplatelet only arm (HR 0.23; 95% CI 0.09 to 0.62; $p=0.002$). The EAC calculated an event rate for the primary outcome (clinical ischaemic stroke) of 0.43 per 100 patient years for the PFOC arm. PFOC was associated with a serious device-related complication rate of 1.4% and a significantly increased risk of new onset AF (6.6% vs. 0.4%, $p<0.001$). However, 83% of the cases of AF or flutter were detected within 45 days after the procedure, and 59% resolved within 2 weeks after onset.
- 3.28 In an update of the RESPECT trial (Carroll et al. 2013), Saver et al. (2017) reported updated outcomes of patients with a median follow up of 5.9 years. Whereas the earlier publication had reported a non-significant trend towards benefit from PFOC for the primary outcome, a significant improvement was observed after extended follow up. Using ITT analysis,

recurrent ischaemic stroke occurred in 18 patients (3.6%) in the PFOC arm compared with 28 patients (5.8%) in the medical therapy only arm. The event rate for the longer follow-up was 0.58 events per 100 patient years for PFOC compared with 1.07 events per 100 patient years for medical therapy only (HR 0.55; 95% CI 0.31 to 0.999; p=0.046).

- 3.29 The two new trials (Mas et al. 2017 and Sondergaard et al. 2017) and the update of the RESPECT trial (Saver et al. 2017) all report positive results for their primary efficacy outcomes, which is in contrast to earlier published evidence on PFOC. The reasons for this are not clear, but could be related to methodological advances in trial design, such as longer follow up time. This is clearly the case in Saver et al. 2017. Additionally, improved diagnostic work up (for example, better echocardiography and the use of provocation manoeuvres designed to raise the pressure in the right atrium) and patient selection (that is, identifying patients where PFO is likely to be causal rather incidental) may have been a factor, as well as incremental improvements to the PFOC devices themselves. If so, this has important implications for real-world clinical practice. Additionally, the removal of more subjective inclusion criteria and outcomes related to TIA may have effectively increased the power of the studies.
- 3.30 These results should also be considered in the context that although relative benefits are clinically significant, absolute benefits are somewhat small. There is now a clear indication that PFOC causes new onset or worsening AF in around 1 in 20 patients, at a relatively young age. This may increase their risk of stroke in later life and thus reduce their quality of life.
- 3.31 No quality of life data were identified in the literature.
- 3.32 Patients in the CtE registry appear to have similar baseline characteristics and indications for treatment as those in the RCTs. Although statistical comparisons could not be performed due to data heterogeneity, the short term peri-procedural results from the CtE registry were consistent with values from RCTs and observational studies reported in the literature. The

data indicate that PFOC is a relatively safe procedure usually requiring one overnight stay in hospital, and that serious in hospital complications are rare. Interpretation of medium-term data (neurological events) was limited by inconsistency in the definitions of outcomes used in the studies and limited follow up data in the registry. Although the RCTs did not report statistically significant superiority of their primary outcomes, there is some evidence to suggest that the AMPLATZER PFO Occluder device results in better outcomes than other devices. Comparison of the registry results with the medical therapy arms of the RCTs did not demonstrate a clear benefit of PFOC in the CtE registry. Comparison with the intervention arms (that is, patients from RCTs receiving PFOC) suggested that patients in the registry were not achieving the benefit reported in the majority of these studies (particularly the more recently published studies). However, inferiority has not been unequivocally shown. The reasons for the apparent lack of efficacy was unclear, but may be related to the method of measurement and definitions of outcomes, particularly the inclusion of subjective outcomes such as TIA.

Costs and cost effectiveness

Systemic review of cost effectiveness evidence

- 3.33 A systematic review of the economic literature on the cost-effectiveness of PFOC identified one study (Pickett et al. 2014a). It compared PFOC with medical therapy alone from the perspective of the US healthcare system payer. It used clinical data from a meta-analysis (Pickett et al., 2014b) of 3 RCTs (CLOSURE-1 [Furlan et al. 2012], PC [Meier et al. 2013] and RESPECT [Carroll et al. 2013]) and reported that PFOC was cost-effective, having a cost per quality adjusted life year of less than \$50,000 within 3 years of the procedure. The resource and unit cost assumptions adopted in the decision tree analysis were poorly described and there was no transparency of the modelling of events over time. In addition, costs were not generalisable to the NHS England setting, hence the study was judged to have poor internal and external validity. There is therefore material uncertainty on whether its findings on cost-effectiveness apply in

the English setting and more well-conducted cost utility studies, preferably using English costs are required to inform commissioning of the procedure.

Economic analysis

Model structure

3.34 A new model was created by the EAC to estimate the cost consequences of PFOC plus medical therapy (antithrombotic treatment including antiplatelet therapy or oral anticoagulants) compared with medical therapy alone in people who had had a confirmed ischaemic stroke presumed to be due to paradoxical embolism. The model was constructed as a combination of a decision tree to determine PFOC procedural success and operative complications, followed by a Markov model for long term outcomes following discharge from hospital. In the decision tree, people could have a device successfully implanted or not, and could develop major or minor bleeds. The Markov model had 3 health states; stroke-free, neurological event (ischaemic stroke, haemorrhagic stroke or TIA) or death. Once a patient experiences an ischaemic or haemorrhagic stroke, there is a chance in each future cycle that a subsequent stroke can occur. For all patients in each cycle, a TIA can occur regardless of previous neurological events. Complications (development of AF or bleeds) can also occur in each cycle. Death can occur in each cycle but has a higher probability of occurring if a patient has previously experienced a neurological event. The model start age was 45 years, the same as the median age in the CtE registry. The time horizon was 45 years and the cycle length was 1 week. Total costs were reported from an NHS-only perspective and from a wider NHS and social care perspective. A 3.5% discount rate was applied.

Model inputs

3.35 The PFOC CtE registry data, national databases, published studies and clinical opinion were used as sources of model inputs. Patients in the comparator arm (antithrombotic treatment including antiplatelet therapy or

oral anticoagulants) were estimated to have clinical event rates matched to those of the comparator arm of the RESPECT RCT (Carroll et al. 2013).

Costs

3.36 The estimated discounted cost of the PFOC procedure (£8,233) was calculated using data from the CtE register and a costing template completed by the CtE provider sites. NHS Supply Chain provided costs for the device as 'commercial in confidence'. These included overheads of 3% for its internal costs. A further 15% overhead was added to the device costs to meet the procurement and supply costs incurred by NHS trusts to ensure an adequate stock of devices is available for theatres.

Base case results

3.37 When NHS costs only were considered, the total discounted cost of the PFOC pathway was estimated at £12,956, of which procedure-related costs accounted for 63.5% (£8,233). Management of strokes and TIAs was the second largest component (£2,918; 22.5%), followed by medication and primary care (£1,737; 13.4%), with subsequent bleeds accounting for the balance of 0.5% (£68). The total discounted cost of the conservative medical management pathway was estimated at £7,596 per patient. Management of haemorrhagic and ischaemic strokes and TIAs was the largest component (£5,003; 65.9%), followed by medication and primary care (£2,574; 33.9%), with bleeds accounting for the balance of 0.25% (£19). When the costs of PFOC plus medical therapy were compared to the costs of medical therapy alone, the discounted NHS costs were £5,360 per person higher in the PFOC arm over a 45 year time horizon, a 71% increase on the cost of medical therapy only. The benefit from avoided stroke management and medication costs of £2,921 per patient with PFOC was insufficient to offset the initial procedure costs of £8,233 per patient. The cost of the procedure would need to reduce by 65% to £2,854 before the NHS could achieve financial breakeven on the procedure.

- 3.38 When both NHS and social care costs were considered, the total discounted cost per person receiving a PFOC procedure over a 45 year time horizon was estimated at £15,094. This was £3,733 higher than the estimated total discounted costs per person for medical therapy alone (£11,360). The benefits from avoided stroke management (£3,711) and reduced costs in primary care (£837) with PFOC were insufficient to offset the initial procedure costs of £8,233 per patient.
- 3.39 The model predicted that the total number of strokes (ischaemic, haemorrhagic and subsequent strokes) per 1,000 patients over a 45 year time horizon reduced from 456 when patients are managed on medical therapy alone to 274 after the PFOC procedure (a reduction of 182 strokes or about 45%). Associated with this reduction were 54 forecast fewer deaths in the patients receiving the PFOC procedure. New onset AF events (that is new cases of AF which are additional to the background incidence rate expected in the general population at this age) were, however, forecast to increase to over 60 per 1,000 patients over 45 years with PFOC compared with 25 per 1,000 patients managed on medical therapy only. Total adverse clinical events were forecast to decline by 17% with PFOC from 1,594 per 1,000 patients on medical therapy only to 1,318 per 1,000 patients over 45 years.

Analysis of alternative scenarios

- 3.40 The relative risk reduction for stroke following the PFOC procedure, and the time horizon were the main drivers in the model. Changes in other parameters had little impact on the increase in costs from PFOC over medical therapy alone.

Sensitivity analyses

- 3.41 Deterministic, probabilistic and scenario analyses suggest that PFOC was usually cost incurring. For example, in a probabilistic sensitivity analysis only 13% of the 1,000 iterations resulted in PFOC being cost saving. The results were sensitive to changes in the rates of ischaemic stroke with PFOC and medical therapy alone.

Limitations of the economic analyses

- 3.42 Limitations in the analyses include the uncertainties that arise from extrapolating clinical data, particularly stroke rates and associated mortality, from 5.9 years in a clinical trial to lifetime. Evidence suggests that as patients get older, the likelihood of a stroke not being linked to PFO grows and there is no evidence to demonstrate that PFOC has a benefit for these non-PFO related strokes. In the absence of such evidence the model has assumed the annual event rate for strokes due to PFO observed in the RESPECT study (Carroll et al. 2013) is constant over a person's lifetime. This is equivalent to assuming that the increase in the absolute risk of strokes associated with increasing age are not PFO related and that these strokes cannot be avoided by PFOC.

Emerging economic evidence

- 3.43 An economic analysis (Tirschwell et al. 2017) that is directly relevant to the PFOC CtE registry was identified after the literature search had been conducted. This study reported results for the cost-effectiveness of PFOC plus antiplatelet therapy for the secondary prevention of ischaemic stroke compared to medical therapy alone. The study was set in the USA and used clinical data from the RESPECT study (Carroll et al. 2013) and relevant costs from 2016. It concluded that, at 20 years, the procedure had an incremental cost per quality adjusted life year of \$9,842 (about £7,285 using the average exchange rate for 2016) per patient compared with medical therapy alone, that is, it was cost-effective under conventional willingness to pay thresholds for a quality adjusted life year. This was judged by the EAC to be a well-conducted study but the costs of the procedure and subsequent clinical events did not generalise to the English NHS.

4 Responses to the Commissioning through Evaluation questions

- 4.1 Table 1 lists the questions agreed by NHS England for the CtE scheme, and summarises the answers derived from the project, along with comments from NICE.

Table 1: CtE questions with responses

Q	CtE project question	Conclusions/results from the CtE scheme	NICE comments
1	Does patent foramen ovale closure lower the risk of stroke or other embolic clinical events compared to no intervention (as predicted by natural history studies or from modelling)?	<p>Time to event analysis from the CtE registry reported a rate of 2.2 (95% CI 1.2 to 3.6) neurological events per 100 patient years, of which 1.3 (95% CI 0.6 to 2.5) events per 100 patient years are attributed to ischaemic events. In the absence of natural history or modelling studies identified from the literature, the primary outcome data from the control arm (medical therapy only) of published RCTs was used as a proxy comparator. The control arm data reported point estimate rates of between 1.12 and 3.4 events per 100 patient years. However, a direct comparison with published trial data may not be valid for reasons of methodology and generalisability.</p> <p>The incidence of presumed ischaemic stroke appears to be similar or higher in the registry compared with that reported in the control arms of RCTs. However, as it is not possible to provide a statistical comparison between the data, no firm conclusions can be made about inferiority, superiority, or equivalence.</p>	Clinical efficacy data will be validated through data linkage to HES and ONS mortality data. A report analysing findings from the data linkage is planned for summer 2018.

Q	CtE project question	Conclusions/results from the CtE scheme	NICE comments
2	Can UK clinical teams re-produce the success rates for patent foramen ovale closure reported in existing clinical trials, with equivalent or lower complication rates?	<p>Procedural data were well reported in the registry. Technical success was over 99%, while procedural success was around 95%. This is consistent with published data from trials and observational studies.</p> <p>The incidence of neurological events seen in the registry is higher than those reported in most trials, with the exception of the CLOSURE-1 trial (Furlan et al. 2012), which reported similar results. The observational study by Pezzini et al. (2016) reported a similar composite outcome.</p> <p>There was evidence that the incidence of ischaemic neurological events reported in the registry appeared to be higher than expected compared with published literature. However, the EAC cautions that a direct comparison with published trial data may not be valid for reasons of methodology and generalisability.</p> <p>The incidence of peri-procedural complications observed in the CtE registry was largely consistent with the published literature. New onset or worsening AF appears to be the most common adverse event.</p>	<p>The EAC have interpreted this question to include both technical and procedural success, and longer-term efficacy outcomes. Data linkage to HES and ONS mortality data will not alter the procedural and technical success rates but will help validate longer term clinical outcomes. A report analysing findings from the data linkage is planned for summer 2018.</p>

Q	CtE project question	Conclusions/results from the CtE scheme	NICE comments
3	Is patent foramen ovale closure associated with an improved quality of life for these patients?	<p>There was a numerical improvement in the utility score during the follow-up period, however this was only statistically significant at 6 weeks and 6 months after the PFOC procedure. This was associated with a statistically significant improvement in the dimension of anxiety and depression. The median VAS score also showed a statistically significant improvement at 6 weeks and 6 months after PFOC, compared with before the procedure.</p> <p>No data were identified from the literature to answer this question.</p>	
4	Are there any longer-term cardiac complications associated with the use of these devices [for PFO closure] (e.g. erosion with penetration through the wall of the atrium/aorta)?	<p>The registry did not follow up patients for sufficiently long to answer this question.</p>	
5	Do the commercially available current devices perform equivalently?	<p>The AMPLATZER PFO Occluder (St. Jude Medical) and GORE CARDIOFORM Septal Occluder were the principal devices used in the CtE registry. There was no evidence of difference in efficacy or safety between devices.</p> <p>A comparative RCT reported that the GORE HELEX system (discontinued in 2011) was associated with lower rates of complete occlusion, and greater rates of embolisation, than the AMPLATZER PFO Occluder. However, these results may not be generalisable to the GORE CARDIOFORM Septal Occluder device used in the CtE programme.</p>	

Q	CtE project question	Conclusions/results from the CtE scheme	NICE comments
6	What are the short and medium term risks of percutaneous PFO closure?	Technical success was over 99%, whilst procedural success was around 95%. Although there were a total of 3 recorded deaths (0.3%), serious complications appear to be relatively rare. The overall event rate for all neurological events (in-hospital and post-discharge) was 2.2 per 100 patient years. New onset or worsening AF appears to be the most common adverse event affecting 3.5% of people after discharge from hospital. There were no new safety flags identified from the registry that would require an update of NICE IPG472.	
7	What proportion of patients referred to a multidisciplinary team (MDT) for possible percutaneous PFO closure against Commissioning through Evaluation criteria were considered suitable for the intervention?	It is likely that most centres did not use the registry to capture all cases presented to the MDT meeting, and therefore this data cannot be used to answer the question. The demand for PFOC and therefore budgetary impact are unknown.	
8	Are favourable clinical outcomes with patent foramen ovale closure associated with particular patient characteristics (clinical or demographic)?	There were insufficient data reported in the registry to allow for subgroup analysis. Data from the literature indicates that patients with a larger shunt and/or an atrial septal aneurysm may benefit more from PFOC than patients who lack these risk factors, but this is not conclusive.	Patients who are intolerant or unable to take medical therapies (warfarin/aspirin/other antiplatelets/a combination) may benefit from PFOC.
9	What are the average full procedural costs of percutaneous patent foramen ovale closure to the NHS?	The central estimate of the cost of a PFOC procedure is £8,229 (range £6,939 to £9,251).	

Q	CtE project question	Conclusions/results from the CtE scheme	NICE comments
10	What are the potential cost savings for the NHS in patients receiving percutaneous patent foramen ovale closure?	The PFOC procedure was estimated to cost the NHS an additional £5,360 per patient over their lifetime when compared with medical therapy alone. The PFOC pathway had estimated costs of £12,956 per patient, compared with £7,596 for the medical therapy only pathway. The procedure cost of £8,233 (including bleeds) was not offset by savings in primary care (£837) or strokes and TIA avoided (£2,084).	
11	What is the likely cost-effectiveness of percutaneous PFO closure in the NHS, based on UK costs?	In a cohort of 1,000 patients with similar characteristics to those in the CtE registry, over a 45-year period, PFOC plus medical therapy was estimated to reduce the number of strokes from 456 when patients are managed only on medical therapy to 274, a reduction in strokes of 182 or 40%. Associated with this reduction were 54 forecast fewer deaths in the cohort receiving the PFOC procedure.	

5 Issues for consideration

- 5.1 The following issues should be considered when reviewing the evidence on PFOC and the answers to the specific questions in section 4.

Project process and oversight

- 5.2 NHS England commissions CtE projects from NICE, and NICE manages the projects to a timescale, process and methods devised by NHS England. In June 2017, NHS England published a policy document governing these projects ([Methods: Commissioning through Evaluation](#)), but the majority of the PFOC scheme was developed, conducted and concluded before this document was published. Generally, however, the process followed was similar to the currently published process.
- 5.3 A Cardiology CtE Steering Group was established by NHS England to oversee the project and involved clinical leads and other stakeholders. NICE and the EAC worked closely with the steering group and with the PFOC Individual Technology Group, in the design of the PFOC registry and to ensure all parties were aware of data collection requirements and to reinforce clinical ownership of the project.
- 5.4 NICE is accountable to Ann Jarvis, Head of Acute Programmes for Specialised Services at NHS England, for delivery of the CtE schemes. For this scheme, NICE reported on a quarterly basis via standard reports and monitoring meetings with NHS England.
- 5.5 This project did not follow the planned timelines because at NHS England's request, the clinicians were given an extra 2 months to improve data submission rates. The National Institute for Cardiovascular Outcomes Research (NICOR) was contracted by Newcastle and York EAC to design and host the on-line registry for PFOC procedures, to provide a project management function to promote data entry quality and completeness by commissioned CtE provider sites, and to link registry data with HES and ONS mortality datasets. A Data Access Request Service application was made to NHS Digital for data linkage to HES and

ONS mortality records. This has now been approved and Newcastle and York EAC will carry out the data linkage in order to explore whether the linked data leads to a need to update the clinical, safety and economic data from the CtE project. A report analysing findings from the data linkage is planned for summer 2018.

Reflections from NICE

5.6 The lack of long term outcome data reflects the slow implementation of the CtE scheme. NICE and NHS England have learnt from this and now include a 6 month feasibility study before the start of new schemes. This ensures that procedures can be undertaken and data collected from the start of the scheme.

Strengths and limitations

5.7 The registry had several strengths. It enrolled indicated patients consecutively, reported important clinical outcomes, and represented a pragmatic real-world cohort of patients receiving PFOC as it might be performed in the NHS. Thus the external applicability of the registry to future practice is high, although improvements in the procedure protocol and a learning curve effect may ultimately lead to improved outcomes. Over 1,000 patients were initially recruited onto the registry. This was more than all the other experimental and observational studies identified by the EAC, with the exception of the study by Wallenborn et al. (2013). The Wallenborn study was a retrospective analysis rather than a bespoke prospective registry. The large number of people included in the CtE registry gives it power to detect rarer outcomes and greater precision for event rates, and overall gives increased credibility to the results reported. In addition, following an initial disappointing response from centres in providing follow-up data, this improved considerably towards the end of the scheme such that there was about 700 patient years follow up available for analysis. This improved the precision and certainty of time-to-event analysis. Although follow-up was still not optimal (39.7% for eligible patients at 2 years), completion of data fields was regarded as good.

5.8 The CtE registry had several limitations. It was a single armed study therefore comparisons had to be made implicitly with results published in the literature. This had 2 limitations. Firstly, no statistical or quantitative comparisons could be made with the comparator of interest, which was conservative medical management (use of antiplatelet or oral anticoagulant drugs). Secondly, much of the published literature was not directly comparable to the registry. Specifically, comparison of the CtE data with the trial data was limited by differences in outcome terminology and measurement, and possible issues with generalisability of the population (for instance, recent research on PFO closure suggests that thorough diagnostic workup, including better echocardiography and the use of provocation manoeuvres designed to raise the pressure in the right atrium and improve the detection of PFO, is essential). Thus inferences of equivalence (or not) are subject to considerable uncertainty. Other specific and non-specific limitations with the registry include the following:

- The registry was funded for a maximum follow up of 2 years, meaning that data on long term efficacy outcomes or complications were not available.
- Although data completeness was greater than 75% for the minimum data set, most patients did not reach the 2 year follow up date because the procedures were carried out at different times during the duration of the CtE scheme. Of the 901 patients with an implanted device, only 282 (31.3%) were eligible for follow up at 2 years (that is they had a discharge status of alive at their last hospital visit and reached the second anniversary of their procedure during the data collection phase of the CtE scheme). Data was collected for 112 of these patients (39.7%) at 2 years. It is possible that the cohort of patients receiving treatment early in the project may not be representative of the overall cohort (for example, because the outcomes improved with the number of procedures carried out, that is, there was a learning effect).
- The registry analysis would be more robust with data linkage to the ONS mortality dataset, to validate calculated mortality rates in the CtE

cohort and provide greater coverage. Data linkage to HES could also provide further validation and coverage of morbidity data. A report analysing findings from the data linkage is planned for summer 2018.

- The analysis relies on complete reporting of all event data. Patients who are lost to follow up are censored from the analysis, but it is unclear if these people are representative of the overall cohort.
- Finally, patients may have multiple events (excluding death), but the Kaplan-Meier protocol only analyses time to first event, meaning that if a minor event is followed by a major stroke, the latter will not be counted.

5.9 Initially, 24 neurological events were reported in-hospital or post-discharge (with potential for multiple events per patient). However, late in the data collection phase of the CtE scheme, it was noted that there was a degree of ambiguity in the reporting of outcomes, in particular the classification of neurological events (for example, the permanence of any resulting disability and whether the underlying cause of the event was ischaemic or haemorrhagic in nature). To resolve these issues, NICOR contacted each centre involved in the CtE scheme to ask for clarification on the outcomes in each patient in whom a neurological event had been reported and where there were potential problems with reporting consistency. Two of the clinical leads of the CtE cardiac schemes discussed each case individually and came to concordance on what the neurological outcome(s) were. Neurological events were confirmed for 16 patients. The revised results of the neurological event rate have been included in this report, and are included as an addendum in the evaluation report.

5.10 The registry captured information on the resources required to conduct PFOC, enabling the cost of the procedure to be estimated. This information together with the quality of life data may be of use in any future cost-effectiveness studies. Data linkage to HES will also inform these analyses. A report analysing findings from the data linkage is planned for summer 2018.

6 Equality considerations

- 6.1 PFO is more common in young stroke patients (aged less than 55 years), in whom nearly 40% of strokes are cryptogenic, but no particular equality issues relating to people who have had cryptogenic strokes were identified in the CtE data or in the literature presented.

7 Authors

For NICE

Dr. Helen Powell

Lee Berry

Dr. Hannah Patrick

Mirella Marlow

For Newcastle and York EAC

Dr. Iain Willits

Kim Keltie

Dr. Sam Urwin

Helen Cole

Joyce Craig

Dr. Andrew Sims

For the Cardiology CtE steering group

Dr. Robert Henderson

Dr. Mark de Belder

Professor Nicholas Linker

8 References

Carroll JD, Saver JL, Thaler DE et al. (2013) Closure of patent foramen ovale versus medical therapy after cryptogenic stroke. *New England Journal of Medicine* 368(12): 1092-100

Furlan AJ, Reisman M, Massaro J et al. (2012) Closure or medical therapy for cryptogenic stroke with patent foramen ovale. *New England Journal of Medicine* 66(11): 991-9

Hornung M, Bertog SC, Franke J et al. (2013) Long-term results of a randomized trial comparing three different devices for percutaneous closure of a patent foramen ovale. *European Heart Journal* 34(43): 3362-9

Inglessis I, Elmariah S, Rengifo-Moreno PA et al. (2013) Long-term experience and outcomes with transcatheter closure of patent foramen ovale. *JACC: Cardiovascular Interventions* 6(11):1176-83

Kent DM, Dahabreh IJ, Ruthazer R et al. (2016) Device closure of patent foramen ovale after stroke: Pooled analysis of completed randomized trials. *Journal of the American College of Cardiology* 67(8):907-17

Li J, Liu J, Liu M et al. (2015) Closure versus medical therapy for preventing recurrent stroke in patients with patent foramen ovale and a history of cryptogenic stroke or transient ischemic attack. *Cochrane Database of Systematic Reviews* 9:CD009938

Mas JL, Derumeaux G, Guillon B et al. (2017) Patent foramen ovale closure or anticoagulation vs. antiplatelets after stroke. *New England Journal of Medicine* 377(11): 1011-21

Meier B, Kalesan B, Mattle HP et al. (2013) Percutaneous closure of patent foramen ovale in cryptogenic embolism. *New England Journal of Medicine* 368(12): 1083-91

Mirzaali M, Dooley M, Wynne D et al. (2015) Patent foramen ovale closure following cryptogenic stroke or transient ischaemic attack: Long-term follow-up of 301 cases. *Catheterization & Cardiovascular Interventions* 86(6): 1078-84

Pezzini A, Grassi M, Lodigiani C et al. (2016) Propensity score-based analysis of percutaneous closure versus medical therapy in patients with cryptogenic stroke and patent foramen ovale: The IPSYS registry (Italian Project on Stroke in Young Adults). *Circulation: Cardiovascular Interventions* 9(9)

Pickett CA, Villines TC, Ferguson MA, et al. (2014a). Cost effectiveness of percutaneous closure versus medical therapy for cryptogenic stroke in patients with a patent foramen ovale. *American Journal of Cardiology* 114(10): 1584-9

Pickett CA, Villines TC, Ferguson MA, et al. (2014b). Percutaneous closure versus medical therapy alone for cryptogenic stroke patients with a patent foramen ovale: meta-analysis of randomized controlled trials. *Texas Heart Institute Journal*. 41(4): 357-67

Saver JL, Carroll JD, Thaler DE et al. (2017) Long-term outcomes of patent foramen ovale closure or medical therapy after stroke. *New England Journal of Medicine* 377(11): 1022-32

Sondergaard L, Kasner SE, Rhodes JF et al. (2017) Patent foramen ovale closure or antiplatelet therapy for cryptogenic stroke. *New England Journal of Medicine* 377(11): 1033-42

Stortecky S, da Costa BR, Mattle HP et al. (2015) Percutaneous closure of patent foramen ovale in patients with cryptogenic embolism: a network meta-analysis. *European Heart Journal* 36(2): 120-8

Taggart NW, Reeder GS, Lennon RJ et al. (2017) Long-term follow-up after PFO device closure: Outcomes and complications in a single-center experience. *Catheterization & Cardiovascular Interventions* 89(1): 124-133

Thomson JD, Hildick-Smith D, Clift P et al. (2014) Patent foramen ovale closure with the Gore septal occluder: initial UK experience. *Catheterization & Cardiovascular Interventions* 83(3): 467-73

Tirschwell DL, Marks D, MacDonald L et al. (2017). Cost-effectiveness of percutaneous PFO closure in patients with history of cryptogenic stroke in the United

States. Presentation at ISPOR 22nd Annual International Meeting, 20-24 May 2017, Boston, USA

Wallenborn J, Bertog SC, Franke J et al. (2013) Recurrent events after percutaneous closure of patent foramen ovale. *Catheterization & Cardiovascular Interventions* 82(4): 541-6

Wolfrum M, Froehlich GM, Knapp G et al. (2014) Stroke prevention by percutaneous closure of patent foramen ovale: A systematic review and meta-analysis. *Heart* 100(5): 389-95

Appendix A: Sources of evidence considered in the preparation of the project report

- Commissioning through Evaluation (CtE). Percutaneous closure of patent foramen ovale (PFOC) to prevent recurrent cerebral embolic events: Final report – Newcastle and York External Assessment Centre, February 2018