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NICE OBSERVATIONAL DATA UNIT (ODU)

Commissioning through Evaluation (CtE) Percutaneous Closure of Patent Foramen Ovale (PFOC) to prevent recurrent cerebral embolic events

FINAL REPORT

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Contents

Executive summary

Around 80% of strokes in the UK are of ischaemic origin, with most being due to blockage of arteries in the brain caused by thromboembolism. In around 25% of cases, the putative source of the thromboembolism cannot be found, and these are known as cryptogenic strokes (or strokes of undetermined origin). In patients with cryptogenic stoke who are found to have a patent foramen ovale (PFO), which is present in around 25% of the general population, the stroke may be due to paradoxical embolism. The rationale for PFO closure (a percutaneous procedure which blocks the PFO) is to reduce the reoccurrence of stroke in patients with a prior event caused by presumed paradoxical embolism. Typically, this is a young, relatively healthy population.

In order to evaluate the PFO closure procedure, NHS England has set up a multi-centre observational registry using the process of Commissioning through Evaluation (CtE). The registry was designed to include patients who had had a confirmed ischaemic stroke presumed to be due to paradoxical embolism. The registry recorded a range of clinical outcomes with a maximum follow up of 2 years. The aims of the CtE registry were to provide data on the safety, efficacy and costs of PFO closure in a real-world setting, and specifically to answer 11 pragmatic questions concerning these issues. As the registry was single-armed, a parallel literature search was undertaken in order to present the registry findings in the context of published studies in other populations, and to assess whether procedural outcomes were consistent with previously reported studies. Information gained from the registry will be used to inform future commissioning.

The PFOC analysis included 940 patients of which 901 underwent device implantation. The median age of the patients was 45 years and the large majority did not experience cardiac symptoms from the PFO. Nearly all patients had a device successfully fitted (99.3% [95% CI 98.6 to 99.8%]), with a procedural success rate of 95.1% (95% CI 93.5 to 96.4%). The registry reported a major complication rate of 5.2% (95% CI 3.8 to 7.0%) following discharge, including 3.5% (95% CI 2.3 to 5.0%) of patients who experienced new onset atrial fibrillation. These results were consistent with those reported in RCTs and observational studies from the literature, and emphasise that PFO is a relatively safe procedure. The registry also reported that PFO closure may be associated with a reduction in anxiety and depression.

In the medium term, there was a neurological event rate of 3.4 (95% CI 2.1 to 5.0) per 100 person years (PY) and an ischaemic event rate of 1.3 (95% CI 0.6 to 2.5) per 100 PY over a total aggregated follow-up period of almost 700 PY. These results were similar to the control arms reported in the RCTs, but were numerically inferior to the primary efficacy outcomes reported in the intervention arms of these trials, particularly results reported from two new and one extended clinical trials published in September 2017. However, the validity of indirect comparisons with published data is problematic for several reasons: firstly because of differences in the methodology used between studies (e.g. different definitions used for outcomes); secondly because of issues with generalisability (e.g. diagnostic work up of patients in the included population); and thirdly because of issues with late data entry and quality assurance of registry results in the allotted timeframe **[described in Addendum]**.

In conclusion, the CtE registry has reported data that show that PFO closure has a high technical success rate and is relatively safe in the short and long-term. In terms of clinical efficacy, although neurological and ischaemic event rates appeared ostensibly higher than some published RCTs, the validity of such comparisons is questionable. It is noted that the

natural history of this population of patients outside of tightly controlled experimental studies is not well described.

Any clinical benefits of PFO closure should be considered in the context of the procedural costs, which the EAC has calculated at £8,303 (range of £6,946 to £9,254). Although conclusions cannot be made about the cost effectiveness or cost saving potential of the procedure from the CtE registry data alone, work to address the economics of PFOC is currently in progress. Additionally, further work is on-going to validate the registry efficacy results and, as much as possible, contextualise these against the published literature (including the recently published RCTs).

Abbreviations

AF	Atrial fibrillation
ASD	Atrial septal defect
CG	Clinical guideline
CI	Confidence interval
CT	Computed tomography
CtE	Commissioning through Evaluation
CVA	Cerebrovascular accident
EAC	External Assessment Centre
ECG	Electrocardiograph
ESC	European Society of Cardiology
FU	Follow up
HR	Hazard ratio
ICE	Intracardiac echocardiogram
ICER	Incremental cost-effectiveness ratio
INR	International Normalized Ratio
IPG	Interventional procedures guidance
IQR	Inter-quartile range
ITT	Intention to treat
MDS	Minimum data set
MDT	Multi-disciplinary team
MRI	Magnetic resonance imaging
LAAO	Left atrial appendage occlusion
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NICOR	National Institute for Cardiovascular Outcomes Research
NYHA	New York Heart Association
OR	Odds ratio
PFO	Patent foramen ovale
PFOC	Patent foramen ovale closure
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PY	Person years
QALY	Quality adjusted life year
RIND	Reversible ischaemic neurological deficit.
QoL	Quality of life
RCT	Randomised controlled trial
RR	Relative risk
SD	Standard deviation
SE	Systemic embolism
TIA	Transient ischaemic attack
TOE	Transoesophageal echocardiogram
TTE	Transthoracic echocardiogram

Section 1: Introduction

1.1 NHS ENGLAND COMMISSIONING THROUGH EVALUATION – PATENT FORAMEN OVALE CLOSURE (PFOC)

NICE provides support to NHS England in Commissioning through Evaluation (CtE):

"NHS England's Commissioning through Evaluation (CtE) programme enables a limited number of patients to access treatments that are not funded by the NHS, but nonetheless show significant promise for the future, while new clinical and patient experience data are collected within a formal evaluation programme."

The work commissioned by NICE ('Project RX085') from Newcastle and York (NY) EAC comprises evaluation of three percutaneous cardiac procedures:

- Percutaneous occlusion of the left atrial appendage in non-valvular atrial fibrillation for the prevention of thromboembolism (NICE IPG349, June 2010). Shortened term used is 'LAAO'.
- Percutaneous Closure of Patent Foramen Ovale to prevent recurrent cerebral embolic events (NICE IPG472, December 2013). Shortened term used is 'PFO Closure'.
- Percutaneous mitral valve leaflet repair for mitral regurgitation (MitraClip) (NICE IPG309, August 2009). Shortened term used is 'MitraClip'.

A Cardiology CtE Steering Group is established as a subgroup of the NHS England Cardiothoracic Services Clinical Reference Group (CRG). It reports to the Programme of Care Board for Internal Medicine for NHS England. Three Individual Technology Groups report to the CtE Steering Group on the progress of the above three specialised cardiological interventions which form the cardiac CtE programme.

The National Institute for Cardiovascular Outcomes Research (NICOR) was contracted by NY EAC to design and host an 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 Hospital Episode Statistics (HES) and Office of National Statistics (ONS) mortality datasets. NICOR and the EAC consulted the PFOC Individual Technology Group in the design of the PFOC registry. NICOR were the formal data owner of the registry, and were the applicant to NHS Digital for data linkage with HES and ONS.

NY EAC's objectives in Project RX085 from NICE were to:

- review existing register data fields in each dataset and advise on their suitability for updating and developing NICE guidance;
- advise on the appropriateness of register data fields for each dataset being proposed or considered in relation to clinical and cost effectiveness outcomes to enable NICE to provide NHS England with further data to help inform future commissioning decisions for the procedures;
- establish processes to a) ensure on-going review of the PFOC dataset quality, completeness and coverage, with action plans for improvements where needed and b) deliver regular evaluative reports that are useful for decision making;

- update the literature searches since publication of each NICE interventional procedures guidance (IPG) in order to identify publications of relevance;
- manage the contract with NICOR and participate in the CtE Steering Group for cardiovascular procedures;
- develop a protocol for analysis of data and consult with key partners (listed above) to gather views on the proposed methodology and proposed outputs;
- produce a final report (not intended for publication) answering the CtE evaluation questions set by NHS England (tabulated below);
- present findings in the form of a publishable paper (to be submitted for peer review for a high impact journal). This should be of a standard to be included as an input in the evidence base of the NICE technology appraisals programme (http://www.nice.org.uk/article/PMG9/chapter/Foreword);
- advise on further research that might be needed to generate clinical and cost effectiveness evidence in line with methods used in NICE evaluation programmes, including suitable study designs for such research.

Outputs required by NICE from NY EAC and delivered prior to this final report were:

- Output One [1] - a report for presentation to the CtE Steering Group on all three procedures, analysing the coverage, quality and completeness of the register to date, and making preliminary recommendations about the definitive dataset to inform NHS England's contracts for the procedures with the specialist centres, and to meet NICE's needs in relation to updating guidance. **Completed 28/11/2014**.
- Output Two [2] - a report for submission to the CtE Steering Group for cardiovascular procedures and collaborating partners proposing: a) a process to ensure on-going review of the database quality, completeness and coverage, with action plans for improvements where needed and b) the format of evaluative reports designed to be useful in informing decision making for guidance development. **Completed 04/02/2015**.
- Output Three [3] - a report for submission to NICE and the CtE Steering Group proposing a draft protocol for analysis of data that describes the methods that will be used to compare effectiveness of each of the procedures between propensity-matched cohorts of patients undergoing the range of treatment options (including cost analysis). This will have been circulated for consultation with key partners (listed above) and adjusted as appropriate prior to presentation to NICE. **Completed 31/03/2015.**

The above three outputs from the project, all of which were shared with the CtE Steering Group and approved by them, are used as source material for the general background and methods sections of this final report from NY EAC to NICE.

The NHS England questions for CtE of PFOC were originally presented to NICE, discussed with NY EAC, and edited to the final form presented in the Table 1 below.

Table 1. Patent Foramen Ovale (PFO) Closure to Prevent Stroke

Questions from NHS England	Final version of question, as amended by NICE following discussion with EAC
1. Does patent foramen ovale closure offer these patients a lower risk of stroke or other embolic clinical events compared to those predicted by natural history studies? From modelling, how many strokes would likely have been avoided?	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)?
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?	NICE agrees the question is appropriate
3. Is patent foramen ovale closure associated with an improved quality of life for these patients?	Is patent foramen ovale closure associated with an improvement in quality of life?
4. Are there any longer-term cardiac complications associated with the use of these devices (e.g. erosion with penetration through the wall of the atrium/aorta)?	N/A unless an extended time period for the project is agreed.
5. Do the commercially available current devices perform equivalently?	Which devices are used to undertake PFO? What are the device-specific efficacy and safety outcomes in CtE funded patients undergoing the procedure? In particular, is there any published or register evidence of complications in the long term from percutaneous PFO closure (e.g. erosion with penetration through the wall of the atrium/myocardium/pericardium)?
6. Is the frequency of complications sufficiently low to provide a positive risk-benefit ratio?	What are the short and medium term risks of percutaneous PFO closure? (If the CtE project indicated that this procedure has a more risky safety profile than appears in the current NICE interventional procedures guidance, it could potentially lead to NICE updating the guidance, in line with normal processes.)
7. How many patients with a stroke believed to be due to paradoxical embolism in association with a patent foramen ovale might benefit from PFO closure? i.e. what is the likely clinical need if this procedure becomes routinely commissioned?	What proportion of patients referred to an MDT for possible percutaneous PFO closure against Commissioning through Evaluation criteria were considered suitable for the intervention?
8. What are the characteristics of patients who are successfully treated compared to those in whom treatment is unsuccessful? Are there subsets of patients who get a particularly advantageous result? Conversely, are there subsets of patients for whom this treatment is not effective? Do patients of different gender or from different ethnic origins respond equivalently?	Are favourable clinical outcomes with patent foramen ovale closure associated with particular patient characteristics (clinical or demographic)?
9. What is the true procedural cost of patent foramen ovale closure in the NHS?	What are the average full procedural costs of percutaneous patent foramen ovale closure to the NHS?

Questions from NHS England	Final version of question, as amended by NICE following discussion with EAC
10. What costs savings might occur in the NHS as a result of patent foramen ovale closure?	What are the potential cost savings for the NHS in patients receiving percutaneous patent foramen ovale closure? (**NY EAC note, October 2017**: This question will be answered by a cost consequences analysis to be provided in a separate report to NICE by 29 December 2017.)
11. What is the cost-effectiveness of patent foramen ovale closure based on UK procedural and follow-up costs?	What is the likely cost-effectiveness of percutaneous PFO closure in the NHS, based on UK costs? (**NY EAC note, October 2017**: This question will be answered by a cost consequences analysis to be provided in a separate report to NICE by 29 December 2017.)

1.2 DESCRIPTION OF THE PROCEDURE

The PFOC procedure is described in NICE IPG472:

"Percutaneous closure is performed using local anaesthesia and intravenous sedation, or with the patient under general anaesthesia. A closure device is introduced using a guide wire and delivery sheath through a small incision in the groin into the femoral vein. It is then passed into the heart and across the patent foramen ovale. The closure device is released to close the defect using image guidance such as echocardiography. Devices of differing design and mechanism are available."

Three manufacturers' CE marked devices that are eligible for the CtE programme were available and used in the UK. Each manufacturer had model variants in the PFOC register datasets, as stated. Each device also came in a range of sizes, to suit anatomical differences:

- the 'AMPLATZER' range, manufactured by St. Jude Medical (now owned by Abbott). Three variants listed in the CtE dataset were the AMPLATZER PFO Occluder, the AMPLATZER Septal Occluder and the AMPLATZER Cribriform;
- the 'GORE CARDIOFORM Septal Occluder', manufactured by W. L. Gore and Associates Inc. The V1.6 CtE launch version of the PFOC dataset, (December 2014) specified the 'GORE HELEX Septal Occluder'. However, this had been discontinued by the manufacturer in 2011 and replaced by the GORE CARDIOFORM Septal Occluder. The live version of the CtE dataset was therefore updated in June 2015 and the only variant listed in the dataset was the GORE 'GSO', which is understood to mean the GORE CARDIOFORM Septal Occluder;
- the 'Figulla Flex', manufactured by Occlutech. Three variants listed in the CtE dataset were the Figulla Flex II ASD Occlutech Closure Device, the Figulla Flex II PFO Occlutech Closure Device and the Figulla Flex UNI Occlutech Closure Device.

Percutaneous PFOC received a positive recommendation with normal arrangements from NICE (IPG472). The guidance recommended that the procedure should only be performed in units with appropriate arrangements for urgent cardiac surgical support in the event of complications. NICE IPG472 does not clearly define which patients should be eligible for PFOC, but states: "The optimal treatment for patent foramen ovale in patients who have had a thromboembolic event remains undefined. Medical management with anticoagulation (usually warfarin) or antiplatelet therapy (for example aspirin) is commonly used to reduce

the risk of further paradoxical thrombus emboli. Surgical closure of patent foramen ovale is sometimes performed as an adjunct to other open-heart surgery, but is rarely done on its own because of associated morbidity.”

Section 2: Methods

2.1 CTE PFOC PROVIDERS AND PROGRAMME GOVERNANCE

Hospitals providing the CtE procedures in the 20 centres participating in the PFOC scheme are:

- Barts Health NHS Trust and The Heart Hospital, University College London Hospitals
- Brighton & Sussex University Hospitals NHS Trust
- Central Manchester Hospitals NHS Foundation Trust/University Hospitals of South Manchester NHS Foundation Trust
- Guy's and St Thomas' NHS Foundation Trust
- King's College Hospital NHS Foundation Trust
- Leeds Teaching Hospitals NHS Trust
- Liverpool Heart & Chest Hospital NHS Foundation Trust
- Nottingham University Hospitals NHS Trust
- Oxford University Hospitals NHS Trust
- Papworth Hospital, in partnership with Essex Cardiothoracic Centre
- Royal Brompton & Harefield NHS Foundation Trust
- Royal Wolverhampton NHS Trust
- Sheffield Teaching Hospitals NHS Foundation Trust
- St George's Healthcare NHS Trust
- The Newcastle upon Tyne Hospitals NHS Foundation Trust
- University Hospital Birmingham NHS Foundation Trust
- University Hospitals Bristol NHS Foundation Trust
- University Hospitals Leicester NHS Trust
- University Hospital of North Staffordshire NHS Trust
- University Hospital Southampton NHS Foundation Trust

The criteria used to select the hospitals for the CtE work considered a number of competing factors and are described in the NHS England Specialised Services Circular (SSC) 1452 for PFOC. An advisory panel made recommendations to NHS England as to which providers should be selected to be CtE centres. The final selection of centres was undertaken by the regional Medical Directors.

The NHS England Cardiac CtE Clinical Lead for PFOC is Dr. Robert Henderson, Consultant Cardiologist, Nottingham University Hospitals NHS Trust. Dr. Henderson is Chair of the NHS England PFOC Individual Technology Group. The role of the Group, set out in its Terms of Reference (ToR), is to:

- Work with the EAC and the National Institute for Cardiovascular Outcomes Research (NICOR) on the development of the relevant dataset.
- Define and clarify patient access criteria, where required, within the terms of the published policy statements / specification.
- Ensure that all participating centres are collecting, verifying and uploading data in a timely manner.
- Ensure that all participating centres are collecting follow-up data appropriately.
- Monitor performance of all centres performing procedures as part of CtE and report any concerns to the Steering Group.

- Monitor referrals, patient pathways and waiting times for the relevant procedure at all participating centres (including pathways for patients who do not receive the CtE treatment).

2.2 CTE PFOC COMMISSIONING DETAILS

NHS England commissioned a total of 600 PFOC procedures in each full financial year of the cardiac CtE scheme. Each of the 20 centres was required to do no more than 30 procedures per year. As CtE commenced on 01/10/2014, each centre could do no more than 15 PFOC procedures in 2014/15. Funding was made available by NHS England for each centre to do 30 procedures in 2015/16, making 45 procedures per centre in total.

Owing to slower than anticipated roll-out of the programme, some centres were permitted, by NHS England Specialised Services Circular SSC 1669 (November 2016), to carry on with their 2015/16 activity plans in financial year 2016/17, up to the contracted number of 900 procedures in total for the PFOC CtE programme.

2.3 INCLUSION AND EXCLUSION PATIENT SELECTION CRITERIA

According to the NHS England Specialised Services Circular (SSC) 1452 for PFOC:

“The decision to perform PFO closure in cryptogenic stroke will be made by an MDT which must include a neurologist or stroke physician and a cardiologist. Patients should be considered for PFO closure if they fulfil the following criteria:

- clinical syndrome comprising one or more neurovascular event(s) confirmed by brain imaging demonstrating changes consistent with ischaemia.
- clinical syndrome believed by the MDT to be highly likely to be due to right-to-left intra-cardiac shunting.
- thorough investigation has demonstrated no other likely source of the clinical syndrome
- demonstration of a PFO with significant right to left shunting either spontaneously or during Valsalva
- the patient has been fully informed and consent obtained.

Patients can be referred by cardiologists, stroke physicians or other specialists to a service in a specialist cardiac centre. This must be in line with the specialised service specifications for cardiology and cardiac surgery. Direct referral to cardiac centres from primary care and general practice requesting consideration for PFO closure will not be accepted.”

2.4 PRIMARY DATA COLLECTION

2.4.1 Database details and information governance arrangements

NICOR worked with the CtE PFOC Individual Technology Group and NY EAC to produce the final dataset for PFOC.

NY EAC produced ‘RX085 Output One - Recommendations on three NHS England Commissioning through Evaluation (CtE) registry draft datasets for MitraClip, LAAO and PFO Closure cardiovascular procedures’.[1] (November 2014). This identified and appraised new evidence added to the literature base and public domain since the original NICE IP237/2 overview [4] was published and compared findings against the data fields contained in the draft PFOC CtE dataset.

The final PFOC dataset was developed into the online database by NICOR and the latest version may be downloaded as a Microsoft Excel spread sheet (last updated 13/05/2016).

Regarding information governance arrangements, as Data Controller, NICOR's responsibilities were:

- To ensure that a dataset being proposed or used for national data collection has appropriate independent oversight, and that all relevant data will be made available to NICE for use in developing guidance.
- To provide NY EAC with a monthly download of episode level full raw data sets from each registry (out with normal NICOR data sharing policy and following the 'Use of Data' principles agreed with NY EAC). Data cleansing will happen to usual NICOR schedule. Monthly downloads may be aggregated or incremental. The EAC will provide feedback to NICOR on any data quality / completeness issues observed in the monthly raw data downloads.
- To arrange and undertake data linkage with Hospital Episode Statistics (HES) and Office of National Statistics (ONS) mortality data and provide complete data extract(s) to NY EAC in order to check for extra safety and efficacy, clinical effectiveness or resource utilisation information.
- To arrange and maintain appropriate EQ-5D-5L licensing arrangements to cover all projected patient volumes commissioned by NHS England in its CtE programme. This should include all commissioned follow up visits.
- To provide a telephone helpdesk service for answering technical enquiries / requests and for individual registration and access to each registry web portal. Clinical enquiries will need to go to the NICOR project manager and NY EAC may be co-opted to help NICOR respond to clinical or scientific queries.
- To operate within the general principles of Good Clinical Practice (GCP) in research, as outlined in the Research Governance Framework for Health and Social Care 2005.
- To make all necessary applications to comply with information governance requirements. These include but are not restricted to:

    i complete the Information Governance Statement of Compliance process to the satisfaction of the NHS Health and Social Care Information Centre

    ii demonstrate compliance with the Data Protection Act 1998. This is also particularly relevant when data will leave or enter the EU. Appropriate regard needs to be paid to international regulations

    iii complete the Confidentiality Advisory Group application process to comply with the NHS Health Research Authority requirements for Section 251 approval

2.4.2 Active surveillance

NICOR provided NY EAC with their Minimum Data Standard (MDS) Summary Document for Cardiac CtE **(Confidential)**. Some of the background detail is extracted in the below summary:

"While NICOR undertakes a number of manual and automated data quality control processes, the responsibility for data quality is shared with clinicians and organisations undertaking procedures in the NHS. It is particularly important that data are collected for patients who experience adverse outcomes (such as death, stroke, bleeding) and harm.

NICOR aims to further assist organisations in their data submissions by defining a minimum data standard (an acceptable standard for data submissions to be measured against), to provide feedback to the provider organisations on the data quality of their quarterly submissions and to give organisations the opportunity to improve and resubmit the data should improvements be required."

The final NICOR MDS for PFOC CtE baseline data completeness monitoring contained 19 key fields. Six additional fields were monitored for patient completion of EQ-5D questionnaires and EuroQol data entry (NICOR field identifiers 3.19 to 3.24). These are summarised in Table 2:

Table 2. Fields in registry used for monitoring of data completeness.

NICOR Field identifier	Data Field
1.03	NHS Number
1.06	Birth date
1.10	Postcode
2.03	Reason for treatment
3.08	Hypertension
3.18	Date EuroQol form filled
3.19	EuroQol Mobility
3.20	EuroQol Self-care
3.21	EuroQol Usual activities
3.22	EuroQol Pain / discomfort
3.23	EuroQol Anxiety / depression
3.24	EuroQol Health state today
5.01	Brain scan
5.04	Echo shunt grade
7.01	Medications
8.01	Date of admission
8.03	Date/time of procedure
8.06	Consultant responsible
8.27	Number of devices implanted
8.29	1st Device used
9.01	Device-specific complications
9.04	Neuro/embolic problems
9.10	Status at discharge
9.11	Discharge date
9.13	Successful procedure, no complications

The seven follow-up MDS fields for PFOC data completeness monitoring at 6 weeks were:
10.02 Device still in situ
10.03 Embolisation/retrieval
10.06 Further intervention
10.08 Death
10.13 Neurological event
10.18 Atrial fibrillation
10.27 6 week EQ-5D-5L form filled

The equivalent variables were also monitored for follow up data at 6 months, 1 year, and 2 years.

Summary reports were submitted to NICE by NY EAC on a quarterly basis, to a standard reporting template agreed with NHS England for all CtE projects. Key parameters for each CtE provider were:

- Contracted activity to date: the amount of CtE activity the centre should have performed by this point, according to their contract with NHS England.
- Actual activity to date, as identified through both register entries and active surveillance by NICOR collating a 'SurveyMonkey' questionnaire from the CtE providers.
- Number of cases submitted to the NICOR registry to date. This number could be lower than the above actual activity to date, since active surveillance could identify cases that had not yet been registered.
- Number of cases identified through active surveillance but for which data were not yet submitted to the registry (i.e. the difference between the two previous figures).
- Data completeness (%) was calculated for the subset of all PFOC records where the CtE provider had selected the 'CtE=Yes' check box when submitting the case to the NICOR dataset (this is the 'Number of cases' denominator, below):

  $$\text{Data completeness (\%)} = \frac{\text{Number of completed entries in MDS data fields}}{\text{Number of cases}} \times 100$$

- Later, queries from the CtE providers on this denominator led to refined definitions for Activity, Coverage, Completeness and Follow up (FU) reported. The final defined measures were:
  - Activity: The number of CtE procedures recorded with a procedure date between 01/10/2014 and the date of raw data extract that had an eligible reason for treatment.
  - Coverage: The percentage of patient follow ups reported out of the number of patients reaching the follow up time point in question. A 'reported' follow up had data in any of the MDS follow up fields for the time point in question.
  - Completeness: The percentage of fields with any data out of the number of MDS fields for the time point in question.
  - FU reported: This number included patients reported to have died since the previous follow up visit.

2.4.3 Case eligibility criteria

Inclusion criteria: All pseudonymised NHS procedures recorded in the PFOC CtE registry conducted between 1st October 2014 to 10th August 2017 with recorded reasons for treatment including previous stroke or TIA.

Exclusion criteria: Procedures meeting the inclusion criteria, but with missing procedure date.

2.4.4 Data cleaning

Detailed methods of variable cleaning are described in *Supplementary Material - Table 1*. Data completeness and summary statistics, in terms of distribution of responses, were conducted for each of the data fields available and used to inform variables used and definition of outcomes during the statistical analysis.

2.4.5 Outcomes indicators

a. Clinical

Primary outcome measures (detailed in *Supplementary Material - Table 2*) included: successful device implantation, in-hospital major complications (defined as death, neurological event of ischaemic, haemorrhagic or undetermined origin, device embolization, cardiac structural complications, major vascular problems, endocarditis, oesophageal

rupture, major bleed, and additional surgery), in-hospital minor complications, post-discharge major complications, post-discharge minor complications and confirmed PFO closure on contrast echocardiography (only captured from 6 months post-discharge onwards).

Secondary outcome measures included: death, neurological event, device embolization, major cardiac structural complications, myocardial infarction (MI), major vascular complications, endocarditis, oesophageal rupture, major bleed, additional surgery/intervention, device malfunction, device malposition, rhythm complications, minor cardiac structural complication, transient ST-elevation (no MI), minor embolic events, minor vascular complications, migraine/worsening migraine, oesophageal trauma, nickel allergy and minor bleeds. Detailed definitions of included outcome measures are described in *Supplementary Material – Table 2*.

b. Cost / resource

A bottom-up costing studies of the pathways to insert each of the PFOC devices was conducted.

The methodology adopted to estimate the costs of the PFOC procedure is now described and is similar to that adopted for the other devices.

NY EAC firstly reviewed the draft Excel® costing template provided by the NHS England PFOC Individual Technology Group. Amendments were agreed with the Chair of the Group and the final template provided the 20 centres with detailed instructions on inputting the resources required to conduct each of 3 stages in the relevant pathway being:

- Pre-operative assessment;
- Peri-operative procedure;
- Post-operative management.

The findings from the completed templates on resource use were reviewed by all authors and compared to existing clinical pathways. Where possible, outcomes reported in the PFOC dataset such as number and type of device implanted, type of imaging conducted at each stage in the pathway, procedure duration, primary and secondary operator and length of stay were used. Where such information was not available the 3 clinicians reached a consensus view on the appropriate resources required. Unit costs from NHS national datasets and other English national cost sources were applied to the resources and aggregated to give a total procedural cost. Sensitivity analyses were conducted to provide a high and low range of estimated costs. Full details are provided at Appendix 9, with a summary of results in Tables 7 and 8.

c. Patient experience

From the outset of the cardiac CtE project, it was intended that EQ-5D-5L questionnaires would be issued to all patients at baseline procedure and all subsequent follow-up visits. This should allow pairwise analysis of results over the follow up period. However, as PFO closure is a preventative procedure rather than a therapeutic one, it is unclear whether any symptoms of the condition would be improved, other than the possibility of reduced anxiety and reduced adverse effects of drugs, or less commonly reduced quality of life following stroke or embolism. It is not expected any historical symptoms from the previous cryptogenic stroke will be improved by the intervention, although there may be potentially measureable differences in the non-physical domains, such as reduced anxiety about the possibility of stroke.

2.4.6 Statistical analysis

All scripts for case ascertainment, cleaning, processing and statistical analysis were written in the statistical programming language R [5].

Patient demographics, pre-operative clinical scores and procedural details were compared between the whole cohort and the subgroup of patients with any information recorded from follow-up appointments (at 6 weeks, 6 months, 1 year or 2 years). Fisher's exact tests or Mann Whitney U-tests were used as appropriate. Bonferroni correction was used to adjust the level of significance to take into account multiple comparisons.

Exploratory univariate and exploratory multivariate analyses were conducted for the defined outcome measures. Univariate analyses were conducted for each outcome measure and up to 42 covariates. Bonferroni correction was used to adjust the level of significance to take into account multiple comparisons (between outcome measure and each covariate of interest). Multivariate analyses used generalised linear modelling with binomial error distribution in order to estimate the effect size of covariates. Numeric covariates were centred on their median before inclusion in the multivariate analyses, if appropriate. Binary outcome measures that were anticipated to have a suitable number of observations to allow multivariate analysis included device implanted (Yes/No), major complications in-hospital (Yes/No), and minor complications in-hospital (Yes/No). The resulting binary logistic regression analyses of these outcome measures were checked for convergence and over-fitting, and either modified (e.g. by combining multiple factor levels within covariates and/or reducing the number of covariates) or reported as not valid.

Crude incidence rates for death, neurological events, device embolization, myocardial infarction, additional surgery and peripheral embolic event recorded during the study period were calculated as the number of events per 100 person-years of follow-up. Kaplan-Meier analysis was applied to the time from procedure to the time of the death or first neurological event. Patients who suffered no events and were alive at the end of the study were considered censored.

Confirmed PFO closure at 6 months, 1 year and 2 year follow-up was determined from contrast echocardiography results at rest and with provocative manoeuvre (Appendix 8).

Paired quality of life scores from individual EQ-5D components, visual analogue scores (VAS) and overall utility were compared at each time interval (6 weeks, 6 months, 1 year, 2 years) against pre-operative scores using Fisher's tests or t-tests where appropriate.

2.5 SECONDARY DATA COLLECTION (LITERATURE REVIEW)

The aim of the final PFOC literature review for CtE was to identify key published studies in patients who have had a cryptogenic ischaemic event and summarise results so they align with the requirements of the outputs of NY EAC project RX085, including the 11 questions set by NHS England. A brief summary of the review methods is presented here. A standalone literature review document is available for further information [3].

Firstly, a literature search was performed from July 2013, which was the search date of the original NICE IP237/2 which informed NICE IPG472. The NICE search strategies for replication were sourced through documents supplied by NICE and through communication with the Senior Information Manager at NICE Guidance Information Services. The EAC team and NICE agreed that no quality assessment would be made of the NICE strategies and the intention was to use the NICE-designed strategies as supplied. Some minor edits were

made (for example, the correction of a line-combination error identified in an original strategy, the addition of device trade names not included in the original searches, the deletion of the trade name for a device which never became commercially available / CE marked, and edits to index terms due to changes in MeSH / Emtree indexing). Apart from these minor changes, the terms used in the update strategies reflected those used in the original strategies of NICE IPG472.

The scope of the literature review was intended to broadly reflect the population and intervention covered in the CtE registry. The scope, described in PICO (Population, Intervention, Comparator, Outcomes) format, is summarised in Table 3.

Table 3. Scope of literature review.

Domain	Terms identified from title or abstract	Comment
Population	Patients with PFO at risk of a recurrent neurological event where no other likely cause has been demonstrated	Term is patients with "cryptogenic" stroke
Intervention	Percutaneous closure of PFO	All CE marked devices to be included. Known device models identified in the PFOC CtE dataset are the AMPLATZER range (St. Jude Medical), the GORE CARDIOFORM Septal Occluder (W L Gore and Associates Inc.) and the Figulla Flex range (Occlutech). The earlier V1.6 of the PFOC dataset (used by NICOR at launch of the cardiac CtE programme in December 2014) included the GORE HELEX Septal Occluder (discontinued in 2011).Three other manufacturers were also originally listed as options for selection in the CtE dataset: Ultrasept PFO (Cardia Inc.), FlatStent EF (Coherex Medical) and Nit-Occlude (PFM Medical). These were therefore included in the literature search terms.
Comparator	Any or none	Single arm observational studies will be considered (e.g. registries)
Outcomes	Clinical outcomes Utility and resource use outcomes*	Surrogate and non-clinical outcomes will be excluded.
Study type	All primary studies Secondary studies (systematic reviews and meta-analyses) Economic studies*	Non-systematic reviews, editorials and opinion pieces excluded. Abstracts excluded.
*Economic studies and associated outcomes to be identified for possible future reference.		

Given the timelines of the project and the purpose of the update search, the EAC team and NICE agreed that only the bibliographic databases listed in Table 4 below would be searched. In addition, it was agreed that strategies would be limited to results published in English language only, and that conference-related publication types would be excluded from the Embase search.

Where database functionality allowed, results were limited to records added to the database since the date of the last search, using appropriate fields such as the entry date field in MEDLINE. Where database functionality did not allow this, results were limited by publication date, reflecting the pragmatic context of the search.

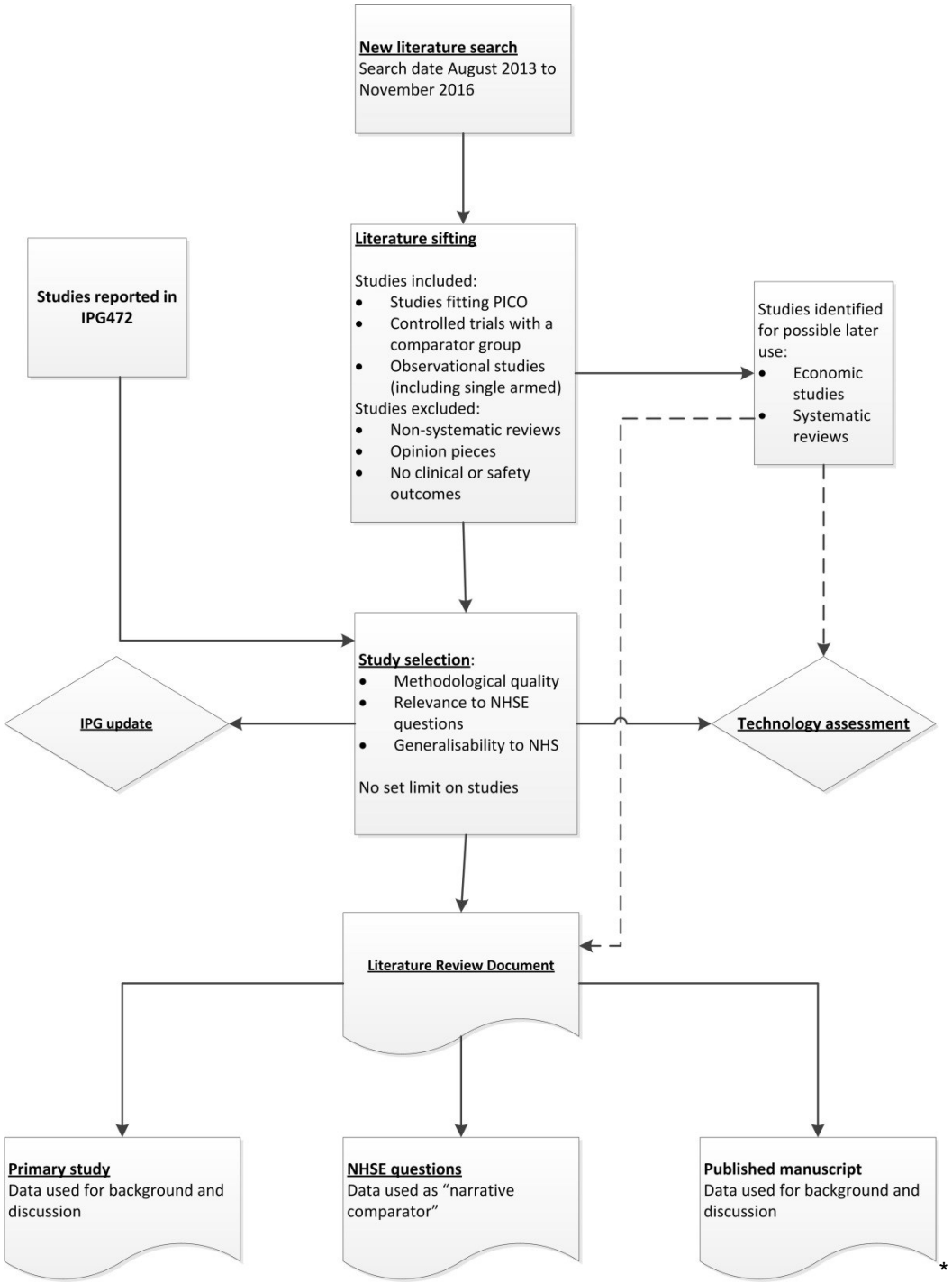
Table 4. Bibliographic databases searched.

Database / information source	Interface / URL
MEDLINE and MEDLINE In-Process	OvidSP
EMBASE	OvidSP
Cochrane Database of Systematic Reviews (CDSR)	Cochrane Library/Wiley Interscience
Cochrane Central Register of Controlled Trials (CENTRAL)	Cochrane Library/Wiley Interscience
Database of Abstracts of Reviews of Effects (DARE)	http://www.crd.york.ac.uk/CRDWeb/
Health Technology Assessment Database (HTA)	http://www.crd.york.ac.uk/CRDWeb/
NHS Economic Evaluation Database (EED)	http://www.crd.york.ac.uk/CRDWeb/

Relevant studies were sifted by two reviewers according to the predefined scope, and these studies were then combined with those reported in IPG472. As this approach identified an unmanageable number of studies, a further selection process was employed to identify studies on the basis of methodological quality and size, with randomised controlled trials (RCTs) and observational studies with 500 or more participants selected for full review, with studies with 100 or more participants being flagged for *ad hoc* inclusion [3]. Systematic reviews and economic studies were also identified.

Figure 1 is a flow diagram of this pragmatic literature review strategy, including the inclusion and exclusion criteria applied to sifting.

Figure 1. Flow chart illustrating the literature review strategy for PFOC.



A brief summary of the results of the literature review is presented in the results section of this final CtE report on PFOC, with full details available in the standalone literature review document [3].

2.6 RESEARCH DESIGN

The study was a procedural registry designed with a maximum 2 years of follow up. The registry was single armed with no comparator or control arm. Data were collected prospectively in accordance with best practice [6, 7].

As discussed in Section 3.2, the current evidence base for the use of PFOC for the preventative treatment of patients with ischaemic stroke thought likely to be caused by a

paradoxical embolism is equivocal (although more recent studies have reported positive benefits, see Section 3.3). Although trial evidence reports a trend towards reduced incidence of recurrent stroke associated with PFOC, statistical significance has not been reported in any single RCT. Additionally, as recurrent strokes in this population are still relatively rare events, the absolute benefit of PFOC may be comparatively small and difficult to accurately gauge. Observational studies that have been performed are mainly single-armed. Comparisons with historical controls, where made, introduce further uncertainty. There is only limited information on how PFOC performs in NHS pathway settings, and the relative efficacy and safety of competing technologies is also poorly understood.

To help clarify this uncertainty, NHS England has requested that the answers to 11 clinical and economic questions should be addressed, using data reported by the CtE registry, and supported by published studies in the literature. These questions have been revised and adjudicated by NICE (see Table 5). Table 5 summarises the *a priori* intended methods for answering each question [8]. However, due to issues with data quality and reporting of published literature, the original methods were not always possible. These limitations have subsequently been annotated in the table.

The EAC performed a pragmatic literature review, which identified the key experimental and observational studies performed to date on PFOC (see Section 3.2). As the CtE register was non-comparative, data from the literature has been used as a proxy control for the register. The relationship between the registry and published literature in answering the NHS England questions is illustrated in Figure 2. Inference has been made by comparing point estimates and confidence intervals where available. Additionally, in some instances where the registry was not sufficiently robust to answer the questions, published evidence was used to directly answer questions.

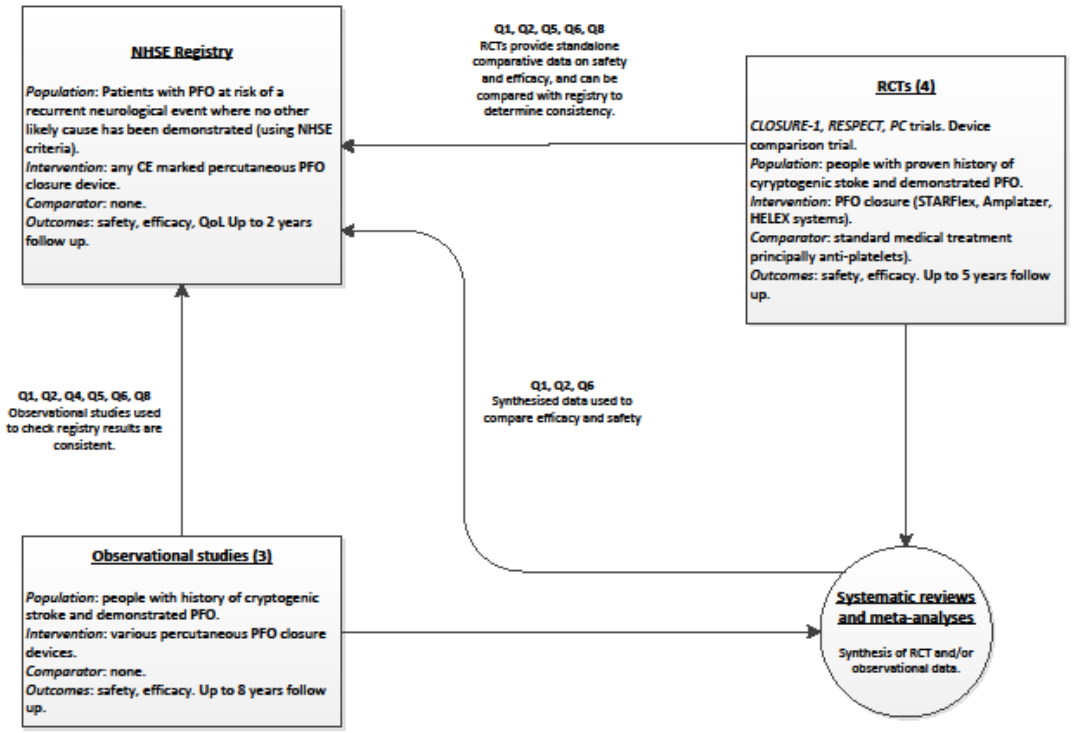
Table 5. Methods used to analyse and report CtE registry data.

Question (NICE modified where applicable)	Can it be answered using registry data?	Key registry data required	Type of analysis	Comment
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)?	No.	Neurological event (type) Rankin score	Survival analysis. Comparison with published RCTs and observational studies.	Incidence of endpoint (stroke and associated events) likely to be too low to be meaningfully compared with data published in the literature.
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?	Yes, partly.	Successful procedure, no complications Neurological event (type) Device specific complication Rhythm complication Cardiac structural complication Neurological/other embolic complication Vascular complications Other complications Bleeding complication Life status	Proportion of people having event with confidence intervals. Comparison with expected rate from published RCTs.	Some outcome events expected to be low, statistical significance unlikely to be reported.
3) Is patent foramen ovale closure associated with an improvement in quality of life?	Yes, partly.	Successful procedure, no complications Quality of life (EQ-5D-5L)	Pairwise ('before and after') analysis of registry data. Correlation and regression analysis.	Significant aggregate changes in quality of life unlikely. [Update: paired analysis limited by relatively poor follow up].
4) Are there any longer-term	No, probably not.	Device embolization	Proportion of people having	Longer-term data collection

Question (NICE modified where applicable)	Can it be answered using registry data?	Key registry data required	Type of analysis	Comment
cardiac complications associated with the use of these devices [for PFO closure] (e.g. erosion with penetration through the wall of the atrium/aorta)?		Cardiac structural complications Rhythm complications Thrombus formation	event with confidence intervals. Survival analysis (Kaplan-Meier).	would be dependent on extension of contracted follow up. [Update: follow up not extended, could feasibly be addressed in future using HES analysis].
5) Which devices are used to undertake PFO? What are the device-specific efficacy and safety outcomes in CtE funded patients undergoing the procedure? In particular, is there any published or register evidence of complications in the long term from percutaneous PFO closure (e.g. erosion with penetration through the wall of the atrium /myocardium/pericardium)?	Yes, partly.	Device manufacturer Efficacy and safety outcomes	Subgroup analysis. Comparative survival curves.	Some subgroups may be low in number (real differences may not be statistically observable).
6) What are the short and medium term risks of percutaneous PFO closure?	Yes, partly.	Key safety and complications outcomes Efficacy outcomes	Descriptive statistics on efficacy and complication data. Narrative comparison with published data.	Expert opinion will be sought on acceptability of risks. This question could lead to an update of IPG109.
7) What proportion of patients referred to an MDT for possible percutaneous PFO closure against Commissioning Through Evaluation criteria were considered suitable for the intervention?	Yes, partly.	Decision to treat	Proportion of patients considered by MDT/patients received PFO closure.	Unknown how many potential candidates do not make the registry at all. [Update: descriptive analysis of indication reported].
8) Are favourable clinical outcomes with patent foramen ovale closure associated with particular patient characteristics (clinical or demographic)?	Yes, partly.	Patient characteristics Efficacy outcomes Complication outcomes Mortality	Subgroup analysis. Bonferroni correction if hypotheses not pre-specified.	Limitations with patient enrolment (power), patient selection and confounding variables (generalisability issues). [Update: low follow up and

Question (NICE modified where applicable)	Can it be answered using registry data?	Key registry data required	Type of analysis	Comment
				primary event rate did not allow for subgroup analysis].
9) What are the average full procedural costs of percutaneous patent foramen ovale closure to the NHS?	Provides inputs.	Devices used, primary and secondary operator, investigations, length of stay initial admission and procedure duration	None.	Procedural costs will be estimated at site level using a pro forma.
10) What are the potential cost savings for the NHS in patients receiving percutaneous patent foramen ovale closure?	Provides inputs.	Patient characteristics Resource use data for procedure, initial admission and re-admissions Efficacy outcomes Complication outcomes	Mean and SD for each key event on pathway.	This question will be answered by a cost consequences analysis to be provided in a separate report to NICE by 29 December 2017.
11) What is the likely cost-effectiveness of percutaneous PFO closure in the NHS, based on UK costs?	Provides inputs.	Patient characteristics Resource use data for procedure, initial admission and re-admissions Efficacy outcomes Complication outcomes Mortality Quality of life	Mean and SD for each parameter.	This question will be answered by a cost consequences analysis to be provided in a separate report to NICE by 29 December 2017.

Figure 2. Relationship between NHS England registry clinical data and published evidence identified in the literature review (questions 1 to 8 [Q1 to Q8]).



Section 3: Results

3.1 PRIMARY DATA COLLECTION (CTE DATABASE)

3.1.1 Numbers of patients treated at each centre

A total of 1126 PFOC procedure records were extracted by NICOR on 10th August 2017. One hundred and thirty one patients did not meet the eligibility criteria, Appendix 1, 119 of which did *not* include eligible reasons for PFOC treatment (multiple reasons permitted): 44 decompression illness (diver), 25 MI (presumed embolic), 13 migraine (with or without aura), 12 peripheral embolus, 11 orthodeoxia-platypnoea or other desaturation syndrome, 8 primary stroke prevention, 1 high-altitude pulmonary oedema, 1 prior to neurosurgical procedure, 15 other, 3 none, and 12 not providing a reason for treatment. A total of 940 PFOC procedures were eligible for analysis, which included 111 (11.8%) non-CtE commissioned procedures i.e. private procedure or those conducted by non-CtE commissioned centres.

Of all procedures concluding with PFOC device implantation, with a discharge status of alive at last hospital visit, follow-up information for CtE commissioned procedures was recorded in 81.9% of cases at 6 weeks, 70.5% at 6 months, 60.8% at 1 year and 39.1% at 2 years(*Supplementary Material – Table 3*).

3.1.2 Summary statistics of patient and procedural characteristics

Patient demographics and procedural characteristics for the cohort are summarised in Appendix 2 and Appendix 3 respectively. No statistical differences were identified between the whole cohort and those with reported follow-up information for any variables. A total of 663 procedures were conducted with planned intra-operative TOE or TTE imaging, 627 of which were recorded under general anaesthesia (94.6%). A total of 206 procedures were conducted with planned intra-operative ICE imaging, 185 of which were recorded under local anaesthesia (89.8%).

3.1.3 Active surveillance (evaluation of coverage)

The data coverage and completeness results, for CtE commissioned procedures only, for the 25 PFOC MDS baseline fields and the 7 specified follow-up fields (to 10/08/2017) are reported in Table 6.

Table 6. Data completeness by provider.

CtE provider	Baseline MDS completeness	Coverage† & completeness‡ at 6 weeks FU	Coverage† & completeness‡ at 6 months FU	Coverage† & completeness‡ at 1 Year FU	Coverage† & completeness‡ at 2 years FU
The Newcastle upon Tyne Hospitals NHS Foundation Trust (FRE)*	98%	92.0% (23/25) coverage 87.6% FU data completeness	50.0% (12/24) coverage 85.7% FU data completeness	42.1% (8/19) coverage 83.9% FU data completeness	14.3% (1/7) coverage 71.4% FU data completeness
Central Manchester Hospitals / University of South Manchester NHS Foundation Trust (MRI/WYT)*	72%	54.2% (13/24) coverage 76.2% FU data completeness	18.8% (3/16) coverage 76.2% FU data completeness	41.7% (5/12) coverage 74.3% FU data completeness	12.5% (1/8) coverage 57.1% FU data completeness
Leeds Teaching Hospitals NHS Trust (LGI)	81%	96.8% (30/31) coverage 82.4% FU data	96.8% (30/31) coverage 80.0% FU data	85.2% (23/27) coverage 78.9% FU data	16.7 (1/6) coverage 14.3 FU data completeness

CtE provider	Baseline MDS completeness	Coverage† & completeness‡ at 6 weeks FU	Coverage† & completeness‡ at 6 months FU	Coverage† & completeness‡ at 1 Year FU	Coverage† & completeness‡ at 2 years FU
		completeness	completeness	completeness	
Liverpool Heart & Chest Hospital NHS Foundation Trust (BHL)	74%	61.5% (32/52) coverage 70.1% FU data completeness	86.5% (45/52) coverage 83.8% FU data completeness	54.0% (27/50) coverage 69.3% FU data completeness	35.5% (11/31) coverage 79.2% FU data completeness
Oxford University Hospitals NHS Trust (RAD)	94%	91.1% (41/45) coverage 96.2% FU data completeness	65.9% (29/44) coverage 96.6% FU data completeness	78.4% (29/37) coverage 97.1% FU data completeness	18.8% (3/16) coverage 95.2% FU data completeness
Brighton & Sussex University Hospitals NHS Trust (RSC)	89%	97.9% (46/47) coverage 71.1% FU data completeness	97.9% (46/47) coverage 69.9% FU data completeness	97.7% (42/43) coverage 69.4% FU data completeness	83.3 (15/18) coverage 67.6 FU data completeness
University Hospitals Bristol NHS Foundation Trust (BRI)	99%	89.2% (58/65) coverage 98.0% FU data completeness	80.3% (49/61) coverage 98.8% FU data completeness	0% (0/51) coverage 0% FU data completeness	0% (0/25) coverage 0% FU data completeness
University Hospital Southampton, NHS Foundation Trust (SGH)	65%	89.2% (33/37) coverage 81.8% FU data completeness	89.2% (33/37) coverage 86.1% FU data completeness	93.3% (28/30) coverage 78.5% FU data completeness	100% (13/13) coverage 79.1% FU data completeness
University Hospital of North Staffordshire NHS Trust (now Royal Stoke University Hospital) (STO)	84%	61.2% (41/67) coverage 43.5% FU data completeness	98.5% (66/67) coverage 59.1% FU data completeness	93.2% (41/44) coverage 43.2% FU data completeness	61.5% (8/13) coverage 48.2% FU data completeness
University Hospitals Leicester NHS Trust (GRL)	95%	92.0% (46/50) coverage 90.1% FU data completeness	68.0% (34/50) coverage 93.3% FU data completeness	57.5% (23/40) coverage 92.5% FU data completeness	54.5% (12/22) coverage 94.0% FU data completeness
Nottingham University Hospitals NHS Trust (CHN)	94%	97.7% (43/44) coverage 94.0% FU data completeness	97.7% (42/43) coverage 94.2% FU data completeness	96.9% (31/32) coverage 94.0% FU data completeness	100% (16/16) coverage 87.5% FU data completeness
University Hospital Birmingham NHS Foundation Trust (QEB)	90%	100.0% (30/30) coverage 85.7% FU data completeness	10% (3/30) coverage 85.7% FU data completeness	43.3% (13/30) coverage 87.9% FU data completeness	63.6 (7/11) coverage 100.0% FU data completeness
Royal Wolverhampton NHS Trust (NCR)	82%	100.0% (26/26) coverage 72.0% FU data completeness	100.0% (26/26) coverage 70.3% FU data completeness	0% (0/24) coverage 0% FU data completeness	7.7% (1/13) coverage 14.3% FU data completeness
Papworth Hospital in partnership with Essex Cardiothoracic Centre (PAP/BAS)*	85%	80.0% (32/40) coverage 79.2% FU data completeness	81.6% (31/38) coverage 74.6% FU data completeness	87.5% (28/32) coverage 63.7% FU data completeness	58.8% (10/17) coverage 50.0% FU data completeness
Guy's and St Thomas' NHS Foundation Trust (STH)	98%	87.0% (47/54) coverage 84.8% FU data completeness	28.3% (15/53) coverage 88.6% FU data completeness	74.4% (32/43) coverage 90.2% FU data completeness	6.7% (1/15) coverage 100.0% FU data completeness
Barts Health NHS Trust & The Heart Hospital, (SBH/UCLH)*	71%	83.3% (35/42) coverage 66.5% FU data completeness	22.0% (9/41) coverage 60.3% FU data completeness	42.9% (12/28) coverage 67.9% FU data completeness	20.0% (1/5) coverage 71.4% FU data completeness
Kings College Hospital NHS Foundation Trust (KCH)	80%	33.9% (20/59) coverage 66.4% FU data completeness	64.3% (36/56) coverage 73.8% FU data completeness	63.8% (30/47) coverage 72.9% FU data completeness	10% (2/20) coverage 71.4% FU data completeness
Royal Brompton & Harefield NHS Foundation Trust	66%	89.2% (58/65) coverage 73.9% FU data	59.3% (35/59) coverage 74.7% FU data	39.6% (19/48) coverage 72.5% FU data	12.5% (2/16) coverage 57.1% FU data

CtE provider	Baseline MDS completeness	Coverage† & completeness‡ at 6 weeks FU	Coverage† & completeness‡ at 6 months FU	Coverage† & completeness‡ at 1 Year FU	Coverage† & completeness‡ at 2 years FU
(NHB/HH)*		completeness	completeness	completeness	completeness
St. George's Healthcare NHS Trust (GEO)	87%	70.6% (12/17) coverage 71.4% FU data completeness	62.5% (10/16) coverage 72.9% FU data completeness	0% (0/15) coverage 0% FU data completeness	0% (0/4) coverage 0% FU data completeness
Total	**84%**	820/848 (96.7%) with device implanted, discharged alive and reaching 6 weeks since procedure date. 666/820 (81.2%) with some degree of FU data **Completeness of FU MDS (versus expected) = 79.6%**	792/820 (96.6%) with device implanted, still alive at 6 weeks FU and reaching 6 months since procedure date. 554/792 (69.9%) with some degree of FU data **Completeness of FU MDS (versus expected) = 80.1%**	652/820 (79.5%) with device implanted, still alive at 6 months FU and reaching 12 months since procedure date. 391/652 (60.0%) with some degree of FU data **Completeness of FU MDS (versus expected) = 75.6%**	276/820 (33.7%) with device implanted, still alive at 1 year FU and reaching 2 years since procedure date. 105/276 (38.0%) with some degree of FU data **Completeness of FU MDS (versus expected) = 75.2%**

FU Coverage† = Actual no. of PFOC procedures with some degree of FU data entered / No. of PFOC procedures eligible for FU for the stated period (%)
NB FU Coverage can only be calculated for cases with a procedure date entered. This is the case for 848/860 (98.6%) of PFOC cases in the registry, to 10/08/2017
FU Completeness‡ = Average completeness of the 7 specified PFOC MDS-FU data fields (%)
***CtE providers named in bold font in the table are separate NHS Trusts operating in partnership as a single contracted CtE provider with NHS England for cardiac CtE.**

3.1.4 Outcomes

a. Clinical

Of the 940 procedures eligible for analysis (Appendix 1), 929 (98.8%) recorded both admission and discharge dates, showing a median length of stay of 1 overnight stay (inter-quartile range 0 to 1, range 0 to 34 days). Device implantation was recorded in 907/940 (96.5%) of eligible procedures, with 901/907 procedures resulting in an implanted device and 6/907 resulting in failure to implant, for reasons categorised as: 3 unable to position device correctly, 1 incorrect size, 1 complication and 1 reporting "other" reason. Exploratory analysis indicated that excess body mass index (BMI) and older age were associated with lower implantation rates. 33/940 procedures (3.5%) did not record whether a device was implanted or not (missing data).

In-hospital major complications (1.0%) were reported in 9 patients, including: 1 death, 3 neurological events (2 ischaemic and 1 other categorised as a CVA/RIND), 3 device embolization events, 1 myocardial infarction (MI), 1 major bleed and 1 requiring additional surgery (surgical retrieval of embolised device). Twenty four patients (2.6%) experienced minor complications, including: 9 new or worsening atrial fibrillation, 5 minor vascular complications, 4 device malposition, 5 minor bleeds, 3 new or worsening migraine and 1 minor cardiac structural complication. Frequencies of in-hospital outcomes for all eligible PFOC patients, and post-discharge outcomes for all eligible PFOC patients with a device implanted are described in Appendix 4. Procedural success (device implanted and no major complications) was achieved in 894 PFOC procedures (95.1%).

The only covariate which was significantly associated with an in-hospital major complication outcome during univariate analysis was right-to-left shunt (without provocation). Therefore, those with weaker evidence of shunts were more likely to experience a major in-hospital

complication. No significant associations were found for the device implanted or in-hospital minor complication outcomes (*Supplementary Material – Tables 4-6*).

For those with a PFOC device implanted, follow-up was reported in 808 patients (89.7%). Major complications occurring post-PFOC procedure discharge were recorded in 42 patients, including: 2 deaths, 23 neurological events, 13 major bleeds, 1 MI, 1 major cardiac structural complication, 1 major vascular complication and 4 requiring additional surgery (device removed/retrieved further intervention with other device or surgical closure) (Appendix 4). One hundred and eighteen patients reported minor complications, including: 61 minor cardiac structural complications, 28 new or worsening atrial fibrillation, 21 new or worsening migraine, 7 minor bleeds, 5 minor vascular complications and 2 air embolisms.

Total crude incidence rates of adverse events are described in Appendix 4. One in-hospital and 2 out-of-hospital deaths have been reported. 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). Neurological events were reported for 26 patients in-hospital or post-discharge (with potential for multiple events per patient). Due to internal inconsistencies in completion and interpretation of registry data field combinations (the combination of mechanism and type of neurological event), the EAC sought narrative confirmation of the recorded events from participating centres. For further information, see Addendum. Kaplan-Meier curves for time to death, ischaemic neurological event and death or any neurological event are shown in Appendix 6. The rate of neurological events was not significantly different between types of device implanted (p=0.26)(Appendix 7).

Echo contrast results over time are shown in Appendix 8.

Use of antiplatelet and anticoagulant medications over time is described in *Supplementary Material – Table 7*. The difference in medication use on discharge compared with pre-procedure was statistically significant. Other medications recorded via free-text fields at pre-procedure, at discharge and during follow-up were available for only 4% of patients, so are not analysed any further.

In reporting changes in quality of life, one can only include individuals who provided data pre-procedure and at specified later time periods. This is to ensure one is comparing the EQ-5D scores of the same individuals over time. The mean utility value pre-procedure was 0.87, which changed to:

- 0.91 at 6 weeks (n= 241, p = 0.02);
- 0.91 at 6 months (n = 207, p =0.008)
- 0.90 at 1 year (n = 125, p = 0.55)
- 0.90 at 2 years (n = 36, p= 0.66)

Hence there was a 0.03 point improvement in quality of life at 12 months from the procedure. Whilst not statistically significant this is a material benefit for the individuals concerned.

The domain registering the greatest benefit from the procedure was reduction in anxiety and depression. A statistically significant improvement was seen in this domain in 241 paired results at 6 weeks post-procedure and in 207 paired results at 6 months post-procedure (*Supplementary Material – Table 8*).

b. Cost / resource (include model here if appropriate)

The overall quality of responses to the PFOC CtE Excel® costing template was poor, but there was 1 well-completed response. NY EAC synthesised the responses to create a list of the resources required at each stage of pathway. In February 2107, Dr Mark de Belder reviewed the template. Following subsequent changes in light of his comments and informed by several more responses from centres, NY EAC updated the template and included cost information. Unit costs were taken from published national datasets (primarily NHS Reference Costs [31] and PSSRU [32]). The NHS Supply Chain provided costs for the device as 'Commercial in confidence' and hence must not be disclosed beyond NICE staff and clinical leads in first instance. Such data are identified in yellow in this report and Appendix 9. NHS Supply Chain price includes overheads of [redacted] for its internal costs. A further 15% has been added to the NHS Supply Chain price for NHS procurement and stores related costs plus property related overheads.

At this stage we also included results from the analyses of data from the centres for as many parameters as possible. These included number and type of device implanted, type of imaging conducted at each stage in the pathway, procedure duration, primary and secondary operator and length of stay. The updated templates were presented at a meeting of the 3 clinical leads in May 2017. Comments from that meeting informed the final pathway and costings.

The 2 rounds of clinical validation was judged essential to ensure the resulting costs have good internal and external validity and thus should generalise to settings across NHS England.

The resultant estimated central cost and high and low cost scenarios for a PFOC procedure conducted in NHS England are shown in Table 7.

Table 7. Central case and range of cost for a PFO closure procedure.

Pathway stage	Central cost	Low cost	High cost
Pre-operative assessment	£286	£229	£343
Peri-operative procedure	[redacted]	[redacted]	[redacted]
Post-operative management	[redacted]	[redacted]	[redacted]
Total	**£8,303**	**£6,946**	**£9,254**

Table 8 analyses the estimated costs by component by stage for the central case. The device accounts for [redacted] of the cost of a PFOC procedure. Investigations form the second largest cost component ([redacted]%), with consumables, staff, length of stay and theatre use each contributing [redacted]% to the cost base. The outpatient follow-up appointment contributes [redacted] to the cost base.

Table 8. Estimated costs by component by stage for central case.

	Pre-op	Peri-op	Post-op	Total	% of Total
Device		[redacted]		[redacted]	[redacted]
Investigation	£128	[redacted]	[redacted]	[redacted]	[redacted]
Consumables	£16	[redacted]		[redacted]	[redacted]
Staff	£142	[redacted]		[redacted]	[redacted]

	Pre-op	Peri-op	Post-op	Total	% of Total
Length of stay			[redacted]	[redacted]	[redacted]
Theatre		[redacted]		[redacted]	[redacted]
Out-patient			[redacted]	[redacted]	[redacted]
Total	**£286**	[redacted]	[redacted]	**£8,303**	**100%**

A full summary of all resources and unit costs is provided in Appendix 9. This also describes the assumptions underpinning the sensitivity analyses.

c. Patient experience

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.

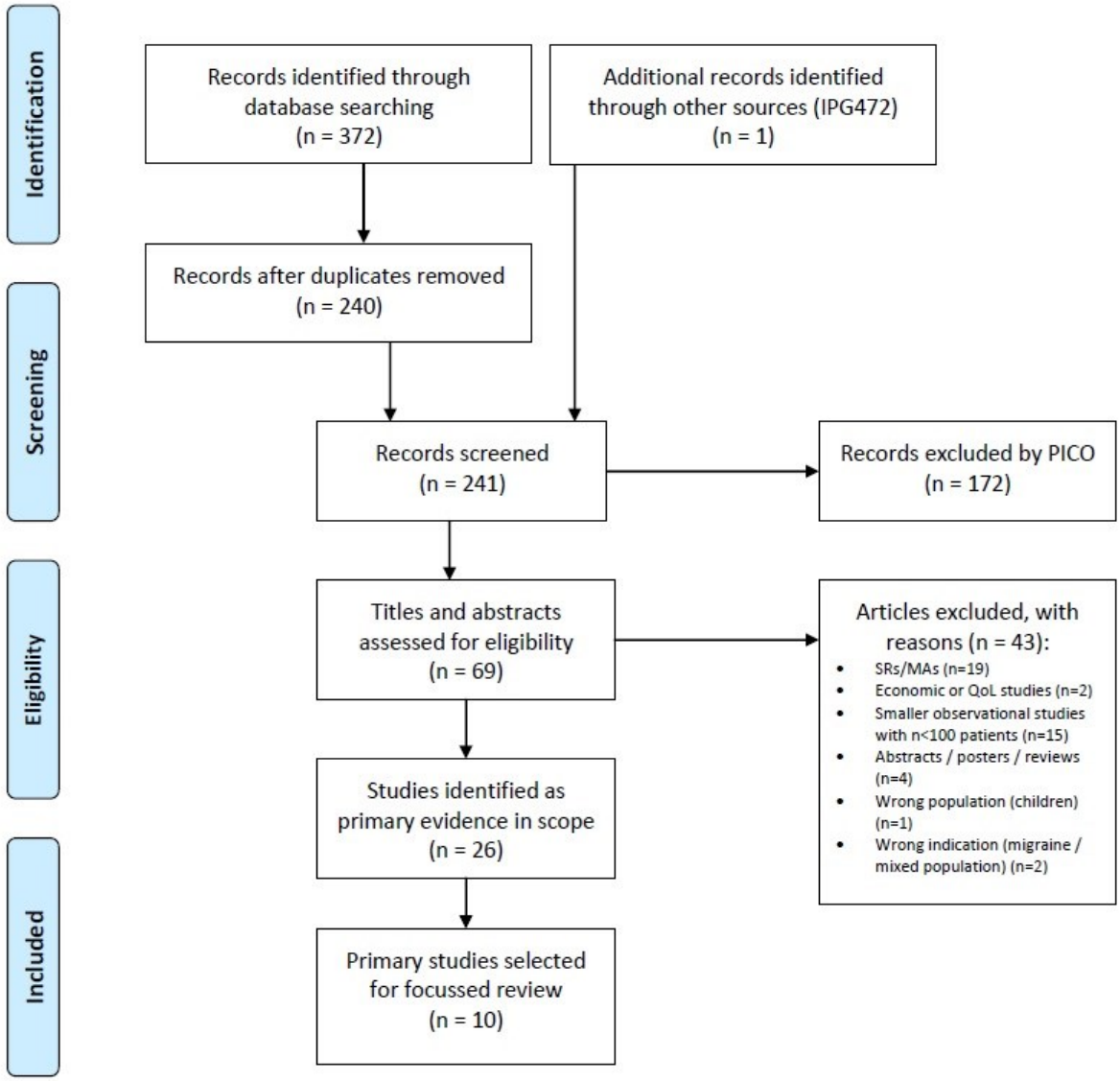
Full EQ-5D results are presented in *Supplementary Material - Table 8*.

3.2 SECONDARY DATA COLLECTION (LITERATURE REVIEW)

The CtE PFOC literature search (August 2013 to November 2016) retrieved 240 potentially relevant articles. Abstracts from these articles were independently assessed for relevance by two EAC researchers. Of these, 161 were excluded immediately after screening as being not relevant to the scope. Of the remaining 79 records, 25 were excluded for various reasons, including study size (18 studies reported on less than 100 patients). Two studies were used in the economic evaluation.

The process of sifting using PRISMA methodology (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) [9] is illustrated in Figure 3 below.

Figure 3. PRISMA schematic of literature search for clinical evidence.



The literature search identified 25 primary publications that were in scope. From these, nine studies were selected for focussed review and 16 were summarised in tabular form. Studies not selected at this stage were smaller observation studies (more than 100 but less than 500 patients) or had methodological or reporting issues. Of the nine studies selected for focussed review, three were RCTs, four were observational studies with more than 500 participants, and two were observational studies set in the UK selected for their generalisability. One RCT reported in IPG472 was also selected and added to the focussed review, making 26 in primary evidence in total. In addition to the primary studies, nineteen secondary studies (systematic reviews and/or meta-analyses) were identified. Although these, as synthesised data, were not technically in scope, four were selected for interim analysis to inform the NHS England questions, as described in the EAC literature review [3].

The principal clinical evidence on the use of PFOC to prevent recurrent ischaemic events is derived from three superiority randomised controlled trials (RCTs). These were the CLOSURE-1 trial (n = 909) [10], the RESPECT trial (n = 980) [11], and the PC trial (n = 414) [12], with the former investigating the use of the now discontinued STARFlex device, and the latter two using the St. Jude Medical AMPLATZER PFO Occluder. The EAC critically appraised these studies and concluded they were of reasonable methodological quality, although all were potentially subject to attrition bias. The RCTs were considered highly

generalisable to the population covered by Commissioning through Evaluation (CtE). The primary outcomes of the RCTs were composites of recurrent ischaemic events and procedural and post-procedural mortality, analysed using intention to treat (ITT) analysis. All the RCTs reported statistically negative results for the primary outcome; that is, there was no significant benefit in PFOC compared with medical therapy alone. Thus, on the basis of these results the experimental evidence for the clinical benefit of PFOC is equivocal (but, in contrast, emerging evidence is reporting PFOC to be associated with significant benefits, see Section 3.3).

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 per protocol or “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 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 events should be considered in the context of peri-procedural and longer term adverse events, such as new onset atrial fibrillation (AF).

The six observational studies selected for focussed review were limited by the lack of a prospectively defined comparator and sources of confounding. A strength of these observational studies was that they were relatively large allowing for a degree of precision in clinical measurements. They provided useful data on procedural efficacy and safety, and some estimates of longer-term prognosis of patients receiving PFOC.

Results from the four systematic reviews were not entirely consistent. An individual patient meta-analysis of the controlled RCTs (n = 2303) reported that PFOC significantly reduced recurrent strokes, and that the AMPLATZER PFO Occluder was associated with a reduction in the composite measure of recurrent stroke, transient ischaemic attack (TIA) and early death HR 0.57 (95% CI 0.3 to 1.00, p=0.0480) [13]. However, a statistically significant benefit was not reported in a Cochrane review of the same studies [14]. A network analysis of three PFOC devices reported high number needed to treat (NNT) indicating low absolute benefits from the device compared with medical treatment alone [15]. Another systematic review (n = 4335) [16] reported significant benefit from the included pooled comparative observational studies, but not from the RCTs analysed.

An important issue identified with the published literature base for the PFOC procedure was that there was evidence that the type of devices employed (which are numerous) may not be clinically equivalent. One RCT [17] (n = 660), of generally poor methodology and reporting, compared the AMPLATZER PFO Occluder device directly with the GORE HELEX device (discontinued in 2011) and the STARFlex device, also since discontinued. It reported that the GORE HELEX device was associated with increased device embolisation, incomplete device closure, and requirement for use of an additional device compared with the AMPLATZER PFO Occluder. However, results from the GORE HELEX device may not be generalizable to the GORE CARDIOFORM Septal Occluder used in the CtE programme. Issues with device equivalence need to be considered when assessing the published evidence on the procedure.

The economic evaluation was limited to evidence from 1 study reported in a full paper [18] and in an abstract by the same authors [19]. It adopted the perspective of the USA

healthcare system payer and compared PFO closure to medical therapy. It used clinical data from a meta-analysis of 3 RCTs 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. Costs did not generalise to the NHS England setting. Hence the study was judged to have poor internal and external validity. There is thus material uncertainty on whether its findings on cost-effectiveness apply in the English setting.

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

Further details are available in the standalone literature review document [3].

3.3 EMERGING IMPORTANT NEW EVIDENCE

The September 2017 publication of the New England Journal of Medicine (NEJM), included three important studies that are directly relevant to the analysis of the CtE registry data. Publication of these studies postdates the PFOC literature search performed by the EAC [3], and it has not been possible to critique the new studies for this report. However, the EAC recognises these studies, which have been peer-reviewed in a high-impact journal, reported data that are very relevant to the present registry. Therefore, a brief summary of the studies is provided, and key results have been used to inform Question One, Question Two, and the Discussion.

The Patent Foramen Ovale Closure or Anticoagulants versus Antiplatelet Therapy to Prevent Stroke Recurrence (CLOSE) trial by Mas *et al.* (2017) was an investigator-initiated, multicentre, randomized, open-label, superiority trial set in France (32 sites) and Germany (2 sites) [20]. Relatively young patients (n = 663, aged 16 to 60 years) who had had a prior ischemic stroke suspected to be caused by embolism mediated through PFO were randomised to three groups in a 1:1:1 ratio (PFOC [several devices and anti-platelet regimens used]: anti-platelet drugs only: oral anticoagulation only). Mean follow up was 5.3 years ± 2.0 years (SD). Comparisons were made between PFOC and anti-platelet groups, and antiplatelet and oral anticoagulation groups. There was a procedural complication rate of 5.9% associated with PFOC, and PFOC was significantly associated with development of new AF (4.6%). However, over the course of follow up, no strokes occurred in the PFOC group (n = 238) compared with 14 strokes in the anti-platelet group (n = 235). This difference was significant (HR, 0.03; 95% CI, 0 to 0.26; $p < 0.001$).

The GORE REDUCE study, by Sondergaard *et al.* (2017), was a multinational, prospective, randomized, controlled, open-label trial [21]. Patients (n = 664) were randomised in a 2:1 ratio to receive one of two GORE PFOC devices (HELEX Septal Occluder, which was discontinued in 2011, or CARDIOFORM Septal Occluder) with anti-platelet therapy, or anti-platelet therapy alone. Patients were aged 18 to 59 years, had had a cryptogenic ischemic stroke within 180 days before randomization, 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 group compared with 12 of 223 patients (5.4%) in the antiplatelet-only group (HR, 0.23; 95% CI 0.09 to 0.62; $p = 0.002$). 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.

The final study published in the NEJM was an update of the RESPECT trial, which has been previously described in the EAC's literature review [3]. This paper reported updated outcomes of patients with a median follow up of 5.9 years [22]. Whereas an earlier publication of the study had reported a non-significant trend towards benefit for the primary outcome [11], a significant improvement was observed after extended follow up. Using ITT analysis, recurrent ischaemic stroke occurred in 18 patients in the PFOC group compared with 28 patients in the medical-therapy group. This was an event rate of 0.58 events per 100 PY compared with 1.07 events per 100 PY (HR 0.55; 95% CI 0.31 to 0.999; p = 0.046).

The two new trials and the update of the RESPECT trial all reported positive results for their primary efficacy outcomes, which is in contrast to earlier trials and publications of PFOC. The reasons for this are not clear, but could be related to methodological advances in the trial design, such as longer follow up time (this is clearly the case in Saver *et al.* [2017] [22]). Additionally, improved diagnostic work up (e.g. improved echocardiography and use of provocation) and patient selection (i.e. identifying patients where PFO is likely to be causal rather incidental) may have been a factor, as well as incremental improvements to the device themselves; if so, this has important implications for real-world clinical practice (see Section 5). Additionally, the removal of more subjective inclusion criteria and outcomes related to TIA may have effectively increased the power of the studies.

These encouraging results should also be considered in the context that although relative benefits are clinically significant, absolute benefits are somewhat small. There is also a clear indication now that PFOC causes new onset AF in around 1 in 20 patients, at a relatively young age; this may increase their risk of stroke in later life and reduce quality of life. Clearly, the risk of new onset AF will have to balanced against the dis-benefit of suffering a thromboembolic event.

3.4 NHS ENGLAND QUESTIONS AND REQUESTS

3.4.1 Question One

> "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)?"

Although it has been reported that cryptogenic stroke is associated with a higher risk of recurrent stroke compared with those where a cause has been identified [23], there is a paucity of information from natural history studies or models in the literature to accurately quantify this risk increase. Therefore, in order to answer this question, data from the registry (where nearly all patients received PFOC) has been compared with the control arms of the RCTs (where patients received similar care to the intervention arms but without the addition of PFOC). The trials that reported data on patients receiving systemic medical treatment only were the CLOSURE-1 trial (2012) [10] (STARFlex), RESPECT trial (2013) [11] (AMPLATZER PFO Occluder) and the PC trial (2013) [12] (AMPLATZER PFO Occluder). Patients in the CtE registry appear to have similar baseline characteristics and indications for treatment as those in the trials.

The registry recorded neurological events occurring in 3 patients in hospital, and a further 23 patients after discharge. Allowing for multiple events in patients, there were a total of 38 events, which were classified as ischaemic (9), undetermined (8), TIA (8), CVA/RND (7), haemorrhagic (2) and "other" (4). No patients died as a result of these events. The event rate was standardised using time to event analysis and compared with data from control arms reported in the literature in Table 9. The time to event analyses of deaths, ischaemic

neurological events and death or any neurological event are illustrated as Kaplan-Meier plots in Appendix 6. **[NOTE: this data has since been revised, see Addendum].**

Table 9. Incidence of strokes in CtE registry and control arms of published RCTs.

Study	Rate of neurological event (events per 100 PY)	Additional information
NHS England CtE registry	All neurological events: 3.4 (95% CI 2.1 to 5.0) Ischaemic event only: 1.3 (95% CI 0.6 to 2.5)	3 patients with events in hospital and 23 patients with events after discharge. 38 events in total, of which 2 were haemorrhagic and no fatal strokes reported.
CLOSURE-1 trial [10]	Stroke: 1.55 TIA: 2.05 Primary composite endpoint*: 3.4	ITT analysis (control group) 2 years follow up
RESPECT trial [11]	1.38**	ITT analysis (control group) Median 2.1 years follow up
RESPECT trial (2017 update) [22]†	Ischaemic stroke: 1.07	ITT analysis (control group) Median 5.9 years follow up
PC trial [12]	Stroke: 0.6 TIA: 0.83 Primary endpoint***: 1.3	ITT analysis (control group) Mean 4.0 years follow up
CLOSE trial [20]†‡	Stroke: 1.12	ITT analysis (control group) Median 5.3 years follow up
GORE REDUCE trial [21]†‡	Clinical stroke: 1.68	ITT analysis (control group) Median 3.2 years follow up

* 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.
** Primary endpoint was a composite of recurrent nonfatal ischemic stroke, fatal ischemic stroke, or early death after randomization. However, all primary events were non-fatal ischaemic strokes.
*** Composite outcome of death, stroke, TIA, or peripheral embolism. No deaths in control arm.
† Trials identified in Section 3.3. These have not been appraised.
‡ Event rate per 100 PY estimated by EAC from raw data counts and mean or median follow up as reported in study.

As the registry data were not exclusive to stroke but also included reversible ischaemic events such as TIA, the primary outcomes reported in the trials provide a reasonable proxy outcome (especially as deaths were uncommon in both the registry and the literature). It can be seen that the point estimate of neurological events from the registry is higher than that seen in the control arms of some of the identified RCTs. The event rate reported from the lower confidence interval (2.1 events per 100 PY) was higher than either of the point estimates for the AMPLATZER trials [11, 12] (1.38 and 1.3 events per 100 PY). However, it is likely that had these studies reported confidence intervals, they would overlap with those reported in registry, inferring there may be no statistical difference in outcomes. The lower confidence limit of the registry did include the point estimate of the CLOSURE-1 trial [10], but comparing point estimates of both trial and registry, the registry event incidence was still higher (4.6 compared with 3.4). The CLOSURE-1 trial employed the discontinued STARFlex system, which may have inferior efficacy compared with the AMPLATZER PFO Occluder [24]. Regarding the newer studies (reported in Section 3.3), the reported outcomes on stroke were similar to those observed in the registry.

Data from the control arm of the individual meta-analysis by Kent *et al.* (2016) reported a primary composite outcome of 2.3 events (ischemic stroke, TIA, or death from any cause) per 100 PY, and an ischaemic stroke rate of 2.2 per 100 PY [13]. However, when only data from the AMPLATZER device trials was considered (from the RESPECT and PC trials), the incidence rate was 1.6 and 1.1 for the primary outcome and ischaemic stroke respectively, which appears lower than reported in the CtE registry.

The comparative RCTs employed a superiority design, because PFOC may be considered as adjunctive to systemic preventative medical treatment (antiplatelet drugs or oral anticoagulation), and, in most cases, additional clinical benefits over and above standard treatment need to be demonstrated to justify its use. Therefore the results reported by the registry, which ostensibly report a similar or worse primary outcome than the control arm from these studies, are unanticipated, although it must be stressed that direct comparisons with published trial data is limited by differences in reported outcomes, outcome definitions, study methodology, and more broad issues with generalisability (e.g. patient population, diagnostic work up etc.).

Conclusion

Time to event analysis has been used to compare the incidence of neurological events from the CtE registry with natural history data from the literature (in some cases using the proxy of primary outcomes from control arms of RCTs). The incidence of presumed ischaemic stroke in the registry appears to be similar or higher in the registry compared with that reported in the RCTs. However, a direct comparison of results from the CtE registry compared with data from trials is unsatisfactory because of residual uncertainty on how comparable these results are, and there are several plausible explanations for the differences seen.

3.4.2 Question Two

> "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?"

For the purposes of this question, "success rates" has been defined separately as technical and procedural success rates, and the longer-term efficacy outcome of incidence of ischaemic stroke incidence. Complication rates refer to peri-procedural complications, which occur in hospital and may be classified as major or minor. Some complications were also

recorded following discharge although interpretation is often confounded by poor reporting of event data. For these outcomes, comparisons have been made either with the intervention arm of RCTs, or data published in the identified observational studies.

Technical and procedural success rates

The technical success of PFOC was defined as the proportion of patients in whom a device was successfully implanted (where it was attempted). Nearly all patients had a device successfully implanted, with a reported rate by participating centres of 99.3% (95% CI 98.6 to 99.8%). Procedural success was defined as technical success in the absence of major complications and was reported as 95.1% (95% CI 93.5 to 96.4%). Thus about one in twenty patients suffered an unsuccessful implantation or a potentially serious procedural complication, with the latter accounting for 1.0% (95% CI 0.4 to 1.8%) of patients. About 1 in 10 patients of those measured had residual shunt after 1 year follow up, which is important as these patients may be at continued risk of paradoxical embolism (see Appendix 8).

The rates reported in the CtE registry are compared with those in the data in Table 10.

Table 10. Comparison of technical and procedural success reported in CtE registry with published literature.

Study		Proportion of successful procedures	Definition/comment
CtE registry		Device implantation 99.3% (95% CI 98.6 to 99.8%) Procedural success 95.1% (95% CI 93.5 to 96.4%)	Device implantation refers to any successful implantation of the occlusion device. Procedural success is successful implantation in the absence of major complications.
RCTs	CLOSURE-1 (2012) [10]	89.4%	Procedural success, defined as "successful implantation of one or more STARFlex devices at the closure site during the index procedure with no procedural complications".
	RESPECT (2013) [11]	Technical success: 99.1% Procedural success: 96.1%	Technical success was successful implantation. Procedural success was technical success in absence of in-hospital serious adverse events.
	PC trial (2013) [12]	95.9%	"Effective closure was defined as closure with no or minimal shunting".
	Device trial (2013) [17]	100%	"Technical success" Aggregated data from all devices
Observational studies	Taggart (2017) [25]	AMPLATZER Septal Occluder: 97% AMPLATZER Cribriform: 92% GORE HELEX: 92% CardioSEAL: 100%	Proportion of patients with successful implant and without residual shunt. Only 4 patients received CardioSEAL.
	Pezzini (2016) [26]	92.2%	Proportion of patients with complete PFO closure (i.e. without residual shunt).
	Inglessis (2013) [27]	Procedural success: 99% Effective closure: 93%	"Procedural success" assumed to mean successful device implantation. "Effective closure" assumed to mean no significant residual shunt.
	Wallenborn (2013) [28]	Successful implantation: 100% Successful closure: 92%	Successful closure defined no residual shunt at 1 month. 5.5% had a small shunt detected. 2.5% had a medium or large residual shunt.

	Thomson (2014) [29]	98%	“Procedural success”.
	Mirzaali (2015) [30]	99%	“Procedural success”.

Direct comparisons with published data are confounded due to differences in definitions of technical or procedural success, which were not always explicitly defined in the literature. However, in general the success rates reported in the registry matched those reported in the literature. The technical and procedural success rates were nearly identical to those reported in the AMPLATZER RESPECT trial [11], which shared the similar definitions. Procedural success in the CtE registry also appeared to be superior to that reported in the CLOSURE-1 trial, which investigated the use of the now discontinued STARFlex device [10].

Similarly high technical success rates were reported in the observational studies, including those performed in UK settings [29, 30]. There was some evidence from the literature that the rate of success was device specific [25] (see Question 5).

Efficacy rates

As reported in Question 1, a total of 38 neurological events in 24 patients were recorded in the CtE registry. One patient was excluded from the time to event analysis, on account of missing data for their procedure date. Of the remaining 23 patients, the calculated event rate was 3.4 (95% CI 2.1 to 5.0) per 100 PY. This event rate is compared with those in the intervention arm of RCTs and data from observational studies in Table 11.

Table 11. Comparison of neurological events with primary efficacy outcomes reported in the published literature.

Study		Proportion patients with primary efficacy outcome. Events per 100 PY unless otherwise stated.	Definition/comment
CtE registry		3.4 (95% CI 2.1 to 5.0) Ischaemic event only: 1.3 (95% CI 0.6 to 2.5)	23 patients, with a recorded procedure date, reported as having a neurological event.
RCTs	CLOSURE-1 (2012) [10]	2.8*	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.
	RESPECT (2013) [11, 22]	0.66 0.58 (extended follow up)	Primary endpoint was a composite of recurrent nonfatal ischemic stroke, fatal ischemic stroke, or early death after randomization. However, all primary events were non-fatal ischaemic strokes ITT analysis data reported.
	PC trial (2013) [12]	0.83**	Composite outcome of death, stroke, TIA, or peripheral embolism. Two deaths in control arm.
	Device trial (2013) [17]	0.76*	The primary outcome was a composite of peripheral embolism, TIA, stroke, cerebral death.
	CLOSE trial [20]*†	0.0	No patients experienced stroke over 5.3 years follow up
	GORE REDUCE [21] †	0.43*	Clinical ischaemic stroke rate over 3.2 years follow up.
Observational studies	Taggart (2017) [25]	0.97	Annualised rate of patients suffering stroke or TIA.
	Pezzini (2016) [26]	2.73*	Ischaemic stroke, TIA, or peripheral embolism.
	Inglessis (2013) [27]	0.79**	Recurrent ischaemic cerebrovascular event.
	Wallenborn (2013) [28]	1.0	Recurrent stroke, TIA, or peripheral embolism.
	Thomson (2014) [29]	N/A	Long-term efficacy not reported in study.
	Mirzaali (2015) [30]	1.53	Combined stroke and TIA.

* Event rate per 100 PY estimated by EAC from raw data counts and mean or median follow up as reported in study.
** Event rate per 100 PY estimated by EAC from raw data counts and person years follow up reported in study.
† Trials identified in Section 3.3. These have not been appraised.

It can be seen that the point estimate of the event rate reported by the CtE registry is higher than that reported by any of the studies identified in the literature search. Furthermore, the lower 95% confidence interval, 2.1, is higher than all the studies with the exceptions of the CLOSURE-1 trial [10] and the observational study by Pezzini *et al.* (2016) [26]. The lower confidence interval of the ischaemic event rate reported in the registry (0.6) was higher than the point estimates reported in the extended RESPECT trial [22] or in the two recently published RCTs [20, 21]. The reasons for this apparent difference is unknown but could be entirely due to differences in study methodology and generalisability (see Section 4.3.1).

Data reported from the individual patient meta-analysis by Kent *et al.* (2016) [13] indicated a rate of 1.5 per 100 PY for the primary composite outcome and 0.7 per 100 PY for ischaemic stroke. Event rates were lower when the STARFlex study was excluded, with rates of 1.0 and 0.4 for the primary outcome and ischaemic stroke reported respectively.

[NOTE: this data has since been revised, see Addendum].

Complication rate

The CtE registry reported an in-hospital rate of major complications of 1.0% (95% CI 0.4% to 1.8%) and a rate of 5.2% (95% CI 3.8% to 7.0%) following discharge. Therefore the overall rate of major complications or adverse events was 6.2%. New onset AF is known to be associated with PFOC [31], and, as a risk factor for embolic stroke, this was selected for further analysis. An in-hospital event rate of 1.0% (95% CI 0.4% to 1.9%) was observed, with a rate of 3.5% (95% CI 2.3% to 5.0%) developing after discharge. Minor complications occurred in 2.6% of patients during their index hospital episode (95% CI 1.6% to 3.8%). On follow up, 14.6% of patients developed minor complications (95% CI 12.2% to 17.2%). The full incidences of major and minor complications (by subtype) are reported in Appendix 4. A comparison with the values published in the literature is reported in Table 12.

Table 12. Major complications or serious adverse effects reported in the registry compared with published literature.

Study		Proportion of major complications/adverse events	Proportion new onset or worsening atrial fibrillation reported	Definition of major complication/adverse event
CtE registry*		In hospital: 1.0% (95% CI 0.4 to 1.8%) After discharge: 5.2% (3.8 to 7.0%)	In hospital: 1.0% (95% CI 0.4 to 1.9%) After discharge: 3.5% (2.3 to 5.0%)	Composite of death, neurological event, device embolisation, major cardiac structural complications, MI, major vascular injury, endocarditis, oesophageal rupture, major bleed, additional surgery.
RCTs	CLOSURE-1 (2012) [10]	3.2%	5.7%	Major vascular procedural complication.
	RESPECT (2013) [11]	4.2%	0.2%	Serious adverse event rate was composite of 17 complications adjudicated to be due to procedure. (Overall serious adverse event rate was 23.0%).
	PC trial (2013) [12]	21.1%	2.9%	Adverse events described as "serious" but not necessarily procedure specific (17.6% in control group).
	Device trial (2013) [17]	N/R	6%	Aggregate adverse event rate not reported in study.
Observational studies	Taggart (2017) [25]	3.4%	In hospital: 1.0% After discharge: 2.9%	Composite of 14 procedural complications.
	Pezzini (2016) [26]	4.9%	1.5%	Serious adverse events.
	Inglessis (2013) [27]	1.6%	N/R	Serious procedural-related adverse event (death, stroke, TIA, device embolisation, tamponade, deep vein thrombosis).
	Wallenborn (2013) [28]	N/R	3.95%	Adverse event rate not reported.
	Thomson (2014) [29]	In hospital: 3% After discharge: 5.7%	2.2%	Early and late complications reported.
	Mirzaali (2015) [30]	2.3%	4.7%	Procedural "minor" complications. Device removal, transient ST elevation, sustained arrhythmia.

NR: Not reported.
* Data could not be aggregated to combined in-hospital and discharge for statistical reasons (poor follow up resulting in reduced denominator in "after discharge" data).

Direct comparisons with the published literature are difficult because there was no consistent terminology used between studies. For instance, the PC trial [12] reported a rate of 21.1% for "serious adverse events" but it is likely the large majority of these were not directly related to the procedure. In addition, data were presented as percentage proportions which is dependent on follow up duration (if post-procedural complications are reported). However, in general, the reported rates of major complications and adverse effects ranged between 2% and 5%, which is consistent with that reported in the registry. In particular, the UK study by

Thomson *et al.*, (2014) [29] reported highly concordant results with the CtE registry. A large meta-analysis of observational studies (n = 7414) found a complication incidence of 4.1 events per 100 PY [32] which would also appear consistent with the CtE registry data.

Development of new onset AF was reported at a rate of between 0.2% for the RESPECT study [11] to 6.0% in the Hornung *et al.*, device comparison trial (2013) [17]. The reported CtE data is consistent with this range. There is evidence from the CLOSURE-1 trial that new onset AF was associated with the STARFlex device [10], although there was also a trend towards this for the AMPLATZER PFO occluder device evidenced by the PC trial [12].

Conclusion

Data from the CtE registry reported that the technical success was close to 100%, whilst the procedural success was around 95%. This high rate of success is consistent with data from trials and observational studies. The rate of serious peri-procedural complications observed by the registry was also largely consistent with the published literature. New onset AF appears to be a risk associated with PFOC reported by the registry and consistently by published data, although direct comparisons are complicated by differing follow up durations of studies.

There is less confidence from the registry data that PFOC performed as effectively as published trial and observational data suggests, with a rate of 3.4 (95% CI 2.1 to 5.0) reported for neurological events, and 1.3 (95% CI 0.6 to 2.5) specifically for ischaemic events. This appears to be materially higher than data reported from published RCTs and observational studies, but interpretation is limited by issues with study methodology and generalisability.

3.4.3 Question Three

> "Is patent foramen ovale closure associated with an improved quality of life for these patients?"

Quality of life (QoL) was measured in the registry at baseline and at follow up (6 weeks, 6 months, 1 year, and 2 years using the EuroQol system (EQ-5D-5L), converted to utility scores. The median baseline utility was 0.91 (IQR 0.82 to 1.00), and this changed to 1.00 at each of the follow up intervals (see *Supplementary material – Table 8*). The mean baseline utility value was 0.87±0.19 and this increased to range from 0.90 to 0.91 at each of the follow up intervals.

A statistically significant change in the dimension of anxiety and depression was recorded at 6 weeks and 6 months post-procedure. Reduced anxiety or depression may have occurred because patients were reassured that their risk of a further stroke was reduced by the procedure.

3.4.4 Question Four

> "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)?"

This question cannot be answered through analysis of CtE registry data, which is restricted to 2 years maximum follow up. Out of 282 CtE patients eligible for follow up at 2 years, 112 (39.7%) provided follow data with no long-term cardiac complications recorded.

The literature search performed by the EAC identified an RCT with 4 years follow up [12] and an observational study with up to 8 years follow up [26], but potential longer term complications, such as atrial wall erosion, were not reported. The RESPECT trial has recently published reported long-term follow up data on patients of up to 10 years [22]. The authors reported the rate of pulmonary embolism was 0.41 per 100 PY in the PFOC group and 0.11 per 100 PY in the medical-therapy group (HR 3.48; 95% CI 0.98 to 12.34; p = 0.04), which is consistent with the putative mechanism of action of PFOC (or related to reduced anticoagulation use in the intervention arm). However, no long-term complications involving the device *per se* were reported.

It is likely that the incidence of long-term complications, such as cardiac erosion, in this population will be low and ascertained mainly by in case reports [33], but these were excluded from the EAC's literature identification.

Conclusion

The registry was not designed to identify potential longer-term complications of longer than 2 years. The incidence of complications appears to be very low before this time period. The EAC is unaware of any signal from the literature to indicate PFOC devices are associated with specific cardiac complications.

3.4.5 Question Five

> "Which devices are used to undertake PFO? What are the device-specific efficacy and safety outcomes in CtE funded patients undergoing the procedure? In particular, is there any published or register evidence of complications in the long term from percutaneous PFO closure (e.g. erosion with penetration through the wall of the atrium/myocardium/pericardium)?"

Devices implanted

The manufacturers of the devices implanted in patients receiving PFOC at first attempt in the CtE registry are listed in Table 13. As can be seen, St. Jude Medical (the AMPLATZER range) and GORE (the CARDIOFORM Septal Occluder) dominated the market share, with Occlutech (the Figulla Flex range) having a smaller presence.

Table 13. Devices used in CtE registry.

Manufacturer (device)	Proportion of devices fitted in the CtE registry
St. Jude Medical (AMPLATZER range)	54.5%
GORE (CARDIOFORM Septal Occluder)	30.1%
Occlutech (Figulla Flex range)	13.1%
Other (inc. combination)	2.3%

Device specific efficacy

Regarding the primary efficacy endpoint of incidence of neurological event, there were 10 events in patients receiving the AMPLATZER range of devices (10/495), 11 in patients receiving the GORE CARDIOFORM Septal Occluder device (11/276), and 3 in those receiving the Occlutech Figulla Flex range of devices (3/110); see Appendix 7. This was an event rate of 2.0% for the AMPLATZER devices compared with 4.0 % for the GORE CARDIOFORM Septal Occluder, but was not significantly different. The AMPLATZER range was associated with a higher rate of major complications than the GORE CARDIOFORM Septal Occluder (1.3% vs. 0%), but again this difference was not significant. Thus overall there was no significant difference seen between devices in terms of efficacy or aggregate safety.

One RCT identified in the literature directly compared three PFOC devices (see full literature review [3]). This was the study by Hornung *et al.* (2013) [17] which was a three armed trial (n = 660) comparing the AMPLATZER PFO Occluder, GORE HELEX (discontinued in 2011) and CardioSEAL STARFlex (also now discontinued) systems with a follow up of 5 years. The primary outcome was a composite of TIA, stroke, or death from neurological causes or any other paradoxical embolism. Secondary endpoints were the individual components of the primary outcome and complications. The primary outcome occurred in 1.4%, 4.1%, and 5.9% of patients with the AMPLATZER, HELEX, and STARFlex devices respectively. The AMPLATZER PFO Occluder was found to be statistically superior to the other devices for the composite outcome (p=0.042), but not any of the component outcomes. Complete PFO closure was recorded in 100% of AMPLATZER devices compared with 96.8% for the HELEX system and 98.8% for the STARFlex system. The HELEX system was found to be statistically inferior to the others in this regard (p=0.004). The HELEX system was also found to be associated with a significantly greater rate of device embolisation (1.3% compared with 0% for the other devices).

Two observational studies also reported limited between-device comparisons. Results from these studies should be considered in the context they are subject to confounding and bias. The study by Inglessis *et al.* (2013) found no difference in the rate of effective of PFO closure in the six devices investigated [27]. The study by Taggart *et al.* (2017) reported that both the AMPLATZER Cribriform device and the GORE HELEX device were associated with a greater rate of residual shunt compared with the AMPLATZER Septal Occluder [25].

Two meta-analyses of the CLOSURE-1, RESPECT and PC trials [10-12] reported a (non-significant) trend towards improved primary outcomes when disc-occluder devices (AMPLATZER PFO Occluder) were analysed compared with outcomes associated with the STARFlex device [13, 14]. A network meta-analysis by Stortecky *et al.* (2015) [15] reported the absolute benefit of the AMPLATZER PFO Occluder, STARFlex, and GORE HELEX systems in terms of number needed to treat (NNT) or number needed to harm (NNH). For the outcome of stroke prevention compared with medical treatment, the AMPLATZER PFO Occluder was associated with greater absolute benefit with an NNT of 29 (NNT 21 to NNT 109) than the GORE HELEX system (NNT 60 [NNT 21 to NNH 10]). The point estimate of the STARFlex device was associated with the potential to do harm (NNH 1518 [NNT 31 to NNH 12]).

There was no evidence from the CtE registry (see Question Four) or the literature regarding long-term adverse effects of device implantation such as cardiac wall erosion.

Conclusion

The AMPLATZER PFO Occluder (St. Jude Medical) and the GORE CARDIOFORM Septal Occluder were the predominant devices used on patients in the CtE registry. There was no evidence from registry data that any device outperformed another or was associated with increased risk of complications. There was some evidence from a comparative RCT that the GORE HELEX system was associated with lower rates of complete occlusion and increased risk of embolisation compared with the AMPLATZER PFO Occluder device. However, it cannot be assumed that published trial results from the GORE HELEX device are directly generalizable to the GORE CARDIOFORM Septal Occluder used in the CtE programme. This indicates that although differences in specific device efficacy have not been measured, clinically important differences in performance are plausible.

3.4.6 Question Six

"What are the short and medium term risks of percutaneous PFO closure?"

Percutaneous PFOC was recommended under normal arrangements in NICE IPG472, which stated "evidence on the safety of percutaneous closure of patent foramen ovale to prevent recurrent cerebral embolic events shows serious but infrequent complications" [34]. Evidence for the safety of the procedure derived from the CtE registry is described in Question Two. Serious complications appear to be relatively rare, with a rate of 1.0% in hospital and 5.2% after discharge. There were a total of 3 recorded deaths (0.3%) (see Appendix 4). This appears to be consistent with published literature.

Conclusion

The evidence from the CtE registry suggests the short and medium term risks of percutaneous PFOC is consistent with the published data and on this basis an update of IP472 is not required.

3.4.7 Question Seven

"What proportion of patients referred to an MDT for possible percutaneous PFO closure against Commissioning through Evaluation criteria were considered suitable for the intervention?"

The CtE registry reported that, once a patient was selected for the procedure at an MDT meeting, the large majority of patients were determined to be suitable candidates for PFOC and proceeded to have the intervention (Table 14). However, it is likely that most centres did not use the registry to capture all cases presented to the MDT meeting; that is, patients not selected for the procedure were not subsequently enrolled into the registry. Therefore this data cannot be used to reliably answer the question.

Table 14. MDT decision on suitability for PFOC.

Decision by MDT (suitability for PFOC)*	Number of patients	Proportion of patients (%)
No	15	1.8
Yes	819	97.6
Unknown	5	0.6
* 839 data fields complete (98.9%), with data missing in 9 (1.1%).		

Thirteen reasons for non-treatment were reported in the 15 patients not selected for PFOC (multiple choices permitted), and were that the presence of PFO could not be confirmed by the imaging specialist (3); only a minor shunt was detected and the patient was deemed

unlikely to benefit (2); PFO present but other mechanism for stroke thought more likely (2); PFO present, but no evidence of cerebral infarct on imaging (1); ASD confirmed so ASD closure performed instead (3); other (2).

The reasons for treatment with PFOC are listed in Table 15, together with indications reported from another UK registry, that of Thomson *et al.* (2013) [29], which reported on experience with the GORE HELEX device. The principal reason for treatment with PFOC reported in the CtE registry was prior cryptogenic stroke (77.6% of patients) or TIA (13.5% of patients), with a combined total of 91.1%, similar to the Thomson registry. Migraine and decompression illness accounted for 5.4% of indications for PFOC. These are not valid reasons for treatment eligibility according to NHS England criteria [35] and are excluded from the CtE analyses (Appendix 1).

Table 15. Reasons for treatment specified at MDT meeting (CtE registry – multiple reasons permitted) and as reported by Thomson *et al.* (2013).

Indication	Proportion (%)	
	CtE registry	Thomson study
Previous single stroke	64.2	83.4
Previous multiple strokes	13.4	
Previous single TIA	7.9	
Previous multiple TIAs	5.6	
Migraine	4.7	2.2
Decompression illness	0.7	Not reported.
Other	3.4*	10.4**
* Desaturation syndrome (0.1%), myocardial infarction (presumed embolic) (1.8%), peripheral embolus (0.5%), prior to neurosurgical procedure (0.1%), other (0.9%). ** Including coronary paradoxical embolus, and embolus to other (noncerebral) organs, residual shunt after previous closure.		

The data reported by the registry did not provide information on absolute number of patients suitable for treatment at a national level and thus likely budgetary impact. The EAC did not identify data from the published literature that could inform a top down analysis to answer this question, which would be dependent on the prevalence and incidence of patients who have had a cryptogenic neurological event suspected to be caused by paradoxical embolism. It is possible a bottom up approach of analysis could be undertaken using centre data from the registry.

Conclusion

The registry reported around 98% of the patients referred for MDT assessment for PFOC progressed to receive the procedure. However, it is unlikely this accurately reflects real-life patient pathways (that is, the registry was not used to capture all cases presented to MDT). It is therefore unknown what proportion of patients were referred for MDT in the first instance, or what the national demand for this service is for this, or other, indication.

3.4.8 Question Eight

> "Are favourable clinical outcomes with patent foramen ovale closure associated with particular patient characteristics (clinical or demographic)?"

Exploratory multivariate analysis was conducted using generalised linear modelling with binomial error distribution in order to estimate the effect of covariates. All numeric covariates were centred on their median before inclusion in multivariate analysis. However, it was found

that the binary logistic regression analyses did not converge, or were over-fitted for the following measures:

- device implanted outcome – covariates: procedure number (tertiles), gender, age, BMI, eGFR, pulmonary hypertension, NYHA (New York Heart Association) dyspnoea status, previous atrial septal procedure, atrial septal aneurysm;
- in-hospital major and minor complications outcomes – covariates: procedure number (tertiles), gender, age, BMI, eGFR, pulmonary hypertension, NYHA dyspnoea status, previous atrial septal procedure, atrial septal aneurysm, intraoperative echo imaging, and device(s) implanted.

Therefore a simpler set of covariates were tested for the CtE data and no significant association between age or sex and death was found.

The CLOSURE-1 trial [10] performed subgroup analysis on the primary outcome using the explanatory variables of sex (male or female); presence of atrial septal aneurysm; shunt size (none or trace, moderate or substantial); indication (stroke or TIA); and baseline medication (none, aspirin alone, warfarin alone, or aspirin plus warfarin) in subgroup analysis. None of these characteristics were significantly associated with improved or worsened outcomes.

The RESPECT trial [11], which found no significant improvement in the primary outcome compared with medical treatment overall (hazard ratio [HR] 0.49 [95% CI 0.22 to 1.11, p=0.08]) performed subgroup analysis on a number of demographic and clinical characteristics. The authors reported two factors that were associated with significantly improved outcomes compared with the control group. These were the presence of atrial aneurysm, which was associated with a HR of 0.19 (95% CI 0.04 to 0.87, p=0.02), and the presence of substantial shunt size (HR 0.18 [95% CI 0.04 to 0.81]). It is mechanistically plausible that repair of more substantial defects could result in greater efficacy gains.

The PC trial [36] reported no significant benefit of PFOC overall, with a HR of 0.63 (95% CI 0.24 to 1.62). Subgroup analysis of the primary outcome was conducted for age (<45 years or ≥45 years); presence of atrial septal aneurysm; index event (stroke or TIA [or pulmonary embolism]); and number of previous cardiovascular events (1 or ≥ 1). There was a trend toward younger people receiving benefit, although this was not significant (HR 0.16 [95% CI 0.02 to 1.31, p=0.09). In contrast to the RESPECT trial, the presence of atrial septal aneurysm was not associated with clinical benefit, and in fact trended towards being a risk (HR 2.09 [95% CI 0.38 to 11.4], p=0.78). However, this study was likely to be underpowered to detect effects in specific subgroups.

The observational study by Taggart *et al.* (2017) [25] performed extensive subgroup analysis. The authors reported the following risk factors that were associated with recurrent neurological events: increasing age (HR 1.04 [95% CI 1.02 to 1.07, p<0.001]); hypertension (HR 2.07 [95% CI 1.15 to 3.72, p=0.15]); diabetes mellitus (HR 3.82 [95% CI 1.84 to 7.94, p<0.001]); right ventricular systolic pressure (HR 1.04 [95% CI 1.01 to 1.07, p=0.013]); and pulmonary artery systolic pressure (HR 1.05 [95% CI 1.02 to 1.08, p<0.001]). It is unclear if statistical correction for multiple comparisons was performed (e.g. Bonferroni correction).

The observational study by Wallenborn *et al.* (2013) [28] performed multivariate analysis of predictors of recurrent ischaemic events. The authors reported the number of prior ischaemic events (HR 1.4 [95% CI 1.2 to 1.7, p<0.001]) and the presence of diabetes mellitus (HR 2.4 [95% CI 1.1 to 5.2, p=0.034]) were prognostic risk factors. However, the

detection of thrombus formation was found to greatly increase the risk of recurrent stroke, with a HR of 6.8 (95% CI 2.4 to 19.3, p<0.001).

The meta-analysis of RCTs by Kent *et al.* (2015) [13], which pooled individual patient data from the three RCTS comparing PFOC with medical therapy [10-12] performed subgroup analysis on the following risk factors: age; sex; smoking status; shunt size (measured by TOE); atrial septal aneurysm; index event (stroke or TIA); history of migraine; and radiology results (superficial stroke or others). In this analysis, none of the risk factors was associated with significantly improved outcomes, although male sex trended to this (p=0.064). The presence of atrial septal aneurysm was associated with a HR of 0.65 (95% CI, 0.34 to 1.23), compared to a HR of 0.71 (95% 0.44 to 1.14) in those without the condition (p=0.845).

Conclusion

No significant associations were found between age or gender and death in the CtE registry. One RCT reported evidence that the use of PFOC in the presence of atrial septal aneurysm and large shunt size was associated with greater clinical benefit, which appears to be mechanistically plausible. However, this effect was not observed by other experimental or observational studies.

3.4.9 Question Nine

> 'What are the average full procedural costs of percutaneous patent foramen ovale closure to the NHS?'

Table 7 demonstrates that the forecast cost for a PFO closure procedure ranges from about £6,950 to over £9,250 with a central estimate of around £8,300. The device cost included in each scenario is £[redacted] per patient [redacted] for one device) and it accounts for between [redacted] to [redacted]% of the total cost, depending on the scenario. This was calculated by using the number of devices opened per patient from the database. The database also reported the devices used by manufacturer across centres. NHS Supply Chain provided the unit cost for each device for the main manufacturers. These data enabled the EAC to calculate an average cost per device and per patient. An additional 15% overhead was added to the NHS Supply Chain cost.

Under the central cost scenario the pre-operative pathway accounted for 3%, the procedure [redacted] and subsequent management [redacted] of total costs respectively.

3.4.10 Question Ten

> 'What are the potential cost savings for the NHS in patients receiving percutaneous patent foramen ovale closure?'

This question will be answered by a cost consequences analysis to be provided in a separate report to NICE by 29 December 2017.

3.4.11 Question Eleven

> 'What is the likely cost-effectiveness of percutaneous PFO closure in the NHS, based on UK costs?'

This question will be answered by a cost consequences analysis to be provided in a separate report to NICE by 29 December 2017.

3.4.12 Summary of answers to NHS England questions

Answers to the NHS England questions are summarised in Table 16.

Table 16. Summary of NHS England answers.

Final version of question, as amended NICE following discussion with EAC	Summary answer (from registry data supplemented by published literature)
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)?	Time to event analysis from the CtE registry reported a rate of 3.4 (95% CI 2.1 to 5.0) neurological events per 100 PY, of which 1.3 (95% CI 0.6 to 2.5) are attributed to ischaemic origin. In the absence of natural history or modelling studies identified from the literature, the primary outcome of control arm 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 PY. However, the EAC cautions that a direct comparison with published trial data may not be valid for reasons of methodology and generalisability. The incidence of presumed ischaemic stroke in the registry 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.
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?	Procedural data were well reported in the registry. Technical success was close to 100%, whilst procedural success was around 95%. This is consistent with published data from trials and observational studies. There was evidence that the incidence of ischaemic 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. The incidence of peri-procedural complications observed in the CtE registry was largely consistent with the published literature. New onset AF appears to be the most common adverse event.
3. Is patent foramen ovale closure associated with an improved quality of life for these patients?	A statistically significant improvement in the dimension of anxiety and depression was recorded at 6 weeks and 6 months post-procedure No data were identified from the literature to answer this question.
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)?"	The registry did not follow up patients for sufficiently long enough to answer this question.

Final version of question, as amended NICE following discussion with EAC	Summary answer (from registry data supplemented by published literature)
5. Do the commercially available current devices perform equivalently?	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 device manufacturers. 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.
6. What are the short and medium term risks of percutaneous PFO closure?	There was no safety flag identified from the registry that would require an update of NICE IPG472.
7. What proportion of patients referred to an 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 indicate that the size of shunt and/or presence of an atrial septal aneurysm may be associated with greater benefits compared with medical management than patients that lack these risk factors, but this is not conclusive.
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 £8,303, range £6,946 to £9,254.
10. What are the potential cost savings for the NHS in patients receiving percutaneous patent foramen ovale closure?	This question will be answered by a cost consequences analysis to be provided in a separate report to NICE by 29 December 2017.
11. What is the likely cost-effectiveness of percutaneous PFO closure in the NHS, based on UK costs?”	This question will be answered by a cost consequences analysis to be provided in a separate report to NICE by 29 December 2017.

Section 4: Discussion

4.1 SUMMARY OF FINDINGS FROM PRIMARY DATA COLLECTION (CTE DATABASE)

The CtE registry enrolled a total of 1126 patients, of which 995 were selected following MDT assessment based on suitability for the procedure (see Appendix 1). Included patients had a median age of 45 years (IQR 36 to 51 years). 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 PFO identified by echocardiography which was thought to be the causal reason for the stroke (through paradoxical embolism). In most cases, the PFO was not associated with a haemodynamic shunt that might have caused symptoms (92.4% patients had no limitation of physical activity as measured by NYHA class). Procedural outcomes were reported in 901 patients (91%), for whom both admission and discharge data were available. Medium term safety and efficacy outcomes were reported in follow-up information in 78.3% procedures at 6 weeks, 68.3% at 6 months, 59.4% at 1 year and 39.7% at 2 years (of eligible patients). There were no significant differences in clinical characteristics between patients who were followed up and all patients at baseline.

Most patients were treated with a St. Jude Medical device from the AMPLATZER range (45.5%) or GORE CARDIOFORM Septal Occluder device (30.1%), with 13.1% receiving an Occlutech device from the Figulla Flex range. There was a high implantation rate of 99.3% (95% CI 98.6 to 99.8%), and procedural success of 95.1% (95% CI 93.5 to 96.4%). Nine patients (1.0%) had a major in-hospital complication, including 1 death. Twenty four patients experienced a minor complication in hospital. The large majority of patients had a one night stay in hospital.

Following discharge, there were 32 additional major complications reported, including 2 deaths. Neurological events were reported for 26 patients during or post-PFOC procedure discharge (with potential for multiple events per patient), consisting of 9 ischaemic, 2 haemorrhagic, 7 undetermined, 8 TIA, 7 CVA/RND and 4 “other” neurological event. Over the course of follow up, the event rate of all neurological events was 3.4 (95% CI 2.1 to 5.0) per 100 PY, and the rate of ischaemic event was 1.3 (95% CI 0.6 to 2.5) per 100 PY, over a total aggregated follow up period of almost 700 person-years.

The central estimate of the cost of the procedure was £8,303 (range £6,946 to £9,254). The largest component of the cost was the device ([redacted]) followed by investigations ([redacted]%). Remaining costs were related to consumables, staff, hospital stay, theatre use and outpatient clinics.

Analysis of limited EQ-5D data indicated that the use of PFOC may relieve anxiety and depression, but there was no measurable impact on quality of life in the other domains.

4.2 COMPARISON TO SECONDARY DATA (RESULTS IN LITERATURE REVIEW)

The EAC performed a literature search which identified three RCTs [10-12] that had compared the PFOC procedure with medical treatment (documented in the EAC’s literature review paper [3]). Although the RCTs did not report statistically significant superiority of their primary outcomes, the EAC considered that there was likely to be some benefit associated with the use of the AMPLATZER PFO Occluder device. However, the absolute benefit may

be modest and should be considered in the context of the potential for adverse events (in particular, new onset AF) and use of NHS resources compared with standard medical preventative treatment. Since the writing of the EAC literature review, three further important, experimental studies have been published. These were the long-term follow up of the RESPECT trial [22], the CLOSE study [20], and the GORE REDUCE study [21]. These studies, which have not been appraised by the EAC, reported that PFOC was associated with significant reductions in the event rate of ischaemic stroke.

The CtE registry provided good data on the procedural efficacy and in-hospital safety of PFOC. Although statistical comparisons could not be performed due to data heterogeneity, peri-procedural outcomes were generally consistent with those reported in the literature from both experimental and observational studies. The data indicate that PFOC is a relatively safe procedure usually requiring one overnight stay, and that serious in hospital complications are rare.

Interpretation of medium-term data (neurological events) was limited by inconsistency of definition of outcomes between studies (such as inclusion of TIA). Comparison of the registry results with control arms of the RCTs was unable to demonstrate a clear benefit of PFOC in the overall cohort enrolled. Comparison with the intervention arms (i.e. patients from RCTs receiving PFOC) suggested that patients in the registry were not achieving the benefit reported in these studies (particularly the more recently published studies). However, interpretation was limited by issues concerning study methodology and generalisability (see Section 4.3.1).

The EAC literature search identified one study which was a cost-utility analysis from the perspective of the USA healthcare system. Using data from a meta-analysis of the 3 older RCTs and US costs, it reported that PFOC was cost-effective over a time horizon of 3 years. However, the EAC judged this study had poor internal and external validity, hence there was material uncertainty on whether its findings on cost-effectiveness apply in the English setting.

In summary, the EAC has identified some concerns regarding the efficacy of PFOC reported in the registry compared with the published literature. Although procedural efficacy and in-hospital complications appear to be broadly consistent, medium-term efficacy rates appear to be similar or slightly inferior to the control arms of RCTs, and possibly inferior to intervention arms. Neurological outcomes from the CtE registry also do not generally compare favourably with other observational studies, although the same caveats regarding making these comparisons (particularly concerning outcome measurement and terminology) apply (see Table 11). 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. It should be emphasised that inferiority has not been unequivocally shown as it was not possible to apply statistical analysis. Additionally, it should be noted that in all the studies, including the recent CLOSE trial where no patients in the intervention arm suffered ischaemic stroke over 5 years of follow up [20], the absolute benefit of PFOC in reducing stroke is small, and the procedure is not without risk (in particular to the development of new onset AF).

4.3 LIMITATIONS AND FUTURE PROPOSALS (FOR NHS ENGLAND REPORT)

4.3.1 Limitations

The CtE registry was a single armed study and thus comparisons had to be made implicitly with results published in the literature [37]. 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, evaluation of CtE results with trial data was limited by differences in outcome terminology and measurement, and possible issues with generalisability of the population (for instance, recent advances in research concerning PFO closure suggest thorough diagnostic workup is essential). Thus inferences of equivalence (or not) of CtE and trial data are subject to considerable uncertainty at best and are invalid at worst.

Other specific and non-specific limitations with the registry include the following:

- Although initially designed for 5 years follow up, registry follow up was limited to a maximum of 2 years. This meant that longer-term efficacy outcomes or data on longer-term complications were not available and questions pertaining to these were not answerable (see Question Four).
- In addition to the 2-year cut off point, most patients were not eligible for assessment at this time point because of the timeframe of the study and associated deadlines. Of the 898 patients who reported discharge data, follow up data at 2 years were only available on 282 (31.3%) at the cut-off date of the study.
- Kaplan-Meier analysis assumed “no event” status of patients unless an event was recorded. Thus 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 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.

An important issue which came to light late in the data collection phase of the study was that the registry had a degree of ambiguity in the reporting of outcomes, in particular concerning the classification of ischaemic event rates (for instance regarding permanence of disability and underlying cause of event [ischaemic or haemorrhagic]). Thus it is possible that there were differences in interpretation of neurological events during data entry. This was possibly compounded by an increase in activity of reporting follow up towards the study deadline. To resolve this issue, the EAC, NICOR, and clinical leads contacted centres directly to validate event rates and present clean data for analysis, which are presented in the Addendum section of this report.

4.3.2 Strengths

The CtE registry had several strengths. Firstly, the registry enrolled indicated patients consecutively and represented a pragmatic real-world cohort of patients receiving treatment with PFOC as performed in the NHS. Thus the external applicability of the registry to future practice is high, although improvements in the procedure protocol and any potential learning curve effect may ultimately lead to improved outcomes.

Secondly, this was a large study, initially recruiting more than 1000 participants. This makes the sample size larger than all the other experimental and observational studies identified by

the EAC with the exception of the study by Wallenborn *et al.* (2013) [28]. However, the Wallenborn study was a retrospective analysis rather than a bespoke prospective registry. The CtE registry's large size gives it power to detect rarer outcomes and precision for more frequent event rates, and overall lends credibility to the results reported.

Thirdly, following an initial disappointing response from centres in providing follow-up data, this improved considerably towards the end of the study, such that there was about 700 PY 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% of eligible patients at 2 years, see *Supplementary Table 3*), completion of data fields was regarded as good.

Finally, the CtE registry reported important clinical outcomes. In addition, the registry captured quality of life data and, through the use of *pro formas* directed at a centre level, estimated the cost of the procedure. This information may be of use in future cost-effectiveness studies.

4.3.3 Future proposals

The registry would be more robust with data linkage to ONS (Office of National Statistics) to validate existing mortality estimates and provide greater coverage. This could be potentially continued beyond the final follow up date of the study (2 years). Potentially, data linkage to HES (Hospital Episodes Statistics) could also provide further validation and coverage of morbidity, as well as informing cost information. The EAC is currently pursuing ONS and HES data linkage for this project but this may not be available in time for publication.

Section 5: Conclusion

The PFOC CtE registry included 995 patients of which 901 underwent device implantation. Patients had had a prior ischaemic stroke (confirmed by cranial imaging) presumed to be due to PFO (confirmed by echocardiography). The median age of the patients was 45 years and the large majority did not experience cardiac symptoms from the PFO. Patients were followed up to 2 years after the procedure was performed, and important clinical outcomes were determined. As the registry was single-armed, implicit comparisons with published literature, previously identified in bespoke review [3], were made in order to answer 11 questions asked by NHS England.

The registry reported that nearly all patients had a device successfully fitted (99.3% [95% CI 98.6 to 99.8%]), with a procedural success rate of 95.1% (95% CI 93.5 to 96.4%). This was comparable to results published in the literatures and emphasised that PFO is a relatively safe procedure. Over the course of around 700 PY analysed, there was a neurological event rate of 3.4 (95% CI 2.1 to 5.0) per 100 PY, and an ischaemic event rate of 1.3 (95% CI 0.6 to 2.5) per 100 PY. As no natural history studies on this population were identified, the EAC compared these event rates with the control arms of RCTs [10-12], including an RCT with extended follow up [22] and two recently published RCTs [20, 21]. Patients in the registry had similar or higher event rates than those receiving drug treatments alone in the RCTs. When compared with the intervention arms of these studies, and most observational studies identified, the event rates appeared to be higher for patients in the registry than these comparator cohorts (Table 11). The registry reported a major complication rate of 5.2% (95% CI 3.8 to 7.0%) following discharge. A notable adverse event reported in the registry was new onset AF, which occurred in 3.5% (95% CI 2.3 to 5.0%) of patients following discharge; similar rates were reported in most the identified studies from the literature search. There was no evidence from the registry that any particular device was superior to another.

The registry reported a possible improvement in the anxiety and depression domain of the EQ-5D, indicating patients may have been reassured by the intervention. The registry was not designed to report long-term adverse effects, and did not provide useful information on the size of the population who might potentially benefit from PFOC. An additional survey performed by the EAC indicated the overall cost per procedure was on average £8,303, with a range of £6,946 to £9,254.

The evidence base for PFOC has expanded greatly over the last 5 years, with several RCTs now being published. Although earlier results on PFOC efficacy were equivocal, recent evidence from RCTs have provided strong evidence that the procedure can reduce the event rate of recurrent ischaemic stroke in carefully selected patients, although the absolute benefits are modest. Results from the CtE registry appeared to show less benefit associated with PFOC, in terms of reducing the incidence of ischaemic stroke, than might be expected from published observational and experimental evidence. The reasons for this are not know but could be related to issues with patient selection (e.g. diagnostic work up) or definitions of outcomes (for instance, inclusion of TIA as an ischaemic neurological event).

Section 6: Acknowledgements

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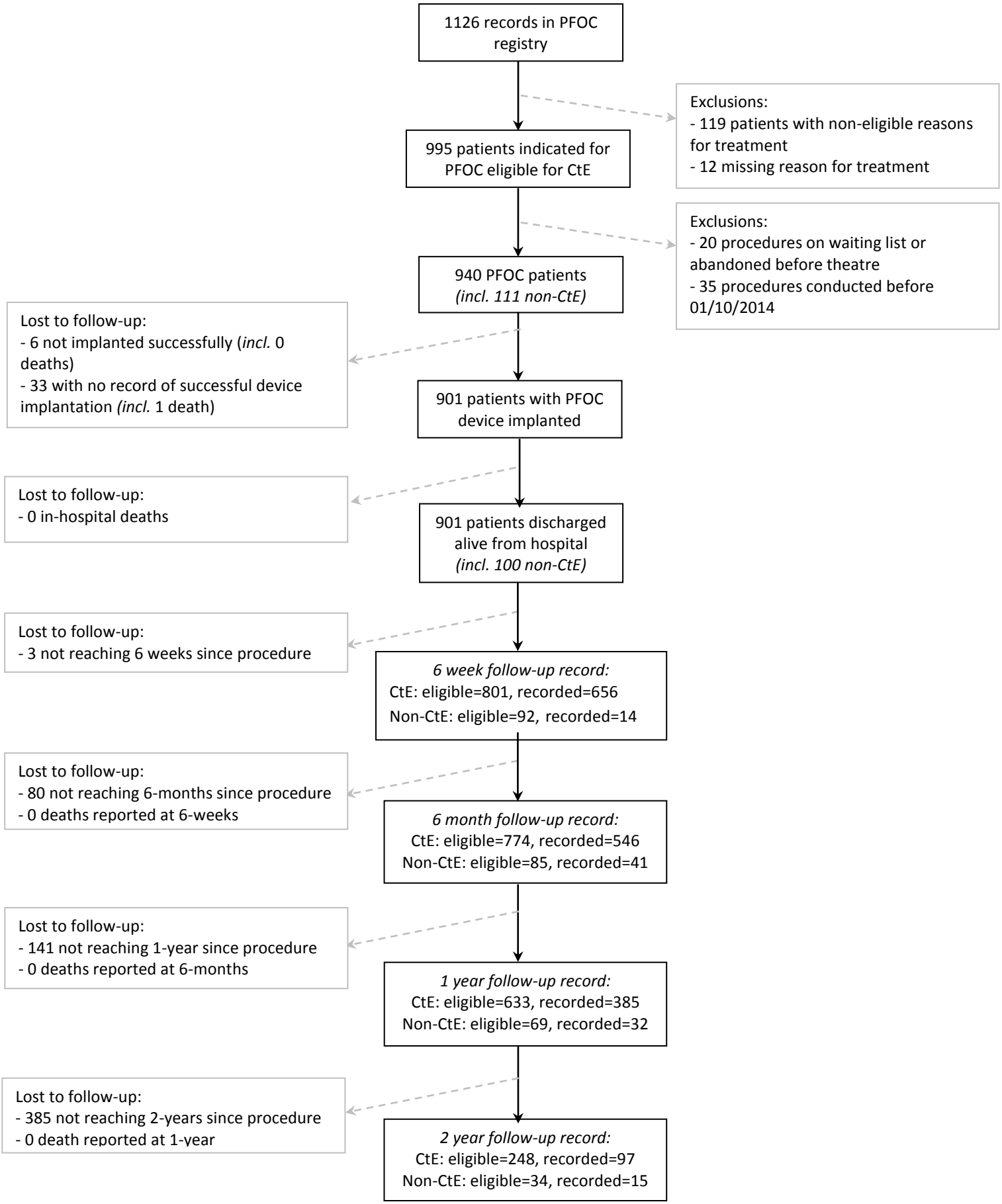
Appendix 1 – Data flow diagram



Appendix 2 – Patient characteristics

Patient characteristics for all eligible PFOC patients and those with recorded information from follow-up appointments.

Patient characteristics†	All eligible PFOC patients (n=940)	All patients with device implanted & follow-up (n=808)	p-value
Female	405 (43.1%)	349 (43.2%)	1.00
Age, years median (Q1,Q3) [range]	45 (36,51) [17-82]	45 (36,51) [17-81]	0.97
BMI, kg/m^2 median (Q1,Q3) [range]	26.5 (23.5,29.6) [14.2-48.9]	26.5 (23.6,29.6) [14.2-48.9]	0.86
Ethnic origin: Caucasian Black Asian Other	 796 (92.0%) 33 (3.8%) 27 (3.1%) 9 (1.0%)	 713 (92.1%) 28 (3.6%) 24 (3.1%) 9 (1.2%)	0.99
eGFR median (Q1,Q3) [range]	94 (82,107) [8-224]	94 (82,107) [12-193]	0.92
Previous venous thrombosis/ thromboembolic disease	40 (4.6%)	34 (4.4%)	0.91
Thrombophilic condition	30 (4.7%)	29 (5.0%)	0.89
Smoking status: Never smoked Ex-smoker Current smoker	 603 (71.4%) 184 (21.8%) 58 (6.9%)	 527 (71.0%) 167 (22.5%) 48 (6.5%)	0.91
Diabetes	26 (2.9%)	22 (2.8%)	1.00
Hypertension	100 (11.2%)	93 (12.0%)	0.65
Hyperlipidaemia	156 (17.8%)	143 (18.8%)	0.61
Congestive Cardiac Failure (CCF)	0 (0.0%)	0 (0.0%)	NA
Pulmonary hypertension	9 (1.0%)	8 (1.0%)	1.00
Peripheral Vascular Disease (PVD)	4 (0.4%)	4 (0.5%)	1.00
Previous Myocardial Infarction (MI)	20 (2.2%)	19 (2.4%)	0.87
NYHA dyspnoea status No limitation of physical activity Slight limitation of ordinary physical activity Marked limitation of ordinary physical activity Symptoms at rest or minimal activity	 808 (92.4%) 52 (5.9%) 11 (1.3%) 3 (0.3%)	 727 (92.4%) 49 (6.2%) 9 (1.1%) 2 (0.3%)	0.98
Previous history of arrhythmia	24 (2.7%)	23 (2.9%)	0.77
Previous atrial septal procedure	10 (1.1%)	7 (0.9%)	0.81
Co-existent valve disease	4 (0.5%)	4 (0.5%)	1.00
Brain scan (MRI/CT) Not conducted Conducted – no ischaemic lesion Conducted – ischaemic lesion	 41 (5.2%) 72 (9.1%) 675 (85.7%)	 39 (5.4%) 65 (8.9%) 623 (85.7%)	0.98
Pre-procedural PFO assessment Transthoracic echocardiogram (CFM or bubble contrast) Transoesophageal echocardiogram (CFM or bubble contrast) Transcranial Doppler Combination	 445 (50.1%) 162 (18.2%) 3 (0.3%) 279 (31.4%)	 377 (48.5%) 138 (17.7%) 3 (0.4%) 260 (33.4%)	0.84
R-to-L shunt detected	793 (96.9%)	704 (97.0%)	1.00
Echo contrast R-to-L shunt (without provocation) None Individual bubbles (<5 per still frame) Clusters/clouds/chamber opacification (≥ 5 per still frame)	 115 (16.5%) 114 (16.4%) 467 (67.1%)	 106 (16.5%) 102 (15.9%) 435 (67.7%)	0.97
Echo contrast R-to-L shunt (with provocation) None Individual bubbles (<5 per still frame) Clusters/clouds/chamber opacification (≥ 5 per still frame)	 12 (1.8%) 8 (1.2%) 647 (97.0%)	 9 (1.5%) 8 (1.3%) 603 (97.3%)	0.90
Transcranial doppler			1.00

Patient characteristics†	All eligible PFOC patients (n=940)	All patients with device implanted & follow-up (n=808)	p-value
Test negative. No microbubbles	88 (79.3%)	83 (79.0%)	
Low-grade shunt 0-10 microbubbles	3 (2.7%)	3 (2.9%)	
Medium-grade shunt >10 microbubbles but without curtain effect	12 (10.8%)	11 (10.5%)	
High grade shunt - curtain effect, when the microbubbles are uncountable	8 (7.2%)	8 (7.6%)	
Atrial septal aneurysm	88 (10.2%)	83 (11.0%)	0.63
Cerebral vascular imaging (by carotid USS or MR/CT angiography)			0.99
Not done	149 (19.3%)	139 (19.5%)	
Normal	594 (76.8%)	547 (76.7%)	
Minor abnormality	22 (2.8%)	19 (2.7%)	
Moderate/severe lesion	8 (1.0%)	8 (1.1%)	
LVEF			1.00
Good (>50%)	805 (99.1%)	734 (99.1%)	
Moderate (30-50%)	7 (0.9%)	7 (0.9%)	
Poor (<30%)	0 (0.0%)	0 (0.0%)	
Aortic atheroma in arch			0.85
Not imaged	615 (74.2%)	552 (73.0%)	
Grade 1	212 (25.6%)	202 (26.7%)	
Grade 2	2 (0.2%)	2 (0.3%)	
Grade 3	0 (0.0%)	0 (0.0%)	
Grade 4	0 (0.0%)	0 (0.0%)	
Medications (pre-op):			0.89
Single antiplatelet	540 (60.4%)	442 (57.7%)	
Dual antiplatelet	162 (18.1%)	144 (18.8%)	
Anticoagulant alone	78 (8.7%)	72 (9.4%)	
Antiplatelet(s) & Anticoagulant(s)	27 (3.0%)	23 (3.0%)	
Other	66 (7.4%)	66 (8.6%)	
None	21 (2.3%)	19 (2.5%)	
PFO tunnel length, mm median (Q1,Q3) [range]	6 (3,10) [1-20]	6 (3,10) [1-20]	0.85
Max PFO diameter, mm median (Q1,Q3) [range]	9 (6,12) [1-30]	9 (6,12) [1-30]	0.90
† Not all data fields were complete for every patient at baseline and follow up. The percentages presented in this table are calculated using the number of patients with each characteristic reported as the denominator.			

Appendix 3 – Procedural characteristics

Procedural details for all eligible PFOC patients and those with recorded information from follow-up appointments.

Procedural characteristic†	All eligible PFOC patients (n=940)	All patients with follow-up (n=808)	p-value
Treating hospital			0.01*
University Hospital of North Staffordshire NHS Trust (now Royal Stoke University Hospital)	75 (8.0%)	72 (8.9%)	
Brighton & Sussex University Hospitals NHS Trust	68 (7.2%)	63 (7.8%)	
University Hospitals Bristol NHS Foundation Trust	66 (7.0%)	62 (7.7%)	
Guy's and St Thomas' NHS Foundation Trust	59 (6.3%)	54 (6.7%)	
Kings College Hospital NHS Foundation Trust	66 (7.0%)	50 (6.2%)	
Nottingham University Hospitals NHS Trust	47 (5.0%)	45 (5.6%)	
Harefield Hospital	55 (5.9%)	39 (4.8%)	
Oxford University Hospitals NHS Trust	46 (4.9%)	42 (5.2%)	
Barts Health NHS Trust	51 (5.4%)	41 (5.1%)	
Liverpool Heart & Chest Hospital NHS Foundation Trust	49 (5.2%)	46 (5.7%)	
University Hospitals Leicester NHS Trust	41 (4.4%)	39 (4.8%)	
University Hospital Southampton, NHS Foundation Trust	39 (4.1%)	37 (4.6%)	
Leeds Teaching Hospitals NHS Trust	35 (3.7%)	32 (4.0%)	
University Hospital Birmingham NHS Foundation Trust	35 (3.7%)	34 (4.2%)	
Spire Bristol	32 (3.4%)	0 (0.0%)	
Royal Wolverhampton NHS Trust	29 (3.1%)	29 (3.6%)	
Papworth Hospital	29 (3.1%)	25 (3.1%)	
The Newcastle upon Tyne Hospitals NHS Foundation Trust	25 (2.7%)	23 (2.8%)	
Essex Cardiothoracic Centre	22 (2.3%)	19 (2.4%)	
St. George's Healthcare NHS Trust	22 (2.3%)	15 (1.9%)	
Central Manchester Hospitals NHS Foundation Trust	24 (2.6%)	16 (2.0%)	
Royal Brompton Hospital	22 (2.3%)	22 (2.7%)	
Sheffield Teaching Hospitals Foundation Trust	3 (0.3%)	3 (0.4%)	
Elective procedure	928 (99.3%)	802 (99.3%)	1.00
Anaesthesia			0.96
General anaesthesia	671 (74.2%)	591 (74.6%)	
Local anaesthesia & sedation	160 (17.7%)	136 (17.2%)	
Local anaesthesia only	73 (8.1%)	65 (8.2%)	
Intra-operative echo imaging			0.99
TOE (planned) or TTE	663 (72.9%)	578 (72.9%)	
ICE planned	206 (22.6%)	177 (22.3%)	
Unplanned	10 (1.1%)	9 (1.1%)	
None	31 (3.4%)	29 (3.7%)	
Atrial septum crossed	864 (98.9%)	763 (99.3%)	0.44
Venous sheath size (F): median (Q1:Q3) [range]	10 (8,11) [6-14]	10 (8,11) [6-14]	0.65
Cerebral protection device used	1 (0.2%)	1 (0.2%)	1.00
No. of devices attempted			0.90
1	854 (96.9%)	779 (96.7%)	
2	24 (2.7%)	23 (2.9%)	
3	3 (0.3%)	4 (0.5%)	
Device used:			0.91
St. Jude Medical (AMPLATZER range)	502 (54.5%)	430 (53.4%)	
GORE CARDIOFORM Septal Occluder	277 (30.1%)	254 (31.6%)	
Occlutech (Figulla Flex range)	121 (13.1%)	105 (13.0%)	
Other (incl. combination)	21 (2.3%)	16 (2.0%)	

Procedural characteristic†	All eligible PFOC patients (n=940)	All patients with follow-up (n=808)	p-value
Fluoroscopy time, mins median (Q1:Q3) [range]	5 (3,8) [0-82]	5 (3,8) [0-78]	0.96
X-ray dose, mGray.cm^2 median (Q1:Q3) [range]	591 (189,1417) [0-20,000]	566 (185,1320) [0-20,000]	0.48
Contrast dose, ml median (Q1:Q3) [range]	0 (0,15) [0-320]	0 (0,10) [0-320]	0.39
Procedural duration, mins median (Q1:Q3) [range]	45 (30,60) [0-229]	44 (30,60) [0-229]	0.58

Note:
† Not all data fields were complete for every patient at baseline and follow up. The percentages presented in this table are calculated using the number of patients with each characteristic reported as the denominator.
* p-value not significant after application of Bonferroni corrections applied for multiple comparisons.

Appendix 4 – Outcomes

Outcomes for all eligible PFOC patients. Note: patients may have multiple events (hence sum of breakdown of complication events is not necessarily equal to total major or minor complications).

	In-hospital (n=940)		After discharge (6w,6m,1y,2y combined) (n=808)	
	Total no. of patients	**% [95% CI]**	**Total no. of patients**	**% [95% CI]**
Major complications:	**9**	**1.0 [0.4:1.8]**	**42**	**5.2 [3.8:7.0]**
Death	1	0.1 [0.0:0.6]	2	0.2 [0.0:0.9]
Neurological event	3	0.3 [0.1:0.9]	23	2.8 [1.8:4.2]
Device embolisation	3	0.3 [0.1:0.9]	0	0.0 [0.0:0.5]
Major cardiac structural complications	0	0.0 [0.0:0.4]	1	0.1 [0.0:0.7]
MI	1	0.1 [0.0:0.6]	1	0.1 [0.0:0.7]
Major vascular injury	0	0.0 [0.0:0.4]	1	0.1 [0.0:0.7]
Endocarditis	0	0.0 [0.0:0.4]	0	0.0 [0.0:0.5]
Oesophageal rupture	0	0.0 [0.0:0.4]	-	-
Major bleed	1	0.1 [0.0:0.6]	13	1.6 [0.9:2.7]
Additional surgery	1	0.1 [0.0:0.6]	4	0.5 [0.1:1.3]
Minor complications:	**24**	**2.6 [1.6:3.8]**	**118**	**14.6 [12.2:17.2]**
Device malfunction	0	0.0 [0.0:0.4]	-	-
Air embolism	0	0.0 [0.0:0.4]	2	0.2 [0.0:0.9]
Malposition	4	0.4 [0.1:1.1]	0	0.0 [0.0:0.5]
New/worsening AF	9	1.0 [0.4:1.9]	28	3.5 [2.3:5.0]
Other arrhythmias	0	0.0 [0.0:0.4]	0	0.0 [0.0:0.5]
Minor cardiac structural complications	1	0.1 [0.0:0.6]	61	7.5 [5.8:9.6]
Transient ST elevation (no MI)	0	0.0 [0.0:0.4]	-	-
Minor embolic events	0	0.0 [0.0:0.4]	0	0.0 [0.0:0.5]
Minor vascular injury	5	0.5 [0.2:1.3]	5	0.6 [0.2:1.4]
Migraine/worsening migraine	3	0.3 [0.1:1.0]	21	2.6 [1.6:3.9]
Oesophageal trauma	0	0.0 [0.0:0.4]	-	-
Nickel allergy	0	0.0 [0.0:0.4]	0	0.0 [0.0:0.5]
Minor bleed	5	0.5 [0.2:1.3]	7	0.9 [0.3:1.8]
Any complication (minor & major combined)	**32**	**3.6 [2.5:5.0]**	**153**	**18.9 [16.3:21.8]**
Device implanted	**901**	**99.3 [98.6:99.8]**	**-**	**-**
Procedural success (device implanted in absence of major complications)	**894**	**95.1 [93.5:96.4]**	**-**	**-**

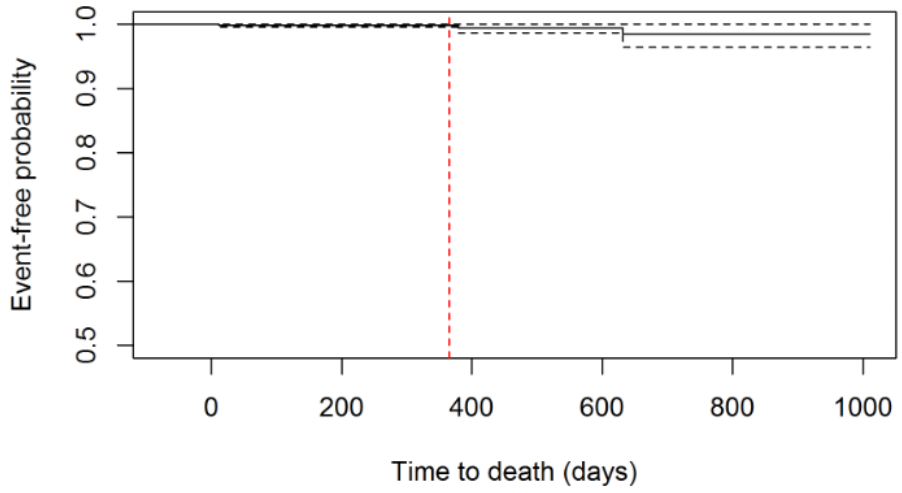
Appendix 5 – Outcomes (time to event analysis)

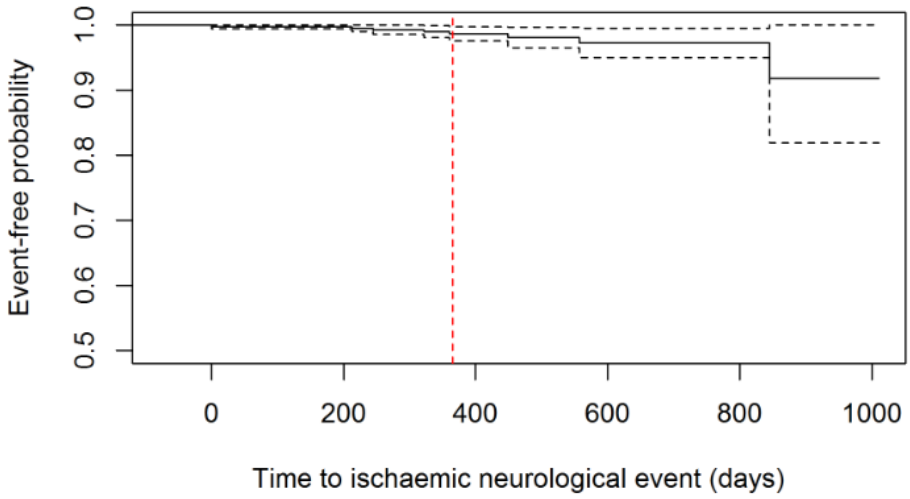
Patient outcomes (in-hospital and after discharge as reported at any follow-up combined) for all eligible PFOC patients.

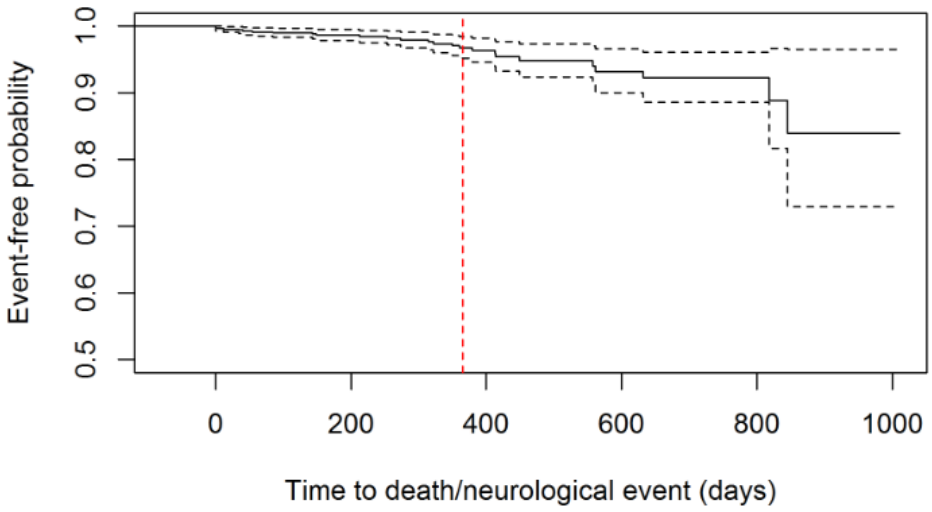
	No. of patients with event	**Total follow-up (person-years)**	**Event rate (per 100 person-years follow-up) [95% CI]**	**No. of patients at risk at 1-year**	**1-year event-free probability (95% CI)**
Major complications:					
Death	3 (0.3%)	698.7	0.4 [0.1:1.3]	304	0.999 [0.996 to 1.000]
Neurological event	23* (2.5%)	684.7	3.4 [2.1:5.0]	294	0.969 [0.953 to 0.985]
Ischaemic event only	*9 (1.0%)*	*691.1*	*1.3 [0.6:2.5]*	*299*	*0.987 [0.976 to 0.998]*
MI	2 (0.2%)	692.9	0.3 [0.0:1.0]	300	0.997 [0.994 to 1.000]
Device embolisation	3 (0.3%)	694.6	0.4 [0.1:1.3]	301	0.997 [0.993 to 1.000]
Additional surgery	5 (0.5%)	694.3	0.7 [0.2:1.7]	302	0.994 [0.989 to 1.000]
Minor complications:					
Peripheral embolism	0 (0.0%)	-	-	-	-
* 24 patients were reported as having a neurological event, however, date of event was missing from 1 patient who was consequently omitted from time to event analysis.					

Appendix 6 – Kaplan-Meier curves

Time to event (solid lines), corresponding 95% confidence limits (dashed lines), and proportions of patients event-free at 1 year (red dashed line).







Appendix 7 – Neurological events by device type

Device Manufacturer	Patients with reported neurological event	Patients with no reported neurological event	TOTAL
St. Jude Medical (AMPLATZER range)	10	485	495
GORE CARDIOFORM Septal Occluder	11	265	276
Occlutech (Figulla Flex range)	3	110	117
TOTAL	24	860	884

Appendix 8 – Echo contrast results

	Echo contrast results	Pre-procedure		6 months		1 year		2 years	
		n	% [95% CI]	n	% [95% CI]	n	% [95% CI]	n	% [95% CI]
At rest	Study done, no bubbles seen	113	16.6 [13.2:20.2]	341	94.2 [92.3:96.6]	158	89.8 [85.8:93.8]	33	86.8 [78.9:97.3]
	Individual bubbles†	109	16.0 [12.6:19.6]	14	3.9 [1.9:6.2]	10	5.7 [1.7:9.7]	2	5.3 [0.0:15.7]
	Clusters/clouds/chamber opacification‡	460	67.4 [64.1:71.1]	7	1.9 [0.0:4.3]	8	4.5 [0.6:8.5]	3	7.9 [0.0:18.4]
Manoeuvre	Study done, no bubbles seen	10	1.5 [0.5:2.7]	270	76.9 [72.9:81.4]	114	72.2 [65.8:79.3]	26	78.8 [66.7:91.5]
	Individual bubbles†	8	1.2 [0.2:2.4]	53	15.1 [11.1:19.6]	23	14.6 [8.2:21.7]	1	3.0 [0.0:15.7]
	Clusters/clouds/chamber opacification‡	633	97.2 [96.2:98.4]	28	8.0 [4.0:12.5]	20	12.7 [6.3:19.8]	6	18.2 [6.1:30.8]

†<5 per still frame
‡≥ 5 per still frame

Appendix 9 – Cost of a PFO closure procedure

Table A.9.1 identified all the inputs and sources used to calculate the central cost. Table A.9.2 provides information on the sensitivity analyses conducted to provide high and low cost ranges.

Table A.9.1 Cost of pathway for a PFO closure procedure

Parameter	Usage	Unit cost	% patients	Total cost	Source
Pre-operative assessment costs					
Consultant cardiologist	50 mins	£104.00 per hr	100%	£86.67	1 MDT of 2 cardiologists and 1 nurse for 15 mins per patient + pre-assessment clinic taking 20 mins cardiologist and 60 mins nurse time. Costs from PSSRU [38].
Nurse band 6	75 mins	£44.00 per hr	100%	£55.00	
Echocardiogram with contrast	1	£87.83	100%	£87.83	Imaging use from clinical experts; costs from NHS Reference costs [39].
ECG	1	£40.35	100%	£40.35	
Blood gases	1	£6.42 - £9.84	100%	£8.13	Tests from clinical experts; costs from 'Preoperative tests' by National Clinical Guideline Centre [40].
Haemostasis of prothrombin time	1	£29.42	6%	£1.82	Tests from clinical experts; warfarin use from database and costs from 'Preoperative tests' by National Clinical Guideline Centre [40].
FBC	1	£3.00	100%	£3.00	Tests from clinical experts; costs from NHS Reference costs [39].
U&E	1	£3.00	100%	£3.00	
Sub-total pre-operative assessment £286					All costs include overheads.
Peri-operative costs:					
Cardiologist	[redacted]				Operators from database, cost PSSRU [38].
Registrar					
Anaesthetist					Staffing structure from clinical experts; cost PSSRU [38].
Cath lab assistant band 3					
Echocardiographer					
Nurse					
Cardiac physiologist					
Radiographer					
Procedural time in theatre	49.7 mins.				Time from database; cost from Information Services Division (ISD) cost of theatres excluding staff and consumables costs[41].
ToE or	73.0%,				Use from database; costed as EY502

Parameter	Usage	Unit cost	% patients	Total cost	Source
ICE or TTE/other	23.5% and 0.1%. None 3.4%				complex echocardiogram for an elective inpatient from NHS Reference costs [38].
Anaesthetic Drugs - Desflurane & Remifentanil	1	[redacted]	[redacted]	[redacted]	Drugs agreed with clinical experts; price from a submitted template.
Local anesthesia - Lidocaine local max 200 mg	1	[redacted]	[redacted]	[redacted]	Drugs agreed with clinical experts; price from BNF [42].
Local anesthesia + sedation midazolam and fentanyl	1	[redacted]	[redacted]	[redacted]	Drugs agreed with clinical experts; prices from BNF [42].
Heparin 2 hrs per surgery and 8/12 hrs after.	1	[redacted]	[redacted]	[redacted]	Drugs from clinical experts; costs from BNF [42].
Cefuroxime X 2 1.5 g, 8 hours apart	1	[redacted]	[redacted]	[redacted]	
Consumables	1	[redacted]	[redacted]	[redacted]	[redacted]
Devices opened per patient	1.04	[redacted]	[redacted]	[redacted]	Number and mix of devices from dataset; cost of device from NHS Supply Chain and includes VAT.
Sub-total peri-operative costs [redacted]					All costs include overheads.
Post-operative management					
Inpatient stay	0.7 days	[redacted]	[redacted]	[redacted]	Stay mean value from dataset; costed using mean cost for codes EY23A to C for Standard Other Percutaneous Transluminal Repair of Acquired Defect of Heart. Reference costs [39]
Transthoracic Echocardiogram	1	[redacted]	[redacted]	[redacted]	Use from database; costed as EY502 complex echocardiogram for an inpatient from NHS Reference costs [39].
Out-patient follow-	1	[redacted]	[redacted]	[redacted]	Use from clinical experts; cost Cardiac Surgery consultant-led outpatients. Reference costs [39].

Parameter	Usage	Unit cost	% patients	Total cost	Source
up					
Sub-total post-operative management [redacted]					All costs include overheads.
GRAND TOTAL [redacted]					

Table A.9.2 Low and high cost scearios for pathway for a PFO closure procedure

Scenarios	Changes from central case	New cost
Pre-operative assessment central cost £286		
Low cost	Use 20% decrease in costs.	£229
High cost	Use 20% increase in other costs.	£343
Peri-operative costs central cost [redacted]		
Low cost	Use first quartile reported for procedure time and 20% decrease in all other costs except device.	£[redacted]
High cost	Use third quartile reported for procedure time and 20% increase in all other costs except device.	£[redacted]
Post-operative management central cost [redacted]		
Low cost	Use length of stay time of 0.5 days and tariff cost for Complex Echocardiogram for Congenital Heart Disease elective patient.	[redacted]
High cost	Use 2 days length of stay and third quartile reported for procedure time and 20% increase in all other costs.	[redacted]
Total cost central case and % accounted for by device:		**£8,303** [redacted]
Total case low cost and % accounted for by device		**£6,946** [redacted]
Total cost high cost and % accounted for by device		**£9,254** [redacted]

Thus the forecast cost for a PFO closure procedure ranges from about £6,950 to £9,250, with the central case being around £8,300. The device cost (£[redacted] per device) accounting for about [redacted] of the total cost.

Addendum

Background

After the initial draft of this report, the EAC and clinical leads became aware that there may be errors in the reporting of the primary outcomes concerning neurological events, ischaemic events, and composite outcomes involving these events. This was partly because of the design of the input fields in the registry, which were ambiguous with the potential for double counting of outcome events, because there were separate fields for the occurrence of a neurological event (with descriptors) and a separate field for type of neurological event, such that:

- Neurological event occurred with the following options: None; Yes, ischaemic; Yes, haemorrhagic; Yes, undetermined; unknown.
- Type of neurological event with the following options: None or not applicable; CVA/RIND; TIA; other; unknown.

It was observed that there were instances where there was logical inconsistency between the data entered in these fields. In addition, there was conflation between the terms CVA (cerebrovascular accident) and RIND (reversible ischaemic neurological deficit (RIND) which were presented as a single option despite meaning quite different things.

To fix this issue, the EAC contacted each provider centre via NICOR to ask for clarification on the outcomes in each patient in whom a neurological event had been reported and there were potential problems with reporting consistency. To date (25th October 2017) there has been an adequate response concerning 23 of the 24 affected patients. Following responses from the provider centres, two clinical leads (RH and MdeB) discussed the narrative each case individually and came to concordance on what the neurological outcome(s) were. This process was fully documented by a clinical scientist (HC) with and records have been kept (available on file). Revised data from this process informed an interim manual analysis, which are the basis of the results in this addendum.

The revised and validated results of the neurological event rate were materially different to those that have been reported in the body of this document. However, as this report has already undergone the consultation process, it was decided that subsequent changes should be made in the form of addendum, ready for incorporation later in the review process. This addendum briefly summarises the changes in results and its implications on the CtE questions and for the report's conclusions.

Revised results

Neurological events included events with permanent (stroke) or transient sequelae (TIA or RIND) of ischaemic or haemorrhagic aetiology. The data reported could discriminate by aetiology, but not by permanence. The revised data reported that 16 patients had a neurological event, of which 15 had a recorded date of event (2 in hospital and 13 following discharge) allowing for time to event analysis. This equated to an overall event rate of 1.7% (95% CI 1.0 to 2.8%). In total, there were 21 events reported, indicating multiple events in some patients. Thus there was a relatively modest reduction in the number of patients experiencing an event (from 24 to 16), and a larger reduction in the overall amount of events reported (from 38 to 21). The crude relative risk in first neurological events in patients between the datasets was 77%. Two patients experienced their first event in-hospital, with

the remaining thirteen first events occurring following discharge. Kaplan-Meier survival analysis (illustrated in Figure A1) indicated that the neurological event rate per 100 PY was 2.2 (95% CI 1.2 to 3.6). The 1 year probability of being event free (i.e. not having a neurological event) was 97.9% (95% CI 96.5 to 99.3%).

Overall, three people died during the study (1 in-hospital and 2 following discharge). *Note that this event rate is unchanged from the original report*. When this data was combined with the neurological event rate, the composite value using Kaplan-Meier analysis was 2.6 events per 100 PY (95% CI 1.5 to 4.1%). One year survival from death or neurological event was 97.7% (95% CI 96.3 to 99.2%).

The revised data reported that nine patients had an ischaemic event, one of which was in-hospital with eight occurring following discharge. Using Kaplan-Meier survival analysis (Figure A2), this equated to an adjusted rate of 1.3 events per 100 PY (95% CI 0.6 to 2.5). Event free survival at 1 year was 98.5% (95% 97.2 to 99.7%).

The original data for outcomes (time to event analysis) is reported in Appendix 5. This is compared with the revised data for neurological events in Table A1.

Table A1. *Number of all neurological events in original dataset compared with revised dataset.*

Event type*	**Original data**		**Revised data**	
	No. of patients with event	**Event rate per 100 PY**	**No. of patients with event**	**Event rate per 100 PY**
Neurological event	23† (2.5%)	3.4 (95% CI 2.1 to 5.0)	15† (1.7%)	2.2 (95% CI 1.2 to 3.6)
* Number of deaths and number of ischaemic events unchanged from original data. † One patient not included in time to event analysis due to missing time to event.				

Implications for NHS England question one

As discussed, the neurological event rate was lower in the revised data set, whilst death rates and rates of ischaemic strokes were unchanged. The revised data is reported in Table A2 (based on Table 9 of the original report).

Table A2. Revised incidence of neurological events in CtE registry and control arms of published RCTs.

Study	**Rate of neurological event (events per 100 PY)**	**Additional information**
NHS England CtE registry	All neurological events: **2.2 (95% CI 1.2 to 3.6)** Neurological event or death: **2.6 (95% CI 1.5 to 4.1%)** Ischaemic event only: 1.3 (95% CI 0.6 to 2.5)	**2 patients with events in hospital and 14 patients with events after discharge. 21 events in total, of which 1 was haemorrhagic and no fatal strokes reported.**
CLOSURE-1 trial [10]	Stroke: 1.55 TIA: 2.05 Primary composite endpoint*: 3.4	ITT analysis (control group) 2 years follow up
RESPECT trial [11]	1.38**	ITT analysis (control group) Median 2.1 years follow up
RESPECT trial (2017 update)	Ischaemic stroke: 1.07	ITT analysis (control group)

Study	Rate of neurological event (events per 100 PY)	Additional information
[22]†		Median 5.9 years follow up
PC trial [12]	Stroke: 0.6 TIA: 0.83 Primary endpoint***: 1.3	ITT analysis (control group) Mean 4.0 years follow up
CLOSE trial [20]†‡	Stroke: 1.12	ITT analysis (control group) Median 5.3 years follow up
GORE REDUCE trial [21]†‡	Clinical stroke: 1.68	ITT analysis (control group) Median 3.2 years follow up

Bold text reports values that have changed following repeat analysis of data (new dataset).

* 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.
** Primary endpoint was a composite of recurrent nonfatal ischemic stroke, fatal ischemic stroke, or early death after randomization. However, all primary events were non-fatal ischaemic strokes.
*** Composite outcome of death, stroke, TIA, or peripheral embolism. No deaths in control arm.
† Trials identified in Section 3.3. These have not been appraised.
‡ Event rate per 100 PY estimated by EAC from raw data counts and mean or median follow up as reported in study

Comparison with the published evidence show that although results from the CtE registry have improved, they are still broadly similar to outcomes seen from the control arms of RCTs. However, all the caveats previously discussed still apply; that is, a direct comparison cannot be made (see Section 4.3.1).

Implications for Question two

The revised version of Table 10, incorporating updated neurological outcome data, is reported in Table A3.

Table A3. Revised comparison of neurological events with primary efficacy outcomes reported in the published literature.

Study		Proportion patients with primary efficacy outcome. Events per 100 PY unless otherwise stated.	Definition/comment
CtE registry		All neurological events: **2.2 (95% CI 1.2 to 3.6)** Neurological event or death: **2.6 (95% CI 1.5 to 4.1%)** Ischaemic event only: 1.3 (95% CI 0.6 to 2.5)	**16 patients, with a recorded procedure date, reported as having a neurological event.**
RCTs	CLOSURE-1 (2012) [10]	2.8*	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.
	RESPECT (2013) [11, 22]	0.66 0.58 (extended follow up)	Primary endpoint was a composite of recurrent nonfatal ischemic stroke, fatal ischemic stroke, or early death after randomization. However, all primary events were non-fatal ischaemic strokes ITT analysis data reported.
	PC trial (2013) [12]	0.83**	Composite outcome of death, stroke, TIA, or peripheral embolism. Two deaths in control

Study		Proportion patients with primary efficacy outcome. Events per 100 PY unless otherwise stated.	Definition/comment
			arm.
	Device trial (2013) [17]	0.76*	The primary outcome was a composite of peripheral embolism, TIA, stroke, cerebral death.
	CLOSE trial [20]*†	0.0	No patients experienced stroke over 5.3 years follow up
	GORE REDUCE [21] †	0.43*	Clinical ischaemic stroke rate over 3.2 years follow up.
Observational studies	Taggart (2017) [25]	0.97	Annualised rate of patients suffering stroke or TIA.
	Pezzini (2016) [26]	2.73*	Ischaemic stroke, TIA, or peripheral embolism.
	Inglessis (2013) [27]	0.79**	Recurrent ischaemic cerebrovascular event.
	Wallenborn (2013) [28]	1.0	Recurrent stroke, TIA, or peripheral embolism.
	Thomson (2014) [29]	N/A	Long-term efficacy not reported in study.
	Mirzaali (2015) [30]	1.53	Combined stroke and TIA.

Bold text reports values that have changed following repeat analysis of data (new dataset).

* Event rate per 100 PY estimated by EAC from raw data counts and mean or median follow up as reported in study.
** Event rate per 100 PY estimated by EAC from raw data counts and person years follow up reported in study.
† Trials identified in Section 3.3. These have not been appraised.

As can be seen, despite the reduction in neurological event rate, the point estimate for this value seen in the registry is higher than those reported in the most trials, with the exception of the CLOSURE-1 trial [10], which reported similar results. The revised data is also similar to the observational by Pezzini *et al.* (2016) [24] which reported a similar composite outcome. However, arguably the most relevant outcome is the rate of ischaemic events, because this is the outcome that PFOC is designed to prevent. As the rate of ischaemic events was unchanged, then so are conclusions with respect to this outcome. Once again, all the caveats previously discussed still apply (see Section 4.3.1).

Conclusion

The revised dataset reported moderately fewer neurological first events and substantially fewer repeat events compared with the original dataset. However, the crude and adjusted rate of ischaemic events was unchanged and this is arguably the most important primary efficacy outcome relating to PFOC. There are limitations in the data, most notably that the clinical sequelae and permanence of neurological events remain poorly described, and this is of vital importance when comparing the outcome data to that in the published literature. Overall the EAC considers that the revised data does not significantly alter the conclusions that can be inferred from comparisons with published data. Such comparisons are limited due to differences in definitions used, methodology, and issues with generalisability, particularly concerning populations.

Figure A1. Time to event (solid lines), corresponding 95% confidence limits (dashed lines), and proportions of patients neurological event-free at 1 year (red dashed line).

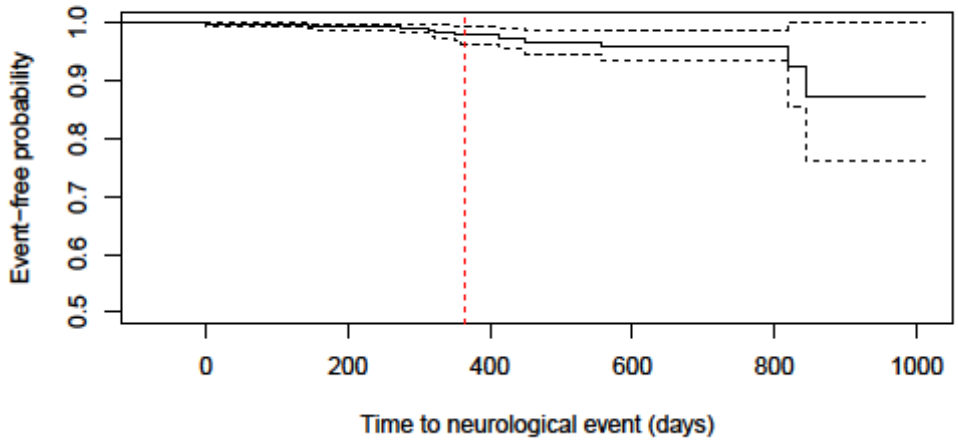


Figure A2. Time to event (solid lines), corresponding 95% confidence limits (dashed lines), and proportions of patients ischaemic event-free at 1 year (red dashed line).