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NICE OBSERVATIONAL DATA UNIT (ODU)

Commissioning Through Evaluation (CtE) Percutaneous Occlusion of the Left Atrial Appendage in Non-Valvular Atrial Fibrillation for the Prevention of Thromboembolism (LAAO) FINAL LINKED DATA REPORT

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Executive Summary

Non-valvular atrial fibrillation (AF), the most common cause of abnormal heart rhythm, causes a five-fold increased risk of thromboembolic stroke. Oral anticoagulation drugs, such as warfarin and direct-acting oral anticoagulants (DOACs) substantially reduce this risk. However, a proportion of people with AF cannot take these drugs due to absolute and relative contraindications, and treatment options for these people are limited. Left atrial appendage occlusion (LAAO) is a non-pharmacological option for reducing the risk of stroke in patients with AF. It is a percutaneous surgical intervention that aims to reduce the risk of thromboembolic stroke by mechanically blocking the entrance to the appendage of the left atrium, which is known to be a frequent source of thromboembolism in patients with AF.

Although the safety and efficacy of LAAO has previously been investigated, real-world data generalisable to the NHS are limited. In order to evaluate the procedure, NHS England set up a multi-centre observational registry using the process of Commissioning through Evaluation (CtE). The registry was designed to include patients with AF with absolute and relative contraindications to anticoagulation and considered to be at high risk of thromboembolic events. The registry recorded a range of clinical outcomes with a maximum follow-up of 2 years. The registry was linked to two routine administrative datasets: Hospital Episode Statistics (HES) Admitted Patient Care (APC), for measurement of hospital admissions and neurological events, and the Office of National Statistics (ONS) mortality dataset, for identification of deaths. Additionally, as the registry was single-armed (i.e. without a comparator group), a parallel literature search was undertaken in order to present the registry findings in the context of published studies in other populations and settings, and to assess whether procedural outcomes were consistent with previously reported studies. Finally, information on procedural costs was collected and used to inform a *de novo* economic model. The aims of the CtE registry were to provide data on the safety, efficacy and costs of LAAO in a real-world setting, and specifically to answer 11 pragmatic questions concerning these issues. Information gained from the registry will be used to inform future commissioning decisions.

From the CtE registry data, a total of 525 patients were eligible for analysis (median CHA_2DS_2-VASc of 4), with 2 year follow-up data available on 70.2% (85/121) of patients reaching 2 years since their LAAO device was implanted. Around 18% of patients were receiving oral anticoagulation immediately before the procedure, but this dropped to around 3% after 2 years of follow-up. The registry reported a technical success rate of 93.6% (95% CI 91.1% to 95.6%) and a procedural success rate of 89.0% (95% CI 86.0% to 91.6%). There was an in-hospital major complication rate of 5.5% (95% CI 3.7 to 7.8%). The rate of procedural mortality was low (1%), with a reported procedural neurological event rate of 0.8% (95% CI 0.2 to 1.9%). These short-term results were consistent with values from randomised controlled trials (RCTs) and observational studies reported in the literature.

Using the linked dataset, the primary composite outcome (death or neurological event) had an annualised incidence rate of 9.9 (95% CI 7.9 to 12.3) per 100 person years (PY) across a total aggregated follow-up period of 817 person-years (with 50 deaths and 45 neurological events reported). A total of 30 ischaemic events were reported across the three datasets (i.e. CtE registry, HES APC, ONS) giving a rate of 3.5 (95% CI 2.3 to 4.9) per 100 PY. Nine

deaths were attributed to neurological events: 6 haemorrhagic, 2 ischaemic and 1 neurological event of unspecified type. Using time to event (Kaplan-Meier) analysis, the composite outcome of freedom from death or neurological event at 1 year was 0.92 (95% CI 0.89 to 0.95, n=387) and 0.83 (95% CI 0.79 to 0.87, n=196) at 2 years. Freedom from neurological events was 0.95 (95% CI 0.93 to 0.97) after 1 year and 0.90 (95% CI 0.87 to 0.93) after 2 years; for mortality the corresponding rates were 0.95 (95% CI 0.93 to 0.97) and 0.90 (95% CI 0.87 to 0.93) for 1 and 2 years respectively. At least 38 of the 45 neurological events have been either independently validated or conflicting information between the registry and HES data sources have been satisfactorily explained.

Direct statistical comparisons with published studies were not possible. Although the mortality, neurological and ischaemic event rates appeared to be higher in the CtE registry than reported in the only published RCTs to date, the PROTECT-AF and PREVAIL trials, results from these studies were not considered generalisable to the CtE registry for two important reasons. Firstly, because patients in the CtE registry had a greater number of comorbidities (including history of stroke) and were at greater risk of ischaemic stroke than those in the published clinical trials; and secondly, because most patients were not receiving warfarin or DOACs, and therefore were unable to benefit from discontinuation of anticoagulation. The incidence of thromboembolic events were numerically lower compared with historic data from epidemiological studies ($CHADS_2$ and CHA_2DS_2-VASc scores), consistent with LAAO being associated with a protective effect.

The estimated cost per LAAO procedure, using data collected directly from participating centres, was £11,800 (range of £9,600 to £13,600) at 2017/18 prices. A cost consequences analysis using a *de novo* economic model was undertaken to compare LAAO plus medical therapy with medical therapy only. Patients entered the Markov model aged 75 years, consistent with the registry, and flowed through the model for 15 years, to aged 90 years. Patients could be in a stroke free state, experience a neurological event (ischaemic or haemorrhagic stroke or transient ischaemic attack) or die. Other events modelled were subsequent stroke or transient ischaemic attack and bleeds. In the LAAO arm, patients had a risk of strokes and bleeds at the rates observed at up to 2 years in the linked dataset. Patients in the comparator arm received medical therapy only and were estimated to have stroke and bleeding risks in accordance with their baseline CHA_2DS_2-VASc and HAS-BLED risk scores. The main cost drivers were the procedure costs for the LAAO pathway, (£11,800 central estimate) and the costs of managing strokes in the NHS and social care.

The results reported estimated NHS costs per patient of £15,491 for LAAO and £8,694 for medical therapy over a 15-year period. The benefit to the NHS from avoided stroke management and medication costs of almost £5,034 per patient with LAAO were insufficient to offset the initial procedure costs of about £11,800 per patient. Hence LAAO was cost incurring for the NHS by about £6,800 per person. However, adopting a wider NHS and social care perspective increased the savings from avoided strokes, as the majority of costs to manage patients with stroke (60% of the total) are incurred in social care settings. Total NHS and social care costs per patient, over 15 years, were essentially the same between the LAAO pathway (£18,725) and medical therapy (£18,551), a difference of £174, less than 1%. The higher cost of the LAAO procedure (about £11,800 per patient) was associated with fewer strokes and reduced medication, saving about £11,660 per patient for the NHS and

social care services. The procedure is thus cost neutral, with the cost of the procedure offset by savings later in the clinical and social care pathway.

The analysis reported clear patient benefits. For a cohort of 1,000 patients, the total number of strokes was forecast to reduce by 65% from over 500 to around 180 over 15 years following the LAAO procedure. This was associated with almost 100 fewer deaths.

With cost consequences analysis, decision makers do not have a threshold-based decision rule to inform their decisions to commission interventions. Rather they look at the incremental costs and incremental benefits and decide if the extra costs are justified by the additional benefits. For the LAAO procedure, if decision makers adopt an NHS perspective, they must judge whether the additional costs to the NHS of about £6,800 per patient are justified, given the forecast savings in strokes and deaths.

In contrast, if decision makers adopt a wider NHS and social care perspective, then the potential savings from reduced social care costs are relevant to inform their decision. Under this perspective, the NHS and social care costs are broadly equivalent over 15 years between undertaking an LAAO procedure or providing medical therapy only. The procedure reduces the number of strokes and deaths, thereby saving costs for the NHS and social services later in the pathway. These savings offset the cost of the procedure, giving cost neutrality in the two arms. However, the LAAO procedure is associated with material patient benefits from avoided strokes and associated reduced mortality. Hence decision makers under this perspective would commission the LAAO procedure as it does not increase costs but does give benefit to patients by reducing the number of strokes and deaths.

In conclusion, the CtE registry has produced evidence that the LAAO procedure is procedurally successful in about 9 out of 10 patients and is associated with a decreased risk of ischaemic events compared with historical epidemiological data in patients with a similar baseline risk. Although clinical outcomes from the CtE cohort appeared worse than published trial data, comparisons were confounded by differences in patient selection, the interventional procedure, and the use of differing drug regimens. Thus further experimental research is required to understand the efficacy of LAAO in this population (with a contraindication to oral anticoagulation or evidence of a thromboembolic event in spite of adequate oral anticoagulant therapy). This may be forthcoming with the publication of the on-going ASAP-TOO trial, although this is not due to complete until 2023. Regarding costs, LAAO was found to be cost incurring from a strictly NHS perspective, but cost neutral when social care was taken into account. As the procedure was associated with material patient benefits, it is probable that LAAO is cost effective from a societal perspective.

Abbreviations

ACP	AMPLATZER Cardiac Plug
A + C	Aspirin and clopidogrel
AF	Atrial fibrillation
APC	Admitted patient care
ASD	Atrial septal defect
BIA	Budget impact analysis
BMI	Body mass index
BP	Blood pressure
CCF	Congestive cardiac failure
CG	Clinical guideline
CHA_2DS_2-VASc	Risk calculator for stroke in people with AF, supersedes $CHADS_2$. Risk factor inputs are congestive heart failure, hypertension, age (2), diabetes, previous stroke or TIA (2), vascular disease.
$CHADS_2$	Risk calculator for stroke in people with AF. Risk factor inputs are congestive heart failure, hypertension, age, diabetes, previous stroke or TIA (2).
CI	Confidence interval
CrI	Credibility interval
CtE	Commissioning through Evaluation
CVA	Cerebrovascular accident
DM	Diabetes Mellitus
DOAC	Direct-acting oral anticoagulant
EAC	External Assessment Centre
EACTS	European Association for Cardio-Thoracic Surgery
eGFR	Estimated glomerular filtration rate
EQ-5D-5L	EuroQol 5 dimensions 5 levels
EHRA	European Heart Rhythm Association (have developed a symptom score for AF)
ESC	European Society of Cardiology
EQ-5D	EuroQol 5 dimensions
EVPI	Expected value of perfect information
FU	Follow-up
HAS-BLED	Risk calculator for major bleed for patients with AF on anticoagulation. Risk factor inputs are hypertension, renal disease, liver disease, stroke history, labile INR, age, medication, alcohol or drug use.
HES	Hospital episode statistics
HR	Hazard ratio
ICD-10	International Statistical Classification of Diseases and Related Health Problems - 10th revision
ICER	Incremental cost-effectiveness ratio
INR	International Normalized Ratio
IPG	Interventional procedures guidance
IQR	Inter-quartile range

ITT	Intention to treat
LAA	Left atrial appendage
LAAO	Left atrial appendage occlusion
LVEF	Left ventricular ejection fraction
MDS	Minimum data standard
MDT	Multi-disciplinary team
MeSH	Medical subject headings
MI	Myocardial infarction
MSS	Medium to severe stroke
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NICOR	National Institute for Cardiovascular Outcomes Research
NYHA	New York Heart Association (classification system for severity of dyspnoea)
OAC	Oral anticoagulants
ONS	Office for National Statistics
OPCS-4	Office of Population Censuses and Surveys Classification of Surgical Operations and Procedures – 4th revision
OR	Odds ratio
PFO	Patent foramen ovale
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PSSRU	Personal Social Services Research Unit
PY	Person-years
QoL	Quality of life
QALY	Quality adjusted life year
RCT	Randomised controlled trial
RIND	Reversible ischaemic neurological deficit
SD	Standard deviation
SE	Systemic embolism
TIA	Transient ischaemic attack
TOE	Transoesophageal echocardiography
WTP	Willingness to pay

Section 1: Introduction

1.1 NHS ENGLAND COMMISSIONING THROUGH EVALUATION – LEFT ATRIAL APPENDAGE OCCLUSION (LAAO)

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 online registry for LAAO 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 LAAO Individual Technology Group in the design of the LAAO 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 registry data fields in each dataset and advise on their suitability for updating and developing NICE guidance;
- Advise on the appropriateness of registry 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 LAAO 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 LAAO were originally presented to NICE, discussed with NY EAC, and edited to the final form presented in the Table 1.

Table 1: Left Atrial Appendage Occlusion (LAAO) in Patients with Atrial Fibrillation.

Questions from NHS England	Final version of question, as amended NICE following discussion with EAC
1. Can UK clinical teams reproduce the success rates for left atrial appendage occlusion reported in existing clinical trials, with equivalent or lower complication rates?	Can UK clinical teams reproduce the short and medium success rates for left atrial appendage occlusion reported in existing clinical trials, with equivalent or lower complication rates?
2. Does left atrial appendage occlusion offer these patients a lower risk of stroke or other embolic clinical events compared to those that would have been predicted on the basis of validated risk scores?	Does left atrial appendage occlusion offer patients a lower risk of stroke or other embolic clinical events in the short and medium term compared with those that would have been predicted on the basis of validated risk scores?
3. Is left atrial appendage occlusion associated with an improved quality of life for these patients?	Is left atrial appendage occlusion associated with an improved 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)?	N/A unless an extended time period for the project is agreed.
5. How many patients with atrial fibrillation with a contra-indication to oral anticoagulants, or who have had a stroke whilst on oral anticoagulants, or who have had a significant bleed whilst taking oral anticoagulants are candidates for left atrial appendage occlusion? i.e. if LAAO for patients with AF who cannot take anticoagulants becomes routinely commissioned, what is the likely clinical need?	How many patients with atrial fibrillation with a contra-indication to oral anticoagulants (including previous significant bleed), or who have had a thromboembolic event despite being on oral anticoagulants, are candidates for left atrial appendage occlusion?
6. Do the commercially available current devices perform equivalently?	Which devices are used to undertake LAAO and what are the device-specific efficacy and safety outcomes in CtE funded patients undergoing the procedure?

Questions from NHS England	Final version of question, as amended NICE following discussion with EAC
7. Is the frequency of complications sufficiently low to provide a positive risk-benefit ratio?	Is the frequency of complications seen with the intervention clinically acceptable? (This question has already been considered by the NICE Interventional Procedures Advisory Committee when developing the IP guidance on this procedure. 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).
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 clinical outcomes from left atrial appendage occlusion associated with particular patient characteristics (clinical or demographic)?
9. What is the true procedural cost of left atrial appendage occlusion in the NHS?	What are the full procedural costs of left atrial appendage occlusion to the NHS?
10. What costs savings might occur in the NHS as a result of left atrial appendage occlusion?	What are the potential cost savings for the NHS through provision of left atrial appendage occlusion for appropriate patients?
11. What is the cost-effectiveness of left atrial appendage occlusion based on UK procedural and follow-up costs?	Is left atrial appendage occlusion cost-effective from the perspective of the NHS?

1.2 DESCRIPTION OF THE PROCEDURE

The LAAO procedure is described in NICE IPG349:

> *"Percutaneous occlusion of the LAA is usually carried out with the patient under general anaesthesia. Using fluoroscopic guidance, a catheter is advanced through the femoral vein into the right atrium and then into the left atrium via a transseptal puncture. The location of the LAA is confirmed and the size of the LAA orifice is established by transoesophageal echocardiography (TOE). An appropriately sized device is selected and deployed in the mouth of the LAA where it is expanded to fit the space.*
>
> *The position and patency of the occlusion device may be confirmed postoperatively using echocardiographic imaging."*

There are currently three CE marked devices that are eligible for the CtE programme, available and used in the UK:

- The ‘WATCHMAN’ device marketed by Boston Scientific;
- The ‘AMPLATZER Cardiac Plug (ACP)’ and ‘AMPLATZER Amulet’ marketed by St. Jude Medical (now owned by Abbott).

Percutaneous LAAO received a positive recommendation with normal arrangements from NICE (IPG349). The guidance recommended that the procedure should be undertaken under the direction of a multi-disciplinary team experienced in the management of patients with atrial fibrillation (AF) at risk of stroke. NICE IPG349 does not clearly define which patients should be eligible for LAAO, but states selection should be performed by a multi-disciplinary team and ‘Patients should be considered for alternative treatments to reduce the risk of thromboembolism associated with AF, and should be informed about these alternatives’.

Section 2: Methods

2.1 CTE LAAO PROVIDERS AND PROGRAMME GOVERNANCE

Hospitals providing the CtE procedures in the 10 centres participating in the LAAO scheme are:

- Barts Health NHS Trust and The Heart Hospital, University College of London Hospital NHS Foundation Trust;
- Brighton & Sussex University Hospitals NHS Trust;
- Guy's and St Thomas' NHS Foundation Trust;
- Kings College Hospital NHS Foundation Trust;
- Leeds Teaching Hospitals NHS Trust;
- Liverpool Heart & Chest Hospital NHS Foundation Trust;
- Oxford University Hospitals NHS Trust;
- The Newcastle upon Tyne Hospital NHS Foundation Trust and South Tees Hospitals NHS Foundation Trust;
- University Hospitals Leicester NHS Trust;
- University Hospital of North Staffordshire NHS 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) 1453 for LAAO [4]. 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 LAAO is Professor Nicholas Linker, Consultant Cardiologist, South Tees Hospitals NHS Foundation Trust. Professor Linker is Chair of the NHS England LAAO Individual Technology Group. The role of the Group, set out in its Terms of Reference (ToR), is to:

- Work with the EAC and 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 LAAO COMMISSIONING DETAILS

NHS England commissioned a total of 300 LAAO procedures in each full financial year of the cardiac CtE scheme. Each of the 10 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 LAAO 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 450 procedures in total for the LAAO CtE programme.

2.3 PATIENT SELECTION CRITERIA

According to the NHS England Specialised Services Circular (SSC) 1453 for LAAO [4], patient selection criteria were:

- Patients with atrial fibrillation at high risk of thromboembolic stroke (CHA_2DS_2-VASc score of 2 or more) with a contraindication to oral anticoagulation (intolerance, previous significant bleed, high bleeding risk) or evidence of a thromboembolic event in spite of adequate oral anticoagulant therapy;
- Patients can be referred by cardiologists, stroke physicians or other specialists in secondary care to the multidisciplinary team in a specialist cardiac centre. Direct referrals to cardiac centres from primary care and general practice requesting consideration for LAAO will not be accepted;
- Appropriate left atrial appendage morphology and suitability for a trans-septal procedure;
- Patient fully informed and consent provided.

Therefore, in summary, the LAAO procedure was commissioned for those with a contraindication to anticoagulants (including the ‘new’ anticoagulants apixaban, dabigatran, edoxaban and rivaroxaban), or for those receiving adequate anticoagulants but still experiencing a thromboembolic event.

2.4 PRIMARY DATA COLLECTION (CTE REGISTRY)

2.4.1 Database Details and Information Governance Arrangements

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

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' (November 2014) [1]. This identified and appraised new evidence added to the literature base and public domain since the original NICE IP310/2 overview [5] was published and compared findings against the data fields contained in the draft LAAO CtE dataset.

The final LAAO dataset was developed into the online database by NICOR and the latest version may be downloaded as a Microsoft Excel® spreadsheet (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 (outwith 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 LAAO CtE baseline data completeness monitoring contained 30 key fields. Six additional fields were monitored for patient completion of EQ-5D questionnaires and EuroQol data entry (NICOR field identifiers 4.04 to 4.09). 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
1.07	Sex
1.10	Postcode
2.03	Reason for treatment
3.01	Prev MI
3.06	CCF
3.13	DM
3.14	Hypertension
3.15	History of CV or other neurological disease
3.20	Previous peripheral embolism
3.21	Alcohol consumption
3.23	Renal transplant
3.25	Significant liver disease
3.26	Previous bleed
4.03	Date EuroQol form filled
4.04	EuroQol Mobility
4.05	EuroQol Self-care
4.06	EuroQol Usual activities
4.07	EuroQol Pain / discomfort
4.08	EuroQol Anxiety / depression
4.09	EuroQol Health state today
5.01	Current medication
5.02	Concomitant NSAID use

NICOR Field identifier	Data Field
8.10	Aortic atheroma in arch
9.01	Date of admission
9.03	Date/time of procedure
9.12	Consultant responsible
9.32	Device used
9.37	Device deployed successfully
10.02	Device embolization
10.05	Surgical intervention
10.11	Stroke (in-house)
10.20	Life status
10.21	Discharge date
10.23	Successful procedure, no complications

The six follow-up MDS fields for LAAO data completeness monitoring at 6 weeks were:

11.01 Date of 1st FU
11.04 Device still in situ
11.11 Death
11.16 Neurological event
11.23 Oral anticoagulant discontinued
11.24 Date 6 week EuroQol form filled

The equivalent variables were also monitored for follow-up data at 6 months, 12 months and 24 months.

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).
- Initially, data completeness (%) was calculated for the subset of all LAAO 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 LAAO CtE registry conducted between 1st October 2014 to 10th August 2017 with recorded reasons for treatment including: previous bleeding without anticoagulant therapy, previous bleeding with anticoagulant therapy, embolic event in spite of oral anticoagulant, intolerant of oral anticoagulant, poor control of oral anticoagulation, or at risk of severe bleeding.

Exclusion criteria: Procedures 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: device implanted, in-hospital major complications, in-hospital minor complications, extended length of stay (2 or more nights in hospital), post-discharge clinical failure, post-discharge major complications and post-discharge minor complications.

Secondary outcome measures included: death, neurological event, pericardial effusion, embolization, additional intervention, major vascular complication, major bleeding complication, myocardial infarction (MI), acute kidney injury (AKI), endocarditis, device malfunction, device malposition, minor vascular complication, pericardial effusion (conservatively treated), procedural-related arrhythmia, minor bleeding complication, peripheral embolism and oesophageal damage.

b. Cost / resource

A bottom-up costing study of each stage in the pathway to insert LAAO devices was conducted. NY EAC firstly reviewed the draft Excel® costing template provided by the NHS England LAAO Individual Technology Group. Amendments were agreed with the Chair of the Group and the final template provided the 10 centres with detailed instructions on inputting the resources required to conduct each of the three 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 with existing clinical pathways. Where possible, outcomes reported in the LAAO 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 three 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 8, 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 LAAO is a preventative procedure rather than a therapeutic one, it is unclear whether any symptoms of the condition (atrial fibrillation) 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.

2.4.6 Statistical Analysis

All scripts for case ascertainment, cleaning, processing and statistical analysis were written in the statistical programming language R [6].

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 analysis were conducted for the defined outcome measures. Univariate analysis was conducted for each outcome measure and up to 27 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 analysis 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 multivariate analysis, if appropriate. Binary logistic regression analyses were checked for convergence and over-fitting, and either modified (e.g. by reducing the number of covariates) or reported as not valid.

Crude incidence rates for death, neurological events, combinations of death and/or neurological events, peripheral embolism and device malposition 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, first neurological event and the combination of death or first neurological event. Patients who suffered no events and were alive at the end of the study were considered censored.

Paired quality of life scores and utilities 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 PRIMARY DATA COLLECTION (DATA LINKAGE)

2.5.1 Linked Dataset Details

In order to check for extra safety and efficacy, clinical effectiveness or resource utilisation information, patient identifiers (i.e. NHS number, date of birth, gender, postcode, study number, a pseudonymised patient identifier) were extracted from the CtE registry by NICOR, as the data controller, on 5th April 2018 and sent to NHS Digital. CtE records were linked by NHS Digital to the Hospital Episode Statistics (HES) Admitted Patient Care (APC) dataset and the Office of National Statistics (ONS) mortality dataset, using an 8 step matching algorithm [7]. Data from HES included all admissions from matched patients with hospital discharge dates between 1st April 2008 and 1st March 2018. Data from ONS included all deaths from matched patients reported until 1st March 2018. Records from patients with type 2 opt-outs (i.e. those not wishing for their patient information to be used for purposes other than that of their individual care) were removed from both extracts by NHS Digital before releasing the linked data to NICOR. NICOR then removed patient identifiers, replacing with a "Study ID" and provided NY EAC with a pseudonymised linked dataset, as a data co-processor.

2.5.2 Linked Dataset Cleaning

Pseudonymised data from all three data sources (CtE registry, HES and ONS) were analysed by NY EAC. Records with conflicting demographic and administrative details between the data sources were flagged by the EAC to indicate potential error in matching (i.e. matching to incorrect patient). All flagged records were reported to the data controller, NICOR, within a technical issue log. Technical issues and specific examples of

inconsistencies within HES or between HES and ONS datasets were discussed directly with NHS Digital. The demographics were compared between cohorts with a potential mismatch ('red flag') and those which were consistently matched between data sources ('green flag'), in order to confirm that exclusion of potentially mismatched records would not introduce bias into the linked data results. These potentially mismatched patient records were then excluded from the linked data analysis.

2.5.3 Linked Dataset Outcomes

All eligible patients (section 2.4.3) were analysed.
In-hospital complications (major and minor combined) from the registry were defined as described in section 2.4.5a and *Supplementary Material – Table 2*. In-hospital complications from HES were identified from the ICD-10 codes captured in the 20 diagnosis fields using the method recommended by using NHS Clinical Classifications Service [8]. Clinical coding advice was sought from clinical coders within the Newcastle upon Tyne Hospitals NHS Foundation Trust, and Guy's and St Thomas' NHS Foundation Trust.

Total length of follow-up using the CtE registry was calculated from the date of the LAAO procedure and the date of last recorded follow-up (or discharge date in cases where the device was not successfully implanted). Total length of follow-up using the linked dataset was calculated from the date of the LAAO procedure until the date of extract (1st March 2018), or date of death, or date of discharge (in cases where the device was not successfully implanted).

Total all-cause mortality from the linked dataset combined all in-hospital deaths, and all deaths occurring post-LAAO procedure in those discharged from hospital with a device successfully implanted. Deaths due to neurological events were identified from free text entries in the registry and any ICD-10 diagnosis codes in the chapters I60 "Subarachnoid haemorrhage", I61 "Intracerebral haemorrhage", I62 "Other non-traumatic intracranial haemorrhage", I63 "Cerebral infarction" and I64 "Stroke, not specified as haemorrhage or infarction" appearing as the main cause of death reported in the ONS dataset. Deaths were classified as ischaemic using free text entries from registry, and ICD-10 codes from the I63 chapter.

In-hospital neurological events from the linked dataset were determined for all patients with an attempted LAAO procedure, and long-term neurological events determined for all patients discharged alive following successful LAAO implantation. Neurological events were identified in the registry from the "neurological event" and "type of neurological event" data fields captured during procedure, and within 6 week, 6 month, 1 year, 2 year and 3 year follow-up records. Neurological events were identified from HES and ONS by the following ICD-10 codes appearing in any of the 20 diagnosis fields in admissions up to 1st March 2018 (date of data linkage):
G45.8: Other transient cerebral ischaemic attacks and related syndromes
G45.9: Transient cerebral ischaemic attack, unspecified
I60: Subarachnoid haemorrhage
I61: Intracerebral haemorrhage
I62: Other non-traumatic intracranial haemorrhage
I63: Cerebral infarction

I64: Stroke, not specified as haemorrhage or infarction.
Neurological events across all data sources were then categorised as ischaemic (using ICD-10 codes G45.8, G45.9 or any from the I63 chapter), haemorrhagic (any from I60-I62 chapters) or unknown (any from I64 chapter). Clinical coding departments advised that *previous history* of stroke and TIA events should be attributed to different ICD-10 codes making them distinguishable from *new* events; Z86.7 “Personal history of diseases of the circulatory system - Conditions classifiable to I00-I99” which would include a previous history of stroke, and Z86.6 “Personal history of diseases of the nervous system and sense organs - Conditions classifiable to G00-G99, H00-H95” which would include a previous history of TIA. However it was advised that these history codes are also attributed to history of other diseases (not specific to strokes and TIA, *e.g.* Z86.7 may include history of abdominal aortic aneurysm without rupture I71.4, or even history of varicose veins I83.9).

Instances of vascular dementia (described in ICD-10 as “the result of infarction of the brain due to vascular disease, including hypertensive cerebrovascular disease. The infarcts are usually small but cumulative in their effect. Onset is usually in later life.”) were identified from the HES and ONS datasets only (as this was not a recorded data field in the CtE registry) via ICD-10 code F01, and were counted separately from neurological events.

All linked data outcomes were firstly determined for the registry and HES (and ONS where applicable) separately. The total event rates (for each outcome) were then determined using the union of all datasets. Inconsistencies were raised by NY EAC with the data controller, NICOR, within a technical issue log. Responses from CtE providers (to queries raised by NY EAC, via NICOR) were also logged within the technical issue log.

Kaplan-Meier analysis was conducted for total all-cause mortality, total neurological events and the composite outcome which included total neurological events or all-cause mortality. Patients were followed from date of procedure until date of first event, date of discharge (in cases where the device was not successfully implanted), or if no event, then date of extract of HES and ONS datasets (*i.e.* the 1st March 2018). In patients with multiple events (*i.e.* TIA followed by haemorrhagic event, or neurological event followed by death), the time to the earliest event following LAAO admission were used in subsequent Kaplan-Meier analysis.

2.6 SECONDARY DATA COLLECTION (LITERATURE REVIEW)

The aim of the final LAAO literature review for CtE was to identify key published studies in patients with non-valvular atrial fibrillation (AF) 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 (Willits *et al.*, LAAO literature review document [unpublished], November 2016) [9].

Firstly, a literature search was performed from March 2010, which was the search date of the original NICE IP310/2 overview that informed NICE IPG349. 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 IPG349.

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 the Table 3.

Table 3: Scope of literature review

Domain	Terms identified from title or abstract	Comment
Population	Patients with atrial fibrillation at high risk of thromboembolic stroke eligible for LAAO.	NHS England specifies LAAO indicated only in patients with contraindications to anticoagulation or anticoagulation not effective. However, this limit might exclude important studies and population needs to be expanded in order to answer NHS England questions.
Intervention	LAAO	All percutaneous endocardial devices to be included. Known devices recorded in the LAAO registry to 31/07/2016 are WATCHMAN (Boston Scientific), AMPLATZER Cardiac Plug / AMPLATZER Amulet (St. Jude Medical) and WaveCrest (Coherex)
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 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.

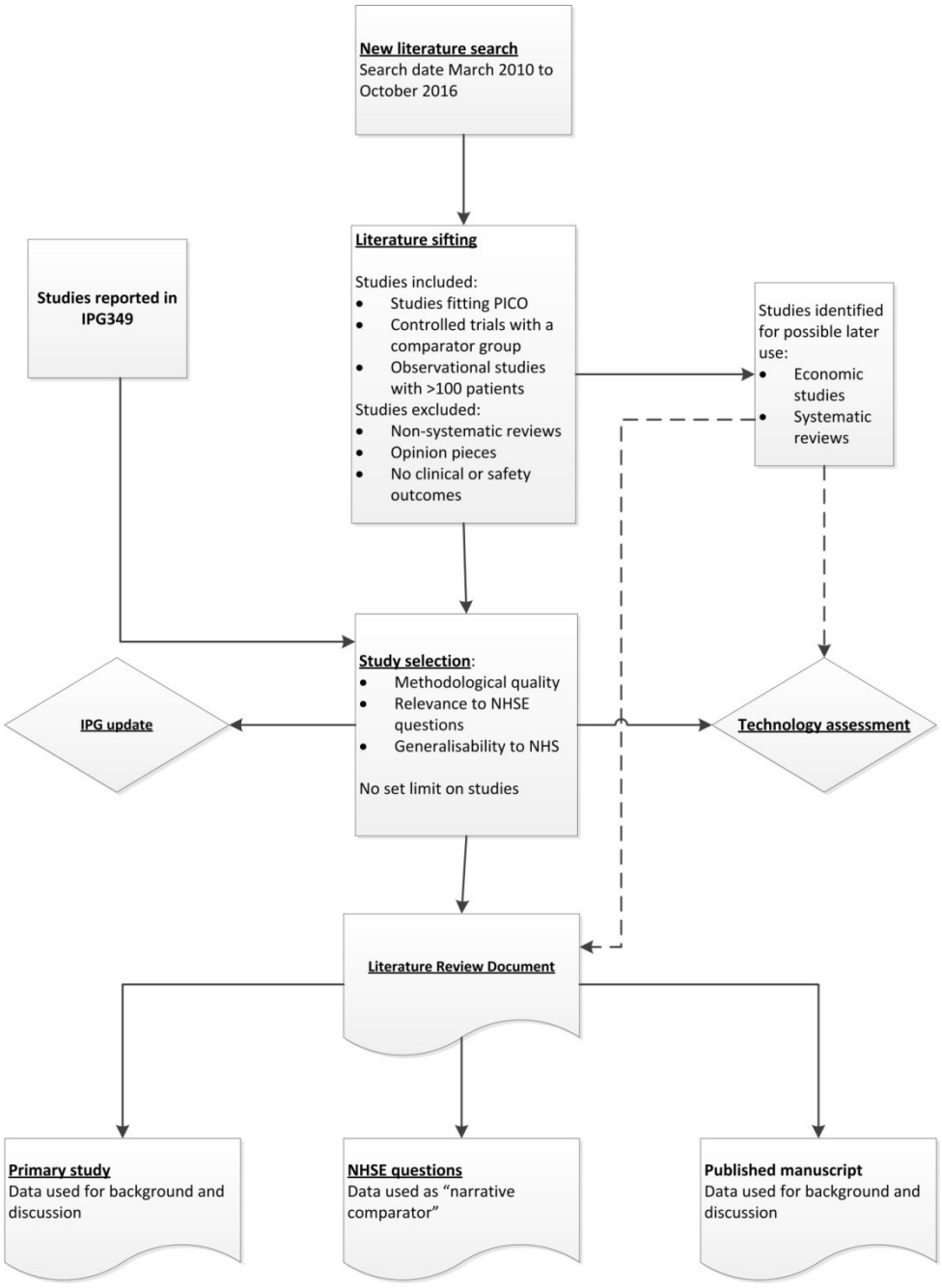
Table 4: Bibliographic databases searched

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 IPG349. 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 200 or more participants selected for full review, and observational studies with 100 or more participants flagged for *ad hoc* inclusion [9]. 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 LAAO.



A brief summary of the results of the literature review is presented in Section 3.3 of this final CtE report on LAAO, with full details available in the standalone literature review document [9].

2.7 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 to best practice [10, 11].

As discussed in Section 3.3, there remains some uncertainty regarding the efficacy and safety of LAAO in the management of patients with AF who have absolute and relative contraindications to warfarin and direct-acting oral anticoagulation drugs (DOACs). In particular, there is an issue concerning the generalisability of trial evidence to this population, and how effective and safe the procedure is in real-world practice. 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, supported by published studies in the literature. These questions have been revised and adjudicated by NICE (see Table 1).

The EAC performed a pragmatic literature review, which identified the key experimental and observational studies performed to date on LAAO. As the CtE register was non-comparative, data from the literature has been used as a proxy control for the register.

Table 5 summarises the *a priori* intended methods for answering each question [3]. 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 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 and linked data (CtE registry/HES/ONS).

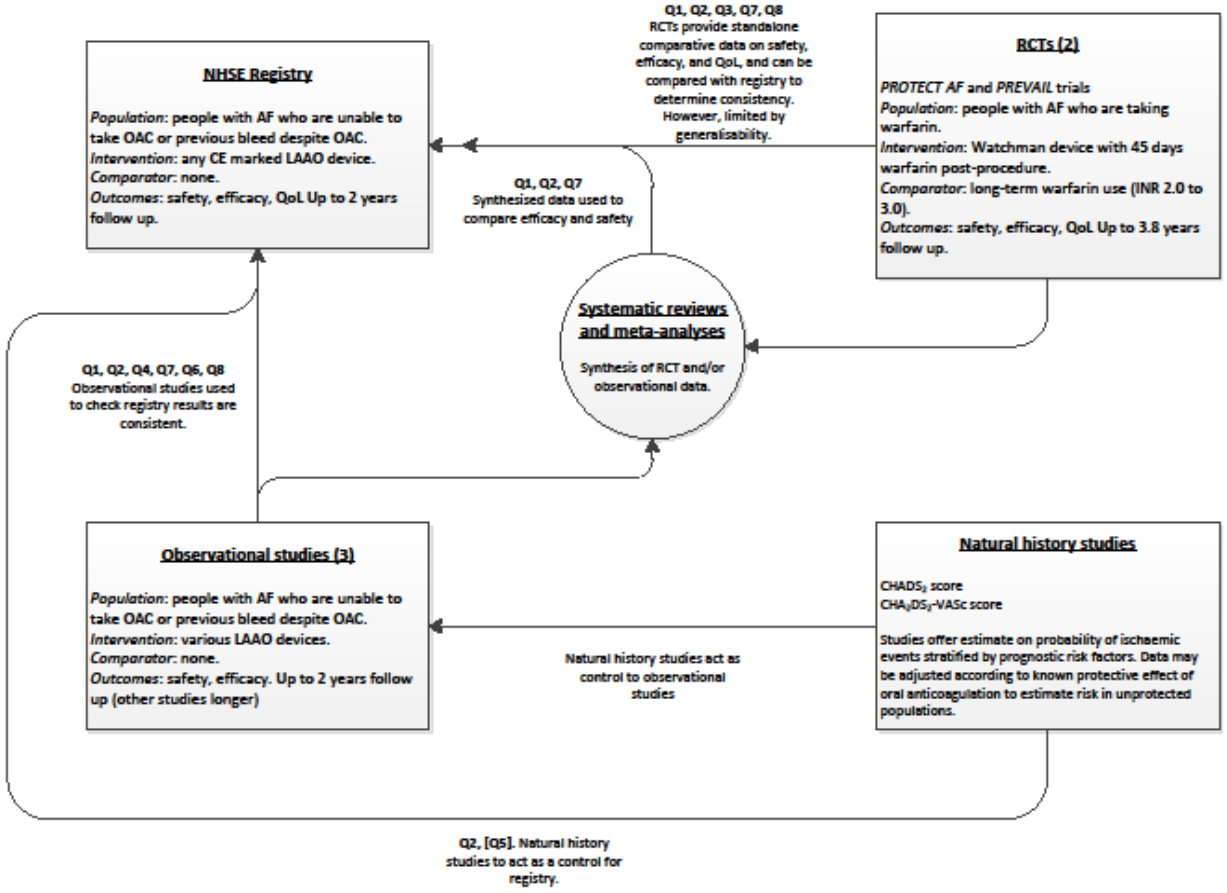
Question (NICE modified where applicable)	Can it be answered using registry data?	Key registry data required	Type of analysis – CtE registry data	Type of analysis - Linked data (CtE registry/HES/ONS)	Comment
1) Can UK clinical teams reproduce the short and medium success rates for left atrial appendage occlusion reported in existing clinical trials, with equivalent or lower complication rates?	Yes, fully.	Mortality rate. Successful device deployment. Successful occlusion of LAA (LAA sealed). Avoidance of neurological events. Device detachment/embolization. Additional surgery. Readmission. Significant bleed.	Pairwise ('before and after') analysis of registry data. Survival analysis. Comparison with published RCTs and observational studies.	Proportion of people having event with confidence intervals. Survival analysis.	Registry does not provide comparative data so this will be matched with published data. Depending on the goodness of fit, a narrative summary or statistical analysis may be possible. [Update: statistical comparison of registry and published data was not possible. Linked data considered more robust for medium-term success rates].
2) Does left atrial appendage occlusion offer patients a lower risk of stroke or other embolic clinical events in the short and medium term compared with those that would have been predicted on the basis of validated risk scores?	Yes, partly.	Cerebrovascular event. Type of cerebrovascular event. Modified Rankin score (90 days). Overt peripheral embolic event.	Proportion of people having event with confidence intervals. Comparison with expected rate using risk algorithms ($CHADS_2$, CHA_2DS_2VASc). Survival analysis (Kaplan-Meier).	Proportion of people having event with confidence intervals. Survival analysis (Kaplan-Meier).	Outcome events expected to be low, statistical significance unlikely to be reported. [Update: Linked data considered more robust for measurement of ischaemic events].
3) Is left atrial appendage	Yes, partly.	Procedural success.	Pairwise ('before	None (QoL not	Significant aggregate

Question (NICE modified where applicable)	Can it be answered using registry data?	Key registry data required	Type of analysis – CtE registry data	Type of analysis - Linked data (CtE registry/HES/ONS)	Comment
occlusion associated with an improved quality of life?		Quality of life (EQ-5D-5L).	and after') analysis of registry data. Correlation and regression analysis.	recorded in HES)	changes in quality of life unlikely. [Update: poor follow-up limited meaningful analysis].
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)?	No, probably not.	Device embolization. LAA sealed. Thrombus. Significant bleed. Cardiovascular event.	Proportion of people having event with confidence intervals. Survival analysis (Kaplan-Meier).	Not conducted at this time	Longer-term data collection would be dependent on extension of contracted follow-up. [Update: follow-up not extended].
5) How many patients with atrial fibrillation with a contra-indication to oral anticoagulants (including previous significant bleed), or who have had a thromboembolic event despite being on oral anticoagulants, are candidates for left atrial appendage occlusion?	Yes, partly.	Decision to treat. Reason for surgery. Plan for treatment. Decision not to offer LAAO.	Proportion with confidence intervals.	None (Medication not recorded in HES)	Includes patients referred for MDT consideration, not referred patients. [Update: descriptive analysis of indication reported].
6) Which devices are used to undertake LAAO and what are the device-specific efficacy and safety outcomes in CtE funded patients undergoing the procedure?	Yes, partly.	Device implanted/used. Safety and efficacy data.	Subgroup analysis. Comparative survival curves.	None (Devices not recorded in HES)	Some subgroups may be low in number (real differences may not be statistically observable). Not possible to separate device effects from cardiac anatomy.
7) Is the frequency of complications seen with the intervention clinically acceptable?	Yes, partly.	Key efficacy data (procedural success). Key complication data.	Descriptive statistics on efficacy and complication data.	Granularity of HES data insufficient to accurately	'Clinically acceptable' is a subjective term, will require expert opinion to

Question (NICE modified where applicable)	Can it be answered using registry data?	Key registry data required	Type of analysis – CtE registry data	Type of analysis - Linked data (CtE registry/HES/ONS)	Comment
			Narrative comparison with published data.	categorise in-hospital adverse events, therefore registry data preferred.	answer. [Update: comparison with published data made. No evidence an update of IPG349 is required on basis of complications].
8) Are clinical outcomes from left atrial appendage occlusion 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.	Not conducted at this time	Limitations with patient enrolment (power), patient selection and confounding variables (generalisability issues). [Update: low primary event rate did not allow for meaningful subgroup analysis].
9) What are the full procedural costs of left atrial appendage occlusion to the NHS?	Provides inputs.	Devices used, primary and secondary operator, investigations, length of stay initial admission and procedure duration.	Process costing with separate costs for each stage of the clinical pathway.	Not conducted at this time	Procedural costs will be estimated by combining information from the registry and data from sites, collected using a pro forma.
10) What are the potential cost savings for the NHS through provision of left atrial appendage occlusion for appropriate patients?	Provides inputs.	Patient characteristics. Resource use data for procedure, initial admission and re-admissions. Efficacy outcomes. Complication outcomes.	Cost consequences analysis	Not conducted at this time	Findings from a cost consequences analysis using an economic model will be provided in a separate report to NICE.
11) Is left atrial appendage occlusion cost-effective from the	Provides inputs.	Patient characteristics. Resource use data for	Cost consequences analysis	Not conducted at this time	Findings from a cost consequences analysis

Question (NICE modified where applicable)	Can it be answered using registry data?	Key registry data required	Type of analysis – CtE registry data	Type of analysis - Linked data (CtE registry/HES/ONS)	Comment
perspective of the NHS?		procedure, initial admission and re-admissions. Efficacy outcomes. Complication outcomes. Mortality.			using an economic model will be provided in a separate report to NICE.

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 REGISTRY)

3.1.1 Numbers of Patients Treated at Each Centre

A total of 571 LAAO procedure records were extracted by NICOR on 10th August 2017. Forty six patients did not meet the eligibility criteria, Appendix 1, 14 of which did not include eligible reasons for LAAO treatment, such as patient preference, or primary or secondary prophylaxis regardless of issues with anticoagulation. A total of 525 LAAO procedures were eligible for analysis.

Patients were defined as eligible for follow-up at each time point if they had concluded their procedure with LAAO device implantation and had a discharge status of alive at last hospital visit. For all patients eligible for follow-up at each time point, information was recorded in 82.4% of cases at 6 weeks, 80.9% at 6 months (180 days), 76.1% at 1 year and 70.2% 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. The only statistical difference identified between the whole cohort and those with reported follow-up information was the device used (reflecting patients who did not receive a device [“none”] were not followed up).

3.1.3 Active Surveillance (Evaluation of Coverage)

The data coverage and completeness results for CtE commissioned procedures only, for the 30 LAAO MDS baseline fields and the 6 specified follow-up fields are reported in Table 6.

Table 6: Data completeness by CtE-funded provider.

CtE provider	Baseline MDS completeness	Coverage† & completeness‡ at 6 weeks FU	Coverage† & completeness‡ at 6 months (182 days) FU	Coverage† & completeness‡ at 12 months FU	Coverage† & completeness‡ at 24 months FU
The Newcastle upon Tyne Hospitals NHS Foundation Trust /South Tees Hospitals NHS Foundation Trust*	94%	92.5% (37/40) coverage 89.1% FU data completeness	75.0% (30/40) coverage 89.4% FU data completeness	63.9% (23/36) coverage 91.9% FU data completeness	46.2% (6/13) coverage 54.2% FU data completeness
Liverpool Heart & Chest Hospital NHS Foundation Trust	82%	97.4% (74/76) coverage 83.1% FU data completeness	95.9% (70/73) coverage 83.1% FU data completeness	92.9% (52/56) coverage 81.1% FU data completeness	66.7% (14/21) coverage 78.6% FU data completeness
Leeds Teaching Hospitals NHS Trust	96%	97.1% (33/34) coverage 97.0% FU data completeness	67.7% (21/31) coverage 99.2% FU data completeness	51.9% (14/27) coverage 90.5% FU data completeness	100% (7/7) coverage 73.8% FU data completeness
Oxford University Hospitals NHS Trust	96%	98.3% (58/59) coverage 92.2% FU data completeness	63.8% (37/58) coverage 87.4% FU data completeness	87.3% (48/55) coverage 93.8% FU data completeness	81.2% (26/32) coverage 93.6% FU data completeness
Brighton & Sussex University Hospitals NHS Trust	93%	85.4% (41/48) coverage 65.8% FU data completeness	85.4% (41/48) coverage 72.0% FU data completeness	87.9% (29/33) coverage 71.8% FU data completeness	77.8% (7/9) coverage 71.4% FU data completeness
University Hospital of North Staffordshire NHS Trust	86%	24.1% (13/54) coverage 56.4% FU data completeness	92.6% (50/54) coverage 61.0% FU data completeness	97.3% (36/37) coverage 48.6% FU data completeness	84.6% (11/13) coverage 24.2% FU data completeness
University Hospitals Leicester NHS Trust	82%	81.8% (27/33) coverage 91.3% FU data completeness	93.8% (30/32) coverage 93.9% FU data completeness	91.3% (21/23) coverage 92.0% FU data completeness	100% (8/8) coverage 79.2% FU data completeness
Barts Health NHS Trust & The Heart Hospital*	76%	97.1% (34/35) coverage 88.6% FU data completeness	74.3% (26/35) coverage 86.5% FU data completeness	50.0% (12/24) coverage 97.2% FU data completeness	66.7% (2/3) coverage 58.3% FU data completeness
Kings College Hospital NHS Foundation Trust	86%	84.2% (16/19) coverage 81.3% FU data completeness	78.9% (15/19) coverage 83.3% FU data completeness	76.9% (10/13) coverage 83.3% FU data completeness	40% (2/5) coverage 16.7% FU data completeness
Guy's and St Thomas' NHS Foundation Trust	98%	70% (21/30) coverage 71.5% FU data completeness	78.6% (22/28) coverage 75.8% FU data completeness	58.3% (14/24) coverage 50% FU data completeness	50% (2/4) coverage 33.3% FU data completeness
Total**	**89%**	428/431 (99.3%) with device implanted, discharged alive and	418/423 (98.8%) with device implanted, still alive at 6 weeks FU and	328/419 (78.3%) with device implanted, still alive at 6 months FU and	115/411 (28.0%) with device implanted, still alive at 12 months FU and reaching 24

CtE provider	Baseline MDS completeness	Coverage† & completeness‡ at 6 weeks FU	Coverage† & completeness‡ at 6 months (182 days) FU	Coverage† & completeness‡ at 12 months FU	Coverage† & completeness‡ at 24 months FU
		reaching 6 weeks since procedure date. 354/428 (82.7%) with some degree of FU data. **Completeness of FU MDS (versus expected) = 84.2%.**	reaching 6 months since procedure date. 342/418 (81.8%) with some degree of FU data. **Completeness of FU MDS (versus expected) = 81.9%.**	reaching 12 months since procedure date. 259/328 (79.0%) with some degree of FU data. **Completeness of FU MDS (versus expected) = 79.4%.**	months since procedure date. 85/115 (73.9%) with some degree of FU data. **Completeness of FU MDS (versus expected) = 70.4%.**

FU Coverage† = Actual No. of LAAO procedures with some degree of FU data entered / No. of LAAO 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 481/492 (97.8%) of LAAO cases in the registry, to 10/08/2017.
FU Completeness‡ = Average completeness of the 6 specified LAAO 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.**
** Small difference in denominators in this data completeness table, compared with Appendix 1 Data Flow Diagram is due to the definition of 182 days as the 6 month period here, versus 180 days for outcomes analysis.

3.1.4 Outcomes – using CtE registry data only

a. Clinical

A total of 509 procedures (97.0%) recorded both admission and discharge dates, showing a median length of stay of 1 overnight stay (inter-quartile range [IQR] 1 to 1, range 0 to 52 overnight stays). A total of 114 procedures (22.4%) resulted in an extended length of stay (2 or more nights in hospital). Device implantation was achieved in 93.6% of all attempted LAAO procedures, in-hospital major complication occurred in 5.5% and in-hospital minor complications occurred in 4.6% of procedures. Four hundred and forty six procedures (89.0%) were considered a procedural success (i.e. device implanted and no major complications). Frequencies of in-hospital outcomes for all eligible LAAO patients, and post-discharge outcomes for all eligible LAAO patients with a device implanted are described in Appendix 4.

Detailed results from univariate analyses for in-hospital technical success (device implanted), in-hospital major complication and in-hospital minor complication are described in the *Supplementary Material – Tables 4 to 6* respectively. No covariates were significantly associated with these outcomes.

Crude incidence rates of adverse events are described in Appendix 5. Of the 25 reported deaths, 5 occurred in hospital, and 23 had a recorded cause of death, whereas the remaining 2 had entered a non-specific record or stated cause of death to be advised:

- 4 attributed to sepsis (1 of these urinary, 1 with chest infection and 1 query staphylococcal septicaemia);
- 4 attributed to cancer (1 cancer of the caecum with secondary anaemia, 1 oesophageal cancer, 1 metastatic bowel cancer, 1 metastatic lung cancer);
- 3 strokes (2 of these ischaemic strokes and the other not related to LAA [assumed haemorrhagic origin]);
- 2 attributed to intracranial haemorrhage;
- 2 attributed to pneumonia (1 with lung fibrosis);
- 2 attributed to end stage renal failure;
- 1 each attributed to heart failure; air embolism with cerebral oedema; cardiac tamponade; a gastric mass not associated with LAA; chest infection; complications of diabetes.

Nineteen neurological events were reported: 11 ischaemic (one of which was recorded as CVA/RIND), 4 haemorrhagic, and 4 undetermined. The crude event rate for ischaemic stroke (using n=10 events) was 2.6 (95% CI 1.3 to 4.8) events per 100 person-years (PY) follow-up.

Kaplan-Meier curves for time to death, neurological events and death or neurological event are shown in Appendix 6. No significant association was found between death or neurological events and device manufacturer (Appendix 7).

Use of medications over time is described in the *Supplementary Material – Table 7*.

In reporting changes in quality of life, analysis can only be performed in individuals who provided data pre-procedure and at specified later time periods. This is to ensure comparison of the EQ-5D scores of the same individuals over time. The mean utility value pre-procedure was 0.78, which changed to:

- 0.82 at 6 weeks (n= 131);
- 0.83 at 6 months (n=144);
- 0.82 at 12 months (n=101);
- 0.78 at 24 months (n=32).

However, none of these changes reached statistical significance.

No significant changes in individual quality of life (EQ-5D) components or utility scores were observed over time. The domain registering the greatest benefit from the procedure was reduction in anxiety and depression (*Supplementary Material – Table 8*).

b. Cost / resource

Five completed responses to the LAAO CtE Excel® costing template were received but most were incomplete, with only one well-completed response. NY EAC synthesised the responses to create a list of the resources required at each stage of the pathway. In February 2017, 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 [12] and PSSRU [13]). 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 the first instance. Such data are identified in yellow in this report and Appendix 8. NHS Supply Chain price includes overheads of 3% 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, finance and administration related overheads.

At this stage we also included results from the analyses of registry 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 were 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 an LAAO procedure conducted in NHS England were updated from 2015/16 costs to 2017/18 costs using the hospital & community health services index [14]. This was estimated to have increased by 1.8% in each of the two intervening years. This increase was not applied to the cost of the device, the price of which was agreed with manufacturers for the duration of the registry. The resultant costs are shown in Table 7.

Table 7: Central cost and range of costs for an LAAO procedure.

Pathway stage	Central cost	Low cost	High cost
Pre-operative assessment	£820	£428	£1,036
Peri-operative procedure	£9,047	£8,247	£9,808
Post-operative management	£1,931	£946	£2,762
Total	**£11,798**	**£9,622**	**£13,606**

Table 8 analyses the estimated costs by component and stage for the central case. The device accounts for [redacted]% of the cost, with investigations forming the second largest cost component ([redacted]%), staff comprise [redacted]%, consumables and length of stay are each 5%, theatre use contributes about 4% to the cost, with outpatient follow-up being 2%.

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	£657	£[redacted]	£1,146	£[redacted]	[redacted]%
Staff	£147	£[redacted]		£[redacted]	[redacted]%
Consumables	£16	£620		£636	5%
Length of stay			£587	£587	5%
Theatre		£437		£437	4%
Out-patient			£197	£197	2%
Total	**£820**	**£9,047**	**£1,931**	**£11,798**	**100%**

A full summary of all resources and unit costs is provided in Appendix 8. This also describes the assumptions underpinning the sensitivity analyses.

c. Patient experience

Pre-procedure, EQ-5D values were available for 272 patients. At 6 weeks, 131 paired scores were available and these showed a mean gain in utility of 0.02, with 31% of patients reporting improved quality of life, 45% no change and 24% a deterioration. At 6 months, paired data for 144 patients were available. These showed a similar marginal improvement in the utility score of 0.01, with 38% of patients reporting improved quality of life, 36% no change and 26% a deterioration. The mean baseline value was 0.80 ± 0.20; however, the median value of 0.82 was adopted as a measure of central tendency.

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

3.2 PRIMARY DATA COLLECTION (DATA LINKAGE)

3.2.1 Cohort characteristics

Records from a total of 569 LAAO patients were extracted from the NICOR registry on 05/04/2018, of which 523 were eligible for analysis (*i.e.* meeting CtE criteria in Section 2.4.3). 520 of these were records preceding 01/03/2018 (*i.e.* date of data linkage). A total of 495 (95.2%) were matched with the HES APC dataset, of which 35 (7.1%) did not pass internal quality checks with the registry and ONS data, casting serious doubt on their matching to the correct patient (see Appendix 9). Issues associated with all 35 patients not passing internal quality checks were raised to the data controller. No further validation was available (as of 14th September). However, there were no significant differences in baseline characteristics between those which passed the internal quality checks (n=460 'green flags') and those who did not (n=35 'red flags') in terms of age, sex, BMI, diabetes, CHA_2DS_2-VASc scores, EHRA AF scores, NYHA classes, HAS-BLED scores and procedural urgency when Bonferroni correction for multiple comparisons was applied – see *Supplementary Material – Table 9.* Therefore the 35 patients were removed from all subsequent analysis.

The patient demographics of 460 patients included in the linked data analysis are described in Table 9.

Table 9: Patient demographics of records included in the linked dataset.

Patient characteristic†	Eligible patients in linked dataset (n=460)
Female	146 (31.8%)
Age, years median (Q1,Q3) [range]	75 (70,80) [43-91]
BMI, kg/m^2 median (Q1,Q3) [range]	27.4 (24.3,31.2) [10.1-46.1]
Diabetes:	
- No	334 (73.6%)
- Yes (not insulin)	108 (23.8%)
- Yes (insulin)	12 (2.6%)
CHA_2DS_2-VASc median (Q1,Q3) [range]	4 (3,5) [0-8]
HAS-BLED median (Q1,Q3) [range]	4 (3,5) [1-6]
NYHA: - No limitation of physical activity - Slight limitation of ordinary physical activity - Marked limitation of ordinary physical activity - Symptoms at rest or minimal activity	 166 (42.8%) 171 (44.1%) 47 (12.1%) 4 (1.0%)
EHRA AF: - No AF-related symptoms - Mild symptoms; normal daily activity not affected - Severe symptoms; normal daily activities affected - Disabling symptoms; normal daily activity discontinued	 193 (52.0%) 163 (43.9%) 14 (3.8%) 1 (0.3%)
Medications: - Single antiplatelet - Dual antiplatelet - Anticoagulant alone - Antiplatelet(s) & Anticoagulant(s) - Other - None	 122 (27.0%) 25 (5.5%) 65 (14.4%) 6 (1.3%) 51 (11.3%) 183 (40.5%)

† *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.*

3.2.2 In-hospital complications

The registry reported 43 in-hospital complications, HES reported 52. From the union of both datasets, a total of 79/460 (17.2%) LAAO procedures had some degree of complication reported, see Table 10.

Twelve major discrepancies in complications reported by one source (either the CtE registry or HES) and not validated in the other were raised by the NY EAC to NICOR. No further validation was available (as of 14th September 2018).

Table 10: Contingency table of in-hospital complications recorded in the linked dataset.

		HES		Total
		No complication	Complication	
CtE Registry	No complication	381	36	**417**
	Complication	27	16	**43**
Total		**408**	**52**	**460**

Major complications recorded in the CtE registry included: 4 deaths during the LAAO procedural admission (main cause reported as air embolism with cerebral oedema, sepsis, cardiac tamponade, left atrial perforation), 4 neurological events (1 haemorrhagic, 1 CVA/RIND, 2 of undetermined type – all recorded in the registry), 6 instances of tamponade requiring surgical drainage, 4 cases where an embolised device was surgically retrieved, 8 cases where other surgical intervention was required, and 8 life-threatening/disabling clinical bleeds, see Appendix 10.

Complications recorded in HES could not be robustly categorised as major and minor due to a lack of granularity in the ICD-10 codes. However the most common complications reported in HES included: 25 instances of haemorrhage and haematoma complicating a procedure, 3 pericardial effusion (non-inflammatory), 3 retention of urine, 3 accidental puncture and laceration during a procedure, 2 vascular complications following a procedure (including air embolism following procedure), 2 mechanical complications of other cardiac and vascular devices and implants, 2 disruption of the wound, 2 bradycardia, and 2 deaths during the LAAO procedural admission (cause of death from ONS confirmed as anoxic brain damage qualified by other medical procedures as the cause of abnormal reaction of the patient, or of later complication, without mention of misadventure at the time of the procedure - cardiac catheterization, haemorrhage qualified by surgical operation and other surgical procedures as the cause of abnormal reaction of the patient, or of later complication, without mention of misadventure at the time of the procedure – Surgical procedure, unspecified), see Appendix 10. Note 1 in-hospital TIA was captured during the LAAO procedural admission in HES, however as these were not classified specifically as a complication of the procedure, they were not included in the total complications identified from HES in the above table.

3.2.3 All-cause mortality

Of the 460 patient records available for analysis, 4 deaths were recorded during the LAAO procedural admission (0.9% in-hospital mortality), and 29 did not have a successful LAAO device implantation (i.e. 6.3% in-hospital procedural failure).

Of the 427 patients discharged from hospital alive with successful implantation of the LAAO device:

- 28 (6.6%) had no follow-up entered into the registry
- 56 (13.1%) had 1 follow-up entry fully or partially completed

- 121 (28.3%) had 2 follow-up entries fully or partially completed
- 167 (39.1%) had 3 follow-up entries fully or partially completed
- 54 (12.6%) had 4 follow-up entries fully or partially completed
- 1 (0.2%) had 5 follow-up entries fully or partially completed

The total length of follow-up for the 460 records calculated from the CtE registry data was 139,508 days (382.2 person years [PY]) with a mean (SD) 303.3 (239.1), median (Q1,Q3) 276.5 (104.0,412.5) range 0 to 964 days per patient.

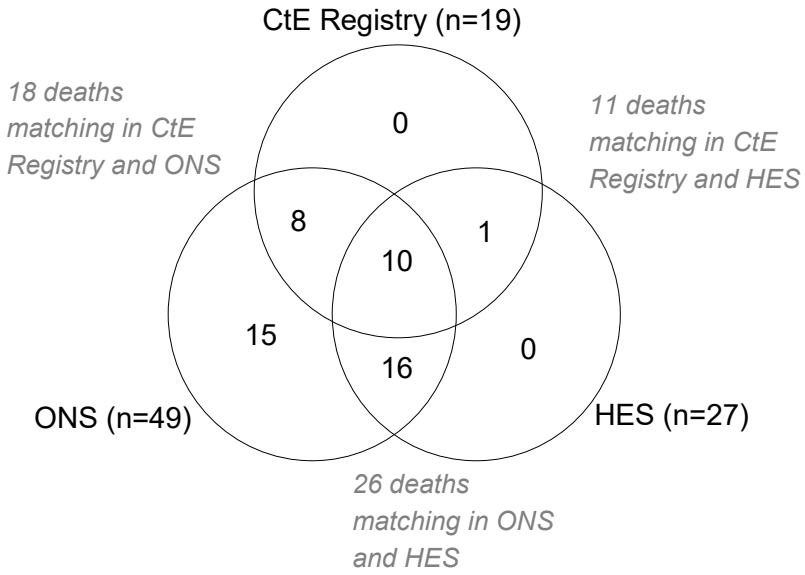
Of the 427 patients discharged alive with successful LAAO implantation:

- 51 (11.9%) had no subsequent hospital admissions recorded in HES following the LAAO procedure
- 86 (20.1%) had 1 hospital admission
- 74 (17.3%) had 2 hospital admissions
- 63 (14.8%) had 3 hospital admissions
- 42 (9.8%) had 4 hospital admissions
- 111 (26.0%) had 5+ hospital admissions (the maximum number of admissions was 165, for one patient having “Continuous intravenous infusion of a therapeutic substance” approximately every 5 days)

The total length of follow-up calculated from the linked dataset was 327,406 days (897.0 PY) with a mean (SD) 711.8 (288.7), median [Q1;Q3] 729.0 [523.2:912.5], range 0 to 1233 days per patient.

A total of 19 deaths were reported by the registry, 27 in-hospital deaths reported in HES, and 49 total deaths reported in ONS, see Figure 3. The total number of deaths (all in-hospital, post-LAAO discharge in those with successful LAAO implantation) occurring across all three data sources (*i.e.* union of the registry, HES, ONS) was 50; 4 of which occurred during the LAAO procedural admission. Total event rate for all-cause mortality (using n=50 events) was 5.6 [4.1:7.3] per 100 PY follow-up, see Table 11 and Figure 4a.

Figure 3: All-cause mortality as reported across the three datasets.



A total of 9 deaths had a neurological event reported as main cause of death (4 of which were reported in the registry):

- 6 intra-cerebral/cranial haemorrhages (occurring 19 days, 7.5 months, 10 months, 14 months, 16 months and 23 months after LAAO procedure)
- 2 ischaemic (occurring 16 days and 5 months after LAAO procedure),
- 1 not specified as haemorrhagic or infarction (occurring 26 months after LAAO procedure).

Medication(s) recorded for all 9 patients with neurological event reported as main cause of death are described in *Supplementary Material – Table 10*. Note that 5 deaths due to neurological event occurred in patients on dual antiplatelet therapy (DAPT); 3 haemorrhagic and 2 ischaemic.

A total of 12 deaths had malignant neoplasm reported as main cause of death (5 of which were reported in registry), 3/12 patients had a diagnosis of neoplasm recorded in HES prior to the LAAO procedure.

3.2.4 Neurological events

The number of patients with reported neurological events was 17 in the registry (4 during LAAO procedure, 13 post-procedure), 41 in HES (6 during LAAO procedure, 40 post-procedure – with 5 patients having a documented event during and after procedure) and 6 deaths in ONS with neurological events as the main cause of death (all occurring post-procedure). Note that of the 40 post-procedural reported neurological events, 32 were documented in the primary diagnosis position interpreted as the cause for admission). The total number of unique patients with reported neurological events occurring across all three data sources (*i.e.* union of registry, HES, ONS) was 50.

- Discrepancies associated with 40 of the neurological events (*e.g.* differences in fact or timing of neurological event reported between clinical registry and routine data sources HES/ONS) were identified and referred to NICOR for investigation, using the technical issue log. Further information was provided for 6 of the events (as of the 14th September 2018): 4 confirmed error in registry and HES correct (3 cases where an ischaemic stroke was not reported in registry, 1 case where an ischaemic stroke was reported in the registry but the date of event was incorrect in the registry by 1 year);
- 1 confirmed coding error in HES and registry correct (related to clinical coding systems having the ability to auto-populate secondary diagnoses with previous episodes of care, easily identified due to repetition of exact coding sequences across multiple episodes of care);
- 1 event likely to have occurred in local hospital (not treating hospital), therefore event status unknown to the treating centre who entered data to the CtE registry.

Given the above received responses from centres, the following set of validation rules were developed retrospectively in order to distinguish ‘new’ from historical neurological events:

1) Assume all neurological events in CtE registry reported during procedure or follow-up are ‘new’ events: this accounts for 17 ‘new’ neurological events, 1 of which had

inconsistency in date of event reported between CtE registry and HES, however date of event recorded in HES was externally validated by centre.

2) Assume all deaths in ONS with main cause being neurological event are 'new' events (ONS gold standard of death reporting): this accounts for 6 'new' neurological events.
3) Assume all in-hospital HES events coded alongside an ICD-10 complication code are 'new' events: this accounts for 1 'new' neurological event.
4) Assume all HES events after last FU date in registry are 'new' events: this accounts for 22 'new' neurological events of which 1 was externally validated with the treating centre.
5) Assume all HES events reported at a different hospital (than the LAAO treating centre) are 'new' events: this accounts for 22 neurological events of which 1 was externally validated with the treating centre.
6) Assume all HES events occurring at same treating hospital (who conducted LAAO implantation), with the date of event occurring between LAAO discharge and latest follow-up were missed from registry as 'new' events: this accounts for 3 'new' neurological events of which 1 was externally validated with the treating centre.

Application of the above retrospectively defined validation rules resulted in 5 neurological events being classified as historical events (rather than 'new' events). In all 5 cases there was evidence of the organisational clinical coding system auto-populating diagnoses from previous visits (4 externally validated as coding error in HES – 1 by clinical team investigated by NICOR, 3 by clinical coding department at treating centre investigated by the NY EAC). The total number of patients reporting 'new' neurological events during or after the LAAO procedure was 45; of which 17 (38%) were reported in the registry and 38 (84%) in HES/ONS. Only 13/45 'new' neurological events were validated (10 confirmed by occurring in both CtE registry and HES/ONS datasets, and 3 appearing in HES only but validated by treating centre following query by NICOR).

Of the 45 patients with reported neurological events:

- 30 (67%) had an ischaemic first event (1 reported as CVA/RIND, with 4 patients reporting multiple neurological events including: 2 TIA followed by haemorrhage, 1 TIA followed by infarction, 1 infarction followed by another infarction),
- 12 (27%) had a haemorrhagic first event (1 patient with multiple events: intraventricular intracerebral haemorrhage followed by an unspecified intracerebral haemorrhage), and
- 3 (7%) were of unknown type.

The event rate for neurological events (using total of n=45 events over 850.4 PY follow-up) was 5.3 (95% CI 3.9 to 7.1) per 100 PY follow-up, see Table 11 and Figure 4b. Event rates of ischaemic events (n=30 events, 869.2 PY follow-up) was 3.5 (95% CI 2.3 to 4.9) per 100 PY follow-up, and haemorrhagic (n=12 events, 890.2 PY follow-up) was 1.3 (95% CI 0.7 to 2.4) per 100 PY follow-up.

Eight patients had a diagnosis of vascular dementia recorded post-LAAO procedure (HES only, not recorded data field in registry): 3 of these patients also had this diagnosis recorded during either the LAAO procedural admission or prior admission dating back to 1st April 2008). Of the new diagnoses (occurring only after LAAO), 1 occurred within 1 year of the

LAAO procedure (at 1 month), and 4 occurred after 1 year (at 16, 21, 31 and 34 months after LAAO procedure).

3.2.5 Composite (death or neurological event)

The event rate for the composite outcome, *i.e.* all-cause mortality or total number of neurological events, (using total n=81 events over 817 PY) was 9.9 (95% CI 7.9 to 12.3) per 100 PY follow-up, see Table 11 and Figure 4c.

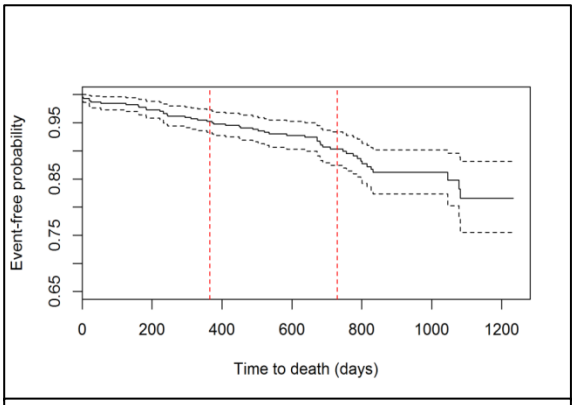
Table 11: Total event rates of primary outcomes: all-cause mortality, neurological events and composite outcome.

	All-cause mortality	Total neurological events	Ischaemic events	Haemorrhagic events	Total neurological events combined with all-cause mortality
No. of patients followed	460	460	460	460	460
Median [Q1;Q3] length of follow-up, days	729 [523 to 912.5]	722.5 [489 to 903.5]	729 [506 to 906]	746.5 [523 to 924]	689 [471.2 to 869.2]
No. of events	50	45*	30	12	81
Total follow-up, person years [range]	897 [0 to 1233 days]	850.4 [0 to 1227 days]	870 [0 to 1227 days]	890 [0 to 1227 days]	817 [0 to 1227 days]
1-year event-free probability [95% CI] (number at risk)	0.953 [0.933 to 0.973] (n=416)	0.949 [0.929 to 0.970] (n=399)	0.967 [0.951 to 0.984] (n=406)	0.986 [0.975 to 0.997] (n=414)	0.919 [0.894 to 0.945] (n=387)
2-year event-free probability [95% CI] (number at risk)	0.904 [0.874 to 0.934] (n=229)	0.898 [0.869 to 0.929] (n=215)	0.933 [0.908 to 0.959] (n=224)	0.973 [0.957 to 0.989] (n=233)	0.826 [0.788 to 0.866] (n=196)
Total event rate, per 100 person years follow-up [95% CI]	**5.6 [4.1 to 7.3]**	**5.3 [3.9 to 7.1]**	**3.5 [2.3 to 4.9]**	**1.3 [0.7 to 2.4]**	**9.9 [7.9 to 12.3]**

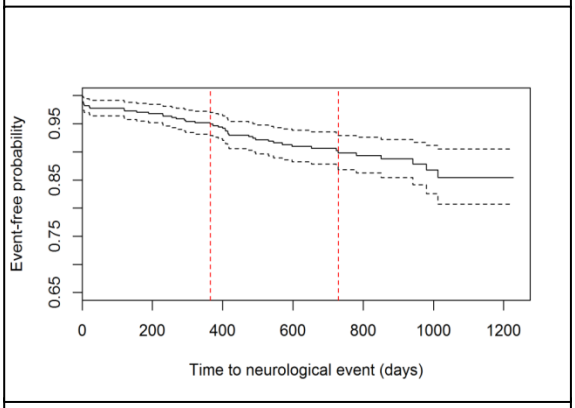
* 3 neurological events of unknown type

Figure 4: Kaplan-Meier analysis for a) all-cause mortality, b) total neurological events, c) all-cause mortality or neurological event

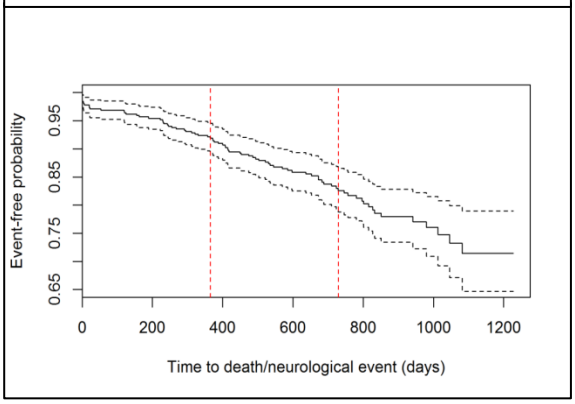
a)



b)



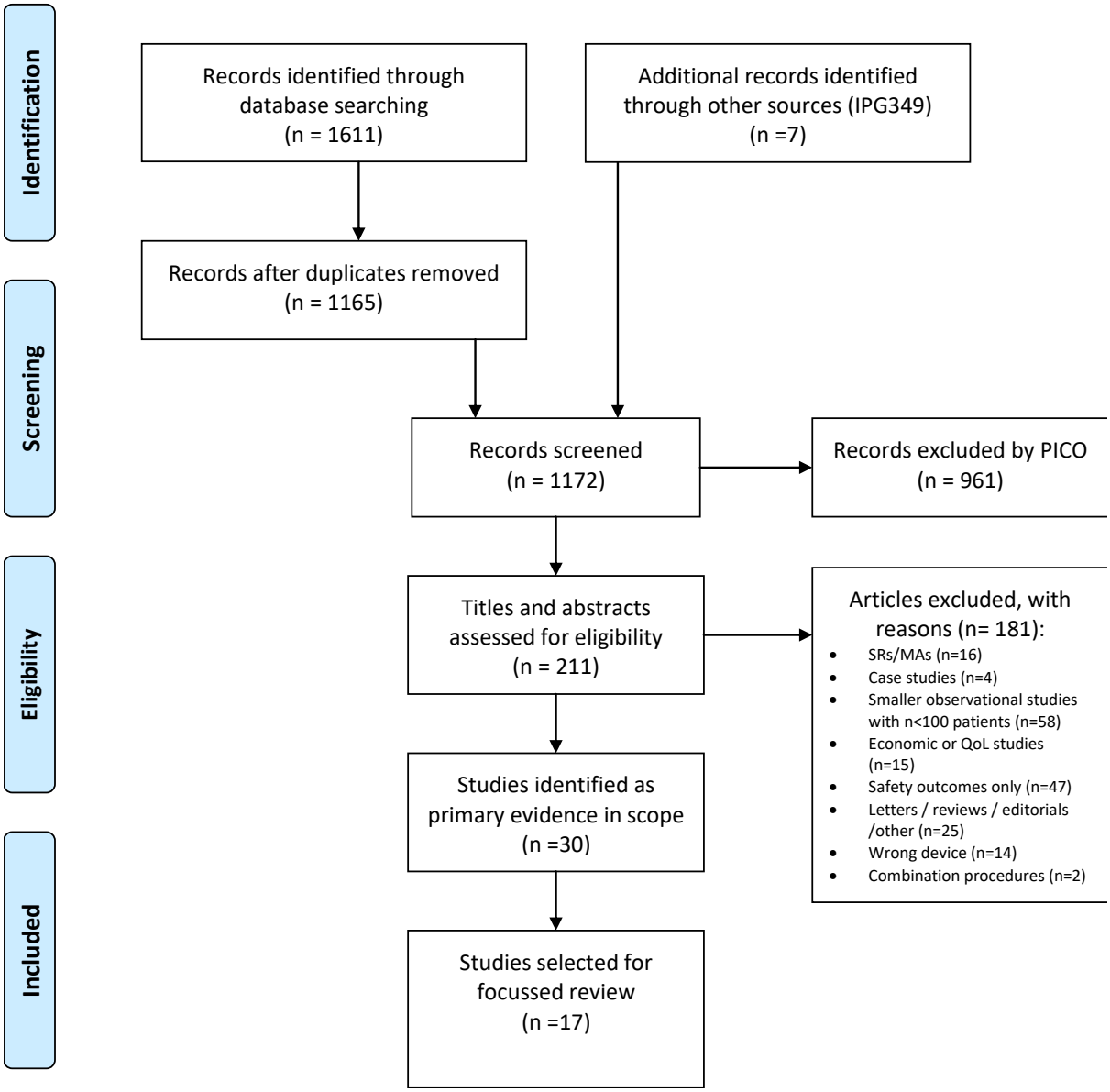
c)



3.3 SECONDARY DATA COLLECTION (LITERATURE REVIEW)

The CtE LAAO literature search retrieved 1,165 potentially relevant articles. Abstracts from these articles were independently assessed for relevance by two EAC researchers. Of these, 961 were excluded immediately after screening as being not relevant to the scope. Of the remaining 211 records, 181 were excluded for various reasons, including 16 studies that were identified as systematic reviews and/or meta-analyses and 15 studies that reported on economic or QoL outcomes. These were used in the economic evaluation. The most prevalent reason for exclusion at the sifting stage was because of study size (58 studies reported on less than 100 patients). The process of sifting using PRISMA methodology (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) [15] is illustrated in Figure 5 below.

Figure 5: PRISMA schematic of literature search for clinical evidence.



The CtE LAAO literature search identified 30 publications in scope. Of these, 17 publications pertaining to 2 RCTs and 3 observational studies were selected for focussed review. The remaining publications were identified as in scope, but were not analysed further, mainly due to study size (more than 100 but less than 200 participants). One study from NICE IPG349 was selected which was the seminal paper of one of the RCTs; the other studies were excluded on the basis that they described a technology not now available to the NHS or reported sample sizes below the threshold specified in the scope (i.e. less than 100 patients). In addition to the primary studies, 16 secondary studies (systematic reviews and/or meta-analyses) were identified; 4 of which were selected for interim analysis. Fifteen potentially informative economic studies were flagged.

The two RCTs identified were the PROTECT-AF (n=707) [16] and PREVAIL trials (n=407) [17]. Both these trials, performed by the same research group, investigated the use of the WATCHMAN device in patients *without* a contraindication to warfarin. Patients were randomised in a 2:1 ratio to receive WATCHMAN (combined with warfarin for minimum 45 days) or chronic treatment with warfarin. The primary outcomes were composites related to efficacy (longer term prevention of ischaemic events) and safety (procedural adverse events and excess bleeding). The EAC appraised these studies and found they showed good methodological quality, but lacked generalisability because of the use of warfarin in both arms. In summary, the results of the PROTECT-AF trial demonstrated non-inferiority compared with warfarin in primary efficacy and safety outcomes at a follow-up of up to 3.8 years; however, the rate of procedure-related adverse effects was a concern, with 4.8% of patients suffering serious pericardial effusion. The PREVAIL trial did not demonstrate non-inferiority in its primary efficacy outcomes, which was attributed to an unusually low event rate in the warfarin arm. However, this study reported a reduction in procedural adverse events compared with the PROTECT-AF trial.

The observational studies were single-armed and therefore of limited methodological quality. The EWOLUTION registry (2016) [18] investigated the use of the WATCHMAN device (n=1014) but was limited to peri-procedural outcomes (mainly 30 days or less). A one-year analysis of the EWOLUTION registry [19], published after the literature search cut-off date, was identified by stakeholders during the consultation process. As this study had been previously appraised [9], and the longer-term results were relevant to those of the registry, this analysis was accepted for this report.

The study by Betts *et al.* (2016) [20] was a retrospective audit of routinely collected data from patients (n=371) undergoing LAAO (any device, principally WATCHMAN or AMPLATZER Cardiac Plug [ACP]). It reported outcomes with a mean follow-up of 24.7 months. The ACP registry (n=1053) [21] investigated this device with a mean follow-up of 13 months. Whilst these trials lacked internal validity and did not provide comparative data, they reflected real-life practice (used mainly in patients ineligible for warfarin), with the study by Betts *et al.* in particularly being highly generalisable, being set in the UK NHS and enrolling patients with similar indications to the registry. Procedural safety was comparable to the RCTs. The EWOLUTION registry, ACP registry, and Betts study all reported superior efficacy outcomes than would be expected according to standardised risk scores.

Results from the four systematic reviews and meta-analyses provided aggregate data of higher precision than individual studies (but were limited in generalisability because of the heterogeneous nature of the contributory studies) [9]. An individual meta-analysis [22] of the 2 RCTs showed broad equivalence of WATCHMAN and warfarin in overall stroke rates, but reported superiority in the prevention of haemorrhagic stroke and cardiovascular death. This was largely supported by a network analysis [23]. Two systematic reviews and meta-analyses of observational data provided further estimates of efficacy and adverse events [24, 25].

The literature review, supplemented by an update in May 2017, identified 15 economic studies that met the inclusion criteria. Evidence from eight economic studies reported that the WATCHMAN LAAO device was cost-effective in certain high cost settings, particularly in North America, compared with patients managed on DOACs or warfarin. Costs in the LAAO arm were initially higher but, over time, savings from fewer strokes result in lower total costs and higher quality-adjusted life years (QALYs) compared with anticoagulants. Financial break-even was around 8 to 10 years depending on the comparator, being shorter with DOACs than warfarin. One study, based on a subset of 547 patients in the PROTECT-AF RCT, reported that at 12 months, patients receiving LAAO had an increase in quality of life compared with baseline, whilst those treated with warfarin experienced a decline [26].

Evidence in the population contraindicated to DOACs or warfarin was limited to 6 studies, of which one generalised to the UK setting [27]. This study used registry data and reported LAAO was cost saving in the contraindicated population with the benefit being higher than for the wider population. However, further evaluations are required to confirm these findings, particularly since it was not based on direct randomised evidence. It is likely patient selection is important and cost-effectiveness will be dependent on the risk of stroke and bleeding. Further evaluations are also required on the relative efficacy and costs of alternative devices.

Further details are available in the standalone literature review document by Willits *et al.* (November 2016) [9].

3.4 NHS ENGLAND QUESTIONS

The aims of the CtE registry were to provide data on the safety, efficacy and costs of LAAO in the real-world NHS setting and specifically to answer 11 pragmatic questions concerning these issues. In this section, the findings from the CtE registry are used to answer these questions and are presented in the context of published studies in other populations. Table 12 summarises some key characteristics that illustrate the risk profile of patients undergoing LAAO in the CtE programme, key clinical trials and large observational studies.

Table 12: Summary of patient characteristics in the CtE registry, linked dataset (CtE registry/HES/ONS) and published literature.

Study		Age in years (SD)	$CHADS_2$ or CHA_2DS_2-VASc score	HAS-BLED score Mean (SD) Median [Range]	Pre-procedure medications
CtE registry (n=525)		Mean: 74.5 (8) Median: 75 [70, 80]	$CHADS_2$ Mean 2.9 (1.3 SD) Median 3 (IQR 2 to 4) CHA_2DS_2-VASc Mean 4.3 (1.5 SD) Median 4 (IQR 3 to 5)	Mean: 3.7 (1.1 SD) Median: 4 (IQR 3 to 5)	Antiplatelet only = 32.0% Anticoagulant only = 18.2% Other or none = 49.8%
Linked dataset (CtE registry/HES/ONS) (n=460)		Mean: 74.4 (8.1) Median: 75 [70, 80]	$CHADS_2$ Mean 2.8 (1.3 SD) Median 3 (IQR 2 to 4) CHA_2DS_2-VASc Mean 4.3 (1.5 SD) Median 4 (IQR 3 to 5)	Mean: 3.7 (1.1 SD) Median: 4 (IQR 3 to 5)	Antiplatelet only = 30.8% Anticoagulant only = 16.6% Other or none = 52.5%
RCTs*	PROTECT-AF (n=707)	LAAO: Mean 71.7, (8.8 SD, range, 46.0 to 95.0) Control: 72.7 (9.2 SD, range 41.0 to 95.0)	Mean $CHADS_2$ = 2.2 (SD N/R)	N/R (likely to be low as patients eligible for warfarin)	100% patients on warfarin.
	PREVAIL (n=407)	LAAO: 74.0, (7.4 SD, range 50.0 to 94.0) Control: 74.9 (7.2 SD, range 53.0 to 90.0)	Mean $CHADS_2$ = 2.6 (SD N/R)	N/R (likely to be low as patients eligible for warfarin)	100% patients on warfarin.
Observational studies	UK registry (Betts) (n=371)	72.9 (8.26)	$CHADS_2$ Mean: 2.63 (1.24) CHA_2DS_2-VASc Mean: 4.22 (1.56)	Mean: 3.34 (1.17)	Not stated but most contraindicated to warfarin. 61% discharged on antiplatelet treatment, 39% on a regimen including anticoagulation.
	EWOLUTION registry (n=1014)	73 (9)	$CHADS_2$ Median: 3 (IQR N/R) CHA_2DS_2-VASc	Mean: 2.32 Median: 2	N/R

Study		Age in years (SD)	$CHADS_2$ or CHA_2DS_2-VASc score	HAS-BLED score Mean (SD) Median [Range]	Pre-procedure medications
			Mean: 4.5 (1.6) Median: 4		
	ACP registry (n=1053)	75 (8)	$CHADS_2$ Mean: 2.8 (1.3 SD) CHA_2DS_2-VASc Mean: 4.5 (1.6 SD)	Mean: 3.1 (1.2) Median: 3	N/R Most patients discharged on dual antiplatelet therapy.
	CAP registry* (n=460)	74 (8)	$CHADS_2$ Mean 2.4 (1.2 SD)	N/R	100% patients on warfarin.
	ASAP registry (n=150)	72.5 (7.4)	$CHADS_2$ Mean: 2.8 (1.2 SD) CHA_2DS_2-VASc Mean: 4.4 (1.7 SD)	N/R	All patients contraindicated to warfarin.

Abbreviations. IQR – inter-quartile range; N/R – not reported; SD – standard deviation.
* The RCTs and CAP registry used LAAO (WATCHMAN) combined with 90 days oral anticoagulation with warfarin as the intervention. Most patients in the observational studies did not take oral anticoagulation.

Qualitative analysis of the baseline characteristics of the study populations show that, in general, patients enrolled into the RCTs were eligible to receive warfarin and indeed received this as part of the intervention (for 45 days post-procedure). Additionally, patients in the PROTECT-AF and PREVAIL trials had lower $CHADS_2$ risk scores than those recruited for the CtE registry. This means that published trial participants were at reduced risk of ischaemic stroke compared to the CtE registry, and therefore it would be expected trial patients would have superior outcomes in this regard, all other things being equal. In contrast, patients enrolled into the observational studies tended to more closely reflect the patients in the CtE registry in terms of ischaemic stroke risk. Crucially, patients in the selected observational studies were relatively or absolutely contraindicated to oral anticoagulation and were therefore a closer match to patients in the CtE registry.

3.4.1 Question One

> "Can UK clinical teams reproduce the short and medium success rates for left atrial appendage occlusion reported in existing clinical trials, with equivalent or lower complication rates?"

For the purposes of answering this question, "short [term] success rates" has been defined as technical and procedural success of device implantation in hospital. In-hospital success and complication rates have been answered directly using data from the registry, which reported these outcomes directly. "Medium [term]" success rates pertains to the prevention of ischaemic neurological events and death associated with LAAO implantation as measured by the registry. This has been answered primarily using HES and ONS linked data (which is considered more comprehensive than registry data in terms of follow-up coverage), but for completeness registry data have also been reported. As longer term follow-up in the registry was limited (see Section 4.4), data were combined over all follow-up periods and presented as annualised event rates (events per 100 person-years [PY]).

Short term success

The technical success of LAAO was defined as the proportion of devices successfully implanted in patients where it was attempted. The reported rate by participating centres was 93.6% (95% CI 91.1% to 95.6%). Procedural success was defined as technical success in the absence of major complications and was reported as 89.0% (95% CI 86.0% to 91.6%). Thus, approximately one in ten procedures carried out was unsuccessful. In those in whom a device was implanted, 434/469 (92.5%) had no leak, 32/469 (6.8%) had a minor leak, 1/469 had a moderate leak (0.2%) and 2/469 (0.4%) had a major leak (Appendix 4).

Clinical failure was reported in 9.1% of patients (95% CI 6.6% to 12.2%) following TOE examination at follow-up. The reasons for clinical failure were: the device was not found *in situ* in 5.9% of patients and in a further 1.6% of patients, the LAA was found not to be sealed, having a large leak (≥3 mm). Four patients (0.8%) were classified as a clinical failure because they suffered a neurological event before hospital discharge.

The short term success rate of LAAO performed through CtE was compared with published data from trials and observational studies (Table 13). Direct comparisons are confounded due to differences in definitions of technical or procedural success, which were not always explicitly defined in the literature. However, it can be seen that short-term success rates are largely consistent with the published data. The PROTECT-AF trial [16] reported a success rate of 91%, which increased to 95% for data reported by the PREVAIL trial [17], an improvement that was partly attributed to the learning curve effect (as both studies were conducted by the same clinical teams). It is likely that the RCT data from this procedural outcome are generalisable to the trial registry, although it was restricted to the WATCHMAN device only.

The UK registry by Betts *et al.* (2016) [20] provided the most generalisable data, which are consistent with the CtE success rates. Data from the other large observational studies [18, 21] reported numerically higher implantation success rates, but appear to be within the confidence intervals of the present CtE study. Two other registries of note by the Holmes group of researchers (WATCHMAN), the Continued Access Protocol (CAP) registry [28] and ASA Plavix Feasibility Study With WATCHMAN Left Atrial Appendage Closure Technology (ASAP) registry [29], reported numerically higher success rates but still within the upper confidence limit of the CtE registry.

Table 13: Summary of technical and procedural success of CtE patients and published data.

Study		Technical and procedural success (95% CI)	Definition*
CtE registry		Technical success: 93.6% (91.1% to 95.6%) Technical success with no leak: 86.6% (83.3% to 89.5%)	Device successfully implanted.
		Procedural success: 89.0% (86.0% to 91.6%)	Device implanted in absence of major complications.
RCTs	PROTECT-AF	91%	Successful implant of those attempted.
	PREVAIL	95.1%	Successful implant of those attempted.
Observational studies	UK registry	92.5%	Defined as "the percentage of successful device implants among patients in whom a device was opened and deployment was attempted"
	EWOLUTION registry	Successful 98.5% Complete seal 91.4%	
	ACP registry	97.3%	Defined as "successful implantation of the ACP in the left atrial appendage".
	CAP registry	95.0%	Successful implant of those attempted.
	ASAP registry	94.7%	Successful implant of those attempted.
* Definitions of procedural or technical success not always reported and not consistent.			

Medium term success

Registry data

The primary purpose of LAAO is to prevent ischaemic stroke in high risk populations (people with AF absolutely and relatively contraindicated to warfarin and DOACs). The registry recorded neurological event rates as a primary efficacy outcome, and, in addition, all-cause mortality as a proxy efficacy outcome. These outcomes were also combined (death or neurological event outcome) which more closely represents the primary outcomes used in the non-inferiority RCTs.

Twenty-five patients died during the CtE registry study period (4.8%), and additionally 19 had neurological events (3.6%). As some neurological events were fatal, this equated to a combined total of 39 major complication events (7.4%). During an aggregated total of almost 400 person-years of follow-up, the annualised event rates were 6.2 per 100 PY for death, 5.0 per 100 PY for all neurological events, and 9.8 per 100 PY for the combined outcome (Appendix 5). There were 10 ischaemic events, giving a rate of 2.6 (95% CI 1.3 to 4.8) per 100 PY.

Time to event Kaplan-Meier analysis was also undertaken. The registry reported that 1 year event free probability for mortality was 0.95 (95% CI 0.93 to 0.97); for neurological events was 0.96 (95% CI 0.93 to 0.98); for ischaemic events was 0.98 (95% CI 0.96 to 1.00); and for the composite measurement of death or neurological event was 0.92 (95% CI 0.89 to 0.95).

HES and ONS linked data

Linked data have superseded the registry data on medium term success (prevention of neurological events) as it is considered the most comprehensive estimate for these outcomes in this patient cohort. Detailed information on all-cause mortality, neurological events and composite outcomes (death or neurological events) are reported in Table 11. Using annualised incidence data, there was a death rate of 5.6 (95% CI 4.1 to 7.3) per 100 PY, a neurological event rate of 5.3 (95% CI 3.9 to 7.1) per 100 PY, and a combined rate of 9.9 (95% CI 7.9 to 12.3) per 100 PY. Most neurological events (67%) were ischaemic in nature, with a rate of 3.5 (95% 2.3 to 4.9) per 100 PY, compared with a haemorrhagic rate of 1.3 (95% CI 0.7 to 2.4) per 100 PY. These data are based on between 817 and 897 total PY follow-up.

The combined event free survival rate using Kaplan-Meier time to event analysis (freedom from death or neurological event) at 1 year was 0.92 (95% CI 0.89 to 0.95, n=387) and 0.83 (95% CI 0.79 to 0.87, n=196) at 2 years. Breaking this down to the constituent outcomes, freedom from neurological events was 0.949 (95% CI 0.929 to 0.970) after 1 year and 0.90 (95% CI 0.87 to 0.93) after 2 years; for mortality the corresponding rates were 0.95 (95% CI 0.93 to 0.97) and 0.90 (95% CI 0.87 to 0.934) for 1 and 2 years respectively.

The data reported from HES and ONS linkage were broadly comparable with that reported directly by the registry. This adds confidence to the results.

Comparison with literature

Proportional event data, measured as events per 100 PY follow-up, were the most widely reported outcomes of medium term efficacy reported in the identified published studies, and so were useful for making comparisons.

The efficacy outcomes for the registry and linked data, and those reported in the published literature (principally the PROTECT-AF [16] and PREVAIL trials [17]), are shown in Table 14. It is important to acknowledge that the studies and the CtE registry/linked data are not directly comparable because of differences in the sample population (Table 12) and definitions of outcome measures. There is additional uncertainty in comparing rates per 100 PY due to different follow-up durations.

The CtE registry and linked data reported a higher incidence of death, neurological events, and composite of these, than the RCTs. As the lower confidence intervals reported in the registry did not overlap with the upper confidence intervals reported in the RCTs, this suggests a real, significant difference in event rates [30]. Furthermore, the difference in point estimates is large, indicating the difference may be clinically important. It is important to consider these results within the context that there were differences in definitions of events (primary outcome, stroke, neurological event, or death), and that the populations were different (Table 12). However, the event rates are also high compared with those reported in the some of the other observational studies [28, 29], including the UK registry by Betts *et al.* (2016) [20], although death rates were similar in the ACP and ASAP registries.

Table 14: Summary of medium term efficacy outcomes (death and neurological event) from CtE registry, linked dataset (CtE registry/HES/ONS) and eligible studies.

Study		Patient number (PY) informing primary outcome	Primary outcome[1]	Death[2]	Neurological event/ stroke
			Reported in events per 100 person-years follow-up (with 95% CI where applicable).		
CtE registry		525 (402)	9.8 (7.0 to 13.4)	6.2 (4.0 to 9.2)	5.0 (3.0 to 7.8)
Linked dataset (CtE registry/HES/ONS)*		**460 (817)**	**9.9 (7.9 to 12.3)**	**5.6 (4.1 to 7.3)**	**5.3 (3.9 to 7.1)**
RCTs	PROTECT-AF[3] (LAAO arm)	463 (694)	3.0 (1.9 to 4.5)	1.0 (0.6 to 1.5)	1.5 (1.0 to 2.2)
RCTs	PREVAIL[4] (LAAO arm)	269 (N/A)	5.2	2.6	2.2
Observational studies	UK registry (Betts)	371 (706)	N/A	1.8	0.9
Observational studies	EWOLUTION registry	1014 (1325)	N/A	9.8	1.1[5]
Observational studies	ACP registry	1047 (1349)	N/A	N/A	2.3[6]
Observational studies	ASAP registry	150(175)	4.6	5.0	2.3

Abbreviations. N/A: Not available; PY: person-years.

* Preferred dataset.

1. Primary outcome of studies refers to composites of stroke, systemic embolism, and death, which differ slightly between studies. For the CtE registry, this composite consisted of death (by any cause) or any neurological event.
2. For the CtE registry, all deaths were included. For some studies, death was restricted to cardiovascular or unexplained death.
3. Data reported from seminal study (mean follow-up 18 months) [16]. Primary event rate in the extended follow-up study (mean 3.8 years) [31] was 2.3 (95% CI 1.7 to 3.2) per 100 person-years.
4. Event rate estimated by EAC from reported data (using raw event rates and median follow-up).
5. Ischaemic stroke. Combined rate for stroke, TIA, and systemic thromboembolism was 1.5 per 100 person-years.
6. Annualised rate reported (%), equivalent to events per 100 person-years. Thromboembolic event rate (ischaemic stroke plus systemic embolism).

The individual meta-analysis by Holmes *et al.* (2015) [22], which combined data from the PROTECT-AF and PREVAIL RCTs with the CAP and CAP2 registries (the CAP2 registry being an unpublished continued access extension of the PREVAIL trial), reported a rate of all-cause stroke or systemic embolism of 1.75 events per 100 PY. The rate of cardiovascular or unexplained death was reported as 1.1 per 100 PY. A stroke event rate of 1.8 (95% CI 0.7 to 2.5) per 100 PY was reported in the meta-analysis by Xu *et al.* (2016) [25] when studies reporting outcomes of 12 months or less were pooled. The rate was lower (1.2 [95% CI 0.8 to 1.5]) when studies reporting stroke rate from 12 months or longer were pooled.

There are several possible explanations for the ostensibly higher rates of neurological events observed in the CtE registry compared with the literature. Firstly, it may be that the outcomes being compared are not equivalent due to differences in terminology and definitions (that is, it is an “apples and pears” comparison). In the LAAO CtE database, in-hospital neurological events could be recorded by mechanism (ischaemic / haemorrhagic / undetermined / other) and type of event (CVA/RIND, TIA, other). However, at follow-up, only the mechanism of event was recorded. Additionally, there are inherent limitations with the interpretation of linked data (see Section 4.4.1). However, the broad alignment between registry and linked estimates does provide reassurance that the estimates of neurological event rate and death rates are accurate.

Secondly, the rate of neurological events should be considered in the context of time to event analysis and the nature and severity of the events. Time to event analysis of neurological events and death are illustrated by Kaplan-Meier curves in Figure 4. Of the 45 neurological events identified in the linked dataset, 5 occurred in hospital (4 reported in the CtE registry); one was haemorrhagic, two were undetermined mechanism, one with unreported mechanism but type was recorded as a CVA/RIND and one TIA. This is in contrast to the data from the RCTs and associated registries which reported no neurological events directly associated with the procedure [16-18, 21]. However, for three of these four CtE in-hospital events reported in the registry, the modified Rankin Scale score at 90 days post-event was recorded, showing that one patient had no symptoms (Rankin score 0) and the other two had some symptoms, but no significant disability (Rankin score 1). The fourth in-hospital event was an air embolism which resulted in the patient’s death. From the linked dataset there were a further 40 patients experiencing neurological events post-discharge from hospital, which consisted of 28 ischaemic events, 11 haemorrhagic events, and 1 event with unspecified type. Reversible neurological events such as TIA do not appear to have been reported in the published RCTs [16, 17]. Following hospital discharge, at least ten of the recorded events could be considered to be associated with failure of device efficacy (that is, they were ischaemic events that had not been prevented), although a causal link was not demonstrated.

Thirdly, the population receiving LAAO is likely to be different in the CtE registry (and also linked dataset) when compared with the population in the published literature, particularly the RCTs. Patients from the registry had a median $CHADS_2$ score of 3, and a median CHA_2DS_2-VASc score of 4, which was higher than patients enrolled in the PROTECT-AF and PREVAIL trials (mean $CHADS_2$ scores of 2.2 and 2.6 respectively) (see Table 9). Half (50%) of the patients in the registry had suffered a previous cardiovascular accident (CVA), compared with 18% in the PROTECT-AF and 28% in the PREVAIL trial. This means patients in the registry were at higher risk of ischaemic stroke than those in the trials. The relationship of CtE data with $CHADS_2$ and CHA_2DS_2-VASc scores are summarised in Question Two.

Finally, an important consideration is that the patients in the CtE registry (and most of the published observational studies) were at least relatively contraindicated for treatment with warfarin and did not take oral anticoagulation as part of their intervention, which further limits generalisability of the evidence, with the benefits observed in the PROTECT-AF trial largely being derived from a reduction in haemorrhagic rather than ischaemic stroke (see full literature review [9] for discussion). Patients in the registry had a relatively high risk of bleeding as measured by HAS-BLED score, and, as most (around 85%) were not receiving

oral anticoagulation, would not be expected to benefit from LAAO in terms of reduction in haemorrhagic stroke or bleeding events due to discontinuation of oral anticoagulation. The linked dataset reported a haemorrhagic stroke rate of 1.3 (95% CI 0.7 to 2.4) per 100 PY which was materially higher than observed in the intervention arm of PROTECT-AF trial (0.2 [95% CI 0.0 to 0.4] per 100 PY) and similar to the control arm (1.1 (95% 0.5 to 1.8) per 100 PY), highlighting the increased bleeding risk of the CtE cohort.

In-hospital complication rates

The CtE registry recorded detailed information about in-hospital complications and patient coverage for these outcomes was high. Overall, the composite rate of in-hospital complications described as major was 5.5% (95% CI 3.7 to 7.8%). Although the definition of in-hospital “major complication” differs slightly between studies, this figure from CtE is consistent with those published in the literature, which ranged from 2.2% (PREVAIL trial [17]) to 8.7% in the ASAP registry [29]. Due to granularity of ICD-10 codes it was not possible to correspond complications recorded in the CtE registry with those reported in HES APC. Additionally due to the limited descriptors, it was not possible to categorise complications as identified in HES APC as either major or minor. Therefore data reported directly from the registry was preferred.

Breaking down the complications that contributed to the major complication composite outcome, there was no evidence that complications in CtE were better, worse, or inconsistent with those published in the literature. No in-hospital deaths were reported in the RCTs, but the CtE rate of 1.0% (95% CI 0.3 to 2.2%) was consistent with three large published registry studies identified [18, 20, 21]. The rate of pericardial effusion requiring intervention (2.1%) was lower than that reported in the PROTECT-AF trial (4.8%) [16], but consistent with the other studies identified. The proportion of CtE patients experiencing device embolisation at 0.8% (95% 0.2 to 1.9%) was also consistent with other studies. Other major in-hospital complications were generally poorly reported in the literature, making comparisons difficult. The frequency of major in-hospital complications from the registry and published literature is reported in Table 15.

Table 15: Summary of major <u>in-hospital</u> complications for CtE and reported in the literature

Outcome	CtE registry	RCTs*		Observational studies				
		PROTECT-AF	PREVAIL	UK registry	EWOLUTION	ACP registry	CAP registry	ASAP registry
Major complication	**5.5% (3.7 to 7.8%)**	**NR****	**2.2%**	**3.5%**	**3.6 (95% CI 2.5 to 4.9%)*****	**5.0%**	**3.7%**	**8.7%**
Death	1.0% (0.3 to 2.2%)	0%	0%	0.25%	0.7%	0.8%	NR	0%
Neurological event	0.8% (0.2 to 1.9%)	1.1%	NR**	1.35%	0.1%	0.9%	0%	0.7%
Pericardial effusion (requiring intervention)	2.1% (1.1 to 3.7%)	4.8%	0.4%†	0.81%	0.3%	1.2%	2.2%	1.3%
Embolisation	0.8% (0.2 to 1.9%)	0.6%	0.7%	1.35%	0.02%	0.8%	NR	1.3%
Surgical intervention	1.9% (0.9 to 3.5%)	1.9%	NR	0.25%	NR	NR	NR	0.7%
Major vascular injury	1.0% (0.3 to 2.2%)	NR	NR	NR	NR	0.4%	NR	0.7%
Major bleed	1.9% (0.9 to 3.5%)	NR**	0.4%	0.54%	1.0%	1.2%	NR	1.3%
MI	0.4% (0.0 to 1.4%)	NR	NR	NR	NR	NR	NR	NR
AKI (Stage 2 or 3)	0.6% (0.1 to 1.7%)	NR	NR	NR	NR	NR	NR	NR
Endocarditis	0.4% (0.0 to 1.4%)	NR	NR	NR	NR	NR	NR	NR

Abbreviations. NR: Not reported.

* Intervention arm of RCT reported (WATCHMAN plus 45 days warfarin).

** Procedural and post-procedural data not disaggregated.

*** Device or procedure-related adverse event within 30 days of procedure.

† Requiring surgical pericardiocentesis.

Two of the most common adverse events associated with LAAO, major bleeding or haemorrhagic events, have been summarised in two meta-analyses. Wei *et al.* (2016) [24] reported a low frequency of haemorrhagic complications of about 1% (0.01 [95% CI: 0.00 to 0.01]) compared with a rate of 2.6% (95% CI, 1.5% to 3.6%) reported by Xu *et al.* (2016) [25]. The reported rate of pericardial effusion and/or tamponade was similar for both studies and consistent with the other studies, with rates of around 2% (0.02 [95% CI 0.02 to 0.03]) and 2.5% (95% CI 1.8% to 3.2%) respectively.

The incidence of minor in-hospital complications found in the CtE registry has been reported in Appendix 4. An incidence of 4.6% (95% CI 3.0 to 6.7%) reported from the CtE registry was numerically lower than the incidence of more serious adverse events. This compares with a rate of 2.2% reported in the UK registry by Betts (2016) [20] and 1.5% in the ACP registry [21]; however, these studies used different criteria in their definition. Numbers of events were too low in the CtE registry to provide a meaningful analysis of individual event type. It is possible that minor complications were underreported.

Conclusion

Data reported from the CtE registry suggest the rates of technical and procedural success (short-term efficacy) achieved by hospitals participating in the CtE programme are consistent with those published in the literature. HES and ONS linked data, corroborated by registry data, indicated the CtE population was at higher risk of stroke (as measured using the annualised rate of neurological events) following the LAAO procedure, compared with efficacy data that had been previously reported in RCTs and other observational studies. The death rate, although high, was consistent with the EWOLUTION registry [19], which had a similarly-risked population (Table 12). However, overall, the EAC considered that because of differences in the population (particularly concerning inherent stroke risk and the use of oral anticoagulation) and intervention in the registry cohort compared with trial data, clinical equivalence was inconclusive, and it was not possible to determine whether the medium-term efficacy rate was equivalent to other studies or not. The in-hospital major complication rate of LAAO of 5.5% reported in the CtE registry was consistent with that reported in the literature.

3.4.2 Question Two

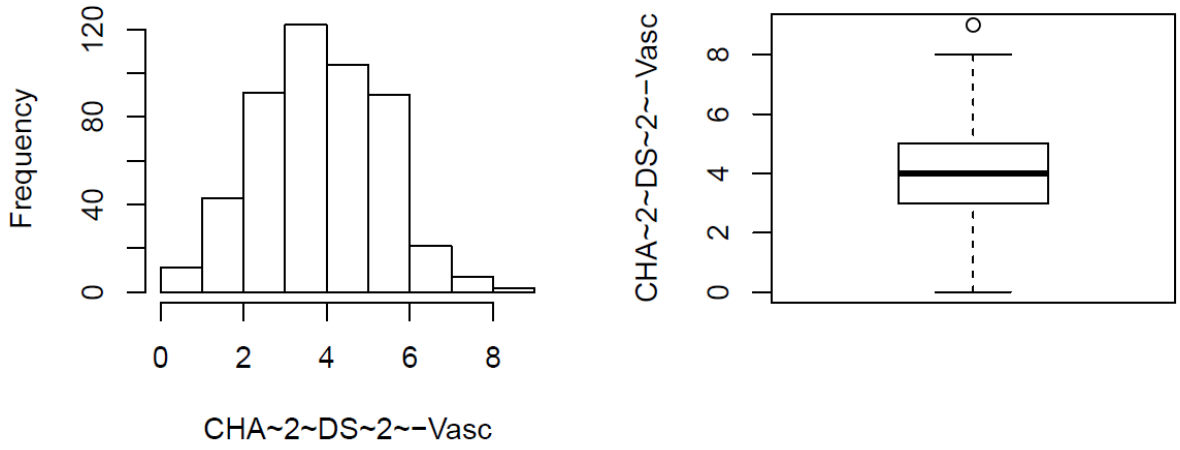
> "Does left atrial appendage occlusion offer patients a lower risk of stroke or other embolic clinical events in the short and medium term compared with those that would have been predicted on the basis of validated risk scores?"

The best known and most extensively used, validated risk scores for embolic stroke risk are the $CHADS_2$ and CHA_2DS_2-VASc scoring systems. The $CHADS_2$ system was developed from the amalgamation of two earlier algorithms developed from the Atrial Fibrillation Investigators (AFI) pooled data and data from the Stroke Prevention and Atrial Fibrillation (SPAF) investigators, and was validated in 2001 against a US database of Medicare insurance claimants (n=2121 PY) [32]. This system has since been largely superseded by the CHA_2DS_2-VASc scoring system, which has been validated in a European cohort of patients (n=1084 subjects) [33]. This has incrementally improved the $CHADS_2$ system by increasing the specificity of age and introducing gender and presence of vascular disease as

additional risk factors. The CHA_2DS_2-VASc algorithm is thought to be a superior predictor of thromboembolic risk [34] and has been incorporated into current NICE clinical guidelines on AF (CG180) [35].

All patients were assessed for their risk of stroke using the $CHADS_2$ and CHA_2DS_2-VASc scores, with patients only being eligible for the CtE registry if they had a CHA_2DS_2-VASc of 2 or more (and contraindications to oral anticoagulation) [4]. The median $CHADS_2$ score of the registry cohort was 3, with a range of 0 to 6. The median CHA_2DS_2-VASc score was 4, ranging from 0 to 9 (the lower range indicating some patients were enrolled who were not technically eligible, according to CtE patient selection criteria). The distribution of CHA_2DS_2-VASc scores is illustrated in Figure 6.

Figure 6: Distribution of CHA_2DS_2-VASc score illustrated by histogram and box and whisker plot (n=525)



The purpose of the risk scores is to predict the risk of an embolic event causing an ischaemic stroke or peripheral embolism in patients not receiving oral anticoagulation. There were ten ischaemic events and no peripheral emboli recorded by the CtE registry. This equates to a crude rate of 2.6 (95% CI 1.3 to 4.8) events per 100 PY. The ischaemic event rate as reported in the linked dataset (with more comprehensive coverage), was 3.5 (95% CI 2.3 to 4.9) per 100 PY. Although comparative statistical analysis is not possible, this result would be consistent with LAAO performing better for this outcome than historical controls not receiving anticoagulation, although confidence intervals do overlap in some instances (see Table 16).

Table 16: Incidence of ischaemic events and peripheral embolism in CtE registry and linked dataset alongside expected rates from the literature.

Risk algorithm system	Risk score (median score from registry)	Expected incidence of thromboembolic event (% per year)	Incidence of thromboembolic events from CtE registry (per 100 PY)	Incidence of thromboembolic events from linked dataset (per 100 PY)
$CHADS_2$ [32]	3	5.9 (95% CI 4.6% to 7.3%)*	2.6 (95% CI 1.3 to 4.8) 383 PY follow-up	3.5 (95% CI 2.3 to 4.9) 870 PY follow-up
CHA_2DS_2-VASc [33]	4	4.0**		
CHA_2DS_2-VASc [36]	4	At 1 year: 9.27 (95% CI 8.71% to 9.86%)*** At 5 years: 6.69 (95% CI 6.41% to 6.99%) At 10 years: 6.46 (95% CI 6.20% to 9.74%)		

*Adjusted rate from exponential survival model, assuming aspirin was not taken.
**Adjusted rate, assuming warfarin provides a 64% reduction in thromboembolic risk.
*** Adjusted rate (excluding patients receiving DOACs) estimates with 1, 5, and 10 years follow-up. Note: EAC has not appraised the source data of this study (from Danish national registry data).

All of the selected observational studies made comparisons with expected thromboembolic events from risk scores. The UK registry by Betts *et al.* (2016) [20] reported that the use of LAAO was associated with a relative risk reduction (RRR) of events of 90.1% and 87.2% compared with expected events using $CHADS_2$ and CHA_2DS_2-VASc scores respectively. The ACP registry by Tzikas *et al.* (2016) [21] reported an estimated 59% reduction in stroke rate compared with expected values using the CHA_2DS_2-VASc score. The update of the EWOLUTION study [19] reported a reduced relative risk of 84% in ischaemic strokes compared with expected values from CHA_2DS_2-VASc predictions.

An important caveat to the use of $CHADS_2$ or CHA_2DS_2-VASc scores is that they predict the frequency of embolic ischaemic events only. However, RCTs have indicated at least some of the benefit conferred by LAAO may be due to a reduction in the requirement for oral anticoagulation and a consequent reduction in the rate of haemorrhagic stroke [22]. It is unclear to what extent the CtE cohort benefitted from this.

Conclusion

Data reported directly from the CtE registry and linked dataset are consistent with LAAO conferring a substantial reduction in ischaemic embolic events as would be expected using $CHADS_2$ or CHA_2DS_2-VASc prediction scores.

3.4.3 Question Three

"Is left atrial appendage occlusion associated with an improved quality of life?"

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 (with quartiles) was 0.82 (0.68, 1.00). The median utility score improved slightly to 0.85 (0.75, 1.00) at 6 weeks, but this was not statistically significant, and remained relatively stable over the remaining course of follow-up (see Table 17). There was a significant increase in visual analogue scores (VAS) observed at 6 weeks (see *Supplementary Material - Table 8*).

Table 17: EQ-5D utility baseline and follow-up scores.

Time point	Utility score (Q1, Q3 quartiles) Number of participants (n)
Baseline (reference)	0.82 (0.68,1.00) 272
6 weeks	0.85 (0.75,1.00) 156
6 months	0.85 (0.74,1.00) 175
1 year	0.84 (0.74,1.00) 124
2 years	0.84 (0.66, 1.00) 40

One relevant study on QoL changes associated with LAAO was identified in the literature. This was the study by Alli *et al.* (2013) [26]. This was a piggyback study performed on the participants of the PROTECT-AF study (in both WATCHMAN arms) using the Short-Form 12 Health Survey (SF-12) measured at baseline and 12 months. The authors reported statistically significant improvements ($p < 0.050$) in QoL in the domains of total physical score, physical functioning, and physical role limitation. This was predominantly due to declining utility scores in those receiving warfarin rather than improvements in those receiving LAAO. There was no statistical improvement in QoL in the mental component domain. The authors of the study hypothesised that improvements in physical wellbeing were due to the knowledge that LAAO was protecting them against stroke which empowered them to be more active. Conversely, subjects receiving warfarin continued to have INR monitoring, dietary restrictions, and were at risk of bleeding which may have curtailed their physical activity. The authors noted that the relatively small sample size and short follow-up, as well as the potential for selection bias, were limitations of the study. This study, which compared patients on warfarin with those who had stopped taking warfarin (but were not contraindicated to it), lacks generalisability to the cohort represented by the CtE registry. Additionally, it did not use the EQ-5D system of QoL analysis favoured by UK guideline groups such as NICE.

Conclusion

CtE registry data showed no statistically significant differences in utility scores associated with the LAAO procedure, although there was a significant increase in VAS scores at 6 weeks. An increase of QoL in the domain of anxiety/depression domain would appear plausible (assuming reassurance conferred by lowering the risk of stroke) but has not been

demonstrated by CtE. One published study of limited generalisability reported that compared with patients continuing with warfarin treatment, LAAO may improve QoL in the physical domains. More research would be required to verify this in the population represented by the CtE registry.

3.4.4 Question Four

> "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)?"

This question cannot be answered through analysis of CtE registry data, which is limited to 2 years maximum follow-up within CtE funding. Out of 121 patients eligible for follow-up at 2 years, only 85 (70.2%) provided follow-up data, with no long-term cardiac complications recorded. The median follow-up time from the linked dataset was 729 days (almost 2 years), however long-term cardiac complications have not yet been investigated.

The literature search performed by the EAC identified observational studies with 4 years follow-up [37] and 5 years follow-up [38], but potential longer term complications, such as atrial wall erosion, were not reported. It is likely that reporting of rare long-term complications will be restricted to case reports, but these were excluded from the EAC's literature identification process.

Conclusion

The registry was designed to identify potential longer-term complications over 5 years, but curtailed to 2 years due to funding restrictions. The EAC is unaware of any signal from the literature to indicate LAAO devices are associated with specific cardiac complications.

3.4.5 Question Five

> "How many patients with atrial fibrillation with a contra-indication to oral anticoagulants (including previous significant bleed), or who have had a thromboembolic event despite being on oral anticoagulants, are candidates for left atrial appendage occlusion?"

This question cannot be fully addressed by data reported in the CtE registry, as the registry was principally concerned with recording explanatory variables and outcomes only in patients already selected for LAAO following a multi-disciplinary team (MDT) meeting. Of the 557 patients indicated for LAAO and eligible for CtE, 29 patients are recorded as not being treated and 24 have no record of successful device implantation (including one death). The reasons for this include unsuitable LAAO anatomy and presence of LAA thrombus. This indicates that, once, selected, the large majority of patients are suitable for the LAAO procedure. However, it is possible that patients undergoing MDT and not being selected for treatment were underreported.

The reasons for selection for LAAO treatment were recorded in the registry, with a 100% completion rate for patients funded through CtE (n=481). The reasons for treatment, together with the similar UK registry by Betts *et al.* (2016) [20], are reported in Table 18.

Table 18: Reasons for LAAO treatment in the CtE registry and registry by Betts *et al.* (2016)

Reason	Proportion of patients (%)	
	CtE registry	UK registry (Betts)
Previous bleeding without anticoagulant therapy	23.4	12.1
Previous bleeding with anticoagulant therapy	57.8	52.8
Embolic event despite use of oral anticoagulant	3.3	3.5
Intolerant of oral anticoagulant	6.9	5.1
Poor control of oral anticoagulation	0.4	3.2
Primary or secondary prophylaxis regardless of issues with anticoagulation	0.2	N/R
Patient preference	0.4	5.4
At risk of severe bleeding	7.1	17.6
Other	0.6	N/R
Abbreviations. N/R - Not recorded.		

The reasons for intervention with LAAO were similar for both registries, with a history of previous bleeding on oral anticoagulation being the indication for over 50% of cases. Less common indications included intolerance or poor control of oral anticoagulation, lifestyle issues, and the patient being considered to be at risk of serious bleeding without a prior history of it.

The absolute number of patients who could potentially benefit from LAAO in England (or any circumscribed area) is unknown but partly depends on strictness of the indication criteria. A survey of 86,671 AF patients found that only 2% of patients have an absolute contraindication to warfarin use, with 60% of these having had a prior intra-cranial haemorrhage [39]. However, in practice 13% of people with AF have been recorded as having a major contraindication to warfarin [40]. Novel oral anticoagulation drugs have a similar, but not exactly equivalent, range of contraindications, and may be suitable for some patients unable to take warfarin, for instance those with poor warfarin control (e.g. labile INRs). The prevalence of AF in England has been recently estimated to be 2.4%, which equates to 1.36 million people [41], with an estimated incidence of 1% in the over 65 population [42]. Given that the majority of the AF population contraindicated to anticoagulation are at relatively high risk of a thromboembolic event (e.g. 72% with CHA_2DS_2-VASc ≥ 2 [33]), this suggests the demand for LAAO nationally (England, with a population of 55 million [43]) may be between 19,500 people to 127,700 people, depending on the proportion of true contraindications for systemic pharmacotherapy. The incidence rate of new onset AF suggests that between 1400 and 9400 people aged over 65 years (comprising 1.7% of population [44]) may become eligible for LAAO each year. However,

following consultation, clinical experts consider the higher estimates of demand are improbable.

Conclusion

Data from the CtE registry cannot be used to specifically answer this question. However, the registry does provide information on the reasons for selection for LAAO, which were primarily concerned with the patients being contraindicated to warfarin (or DOAC) treatment due to previous bleeding episodes. Depending on how contraindication to warfarin (or DOACs) is defined, the EAC has calculated, using a top down approach, that between 19,500 and 127,700 people might benefit from LAAO in England, with 1400 to 9400 people over 65 years becoming eligible for treatment each year, with the lower limits being more plausible.

3.4.6 Question Six

> "Which devices are used to undertake LAAO and what are the device-specific efficacy and safety outcomes in CtE funded patients undergoing the procedure?"

The names and proportions of devices used in patients receiving LAAO reported in the CtE registry are listed in Table 19.

Table 19: Names of devices and proportions used in patients reported in the CtE registry.

Device type	Number of procedures		Proportion of procedures (%)	
Not specified	30		6.6	
WATCHMAN (Boston Scientific)	172		38.1	
AMPLATZER Cardiac Plug (ACP, St. Jude Medical)*	35	247	7.7	54.6
AMPLATZER Amulet*	212		46.9	
Coherex WaveCrest	3		0.7	
*Amulet is next generation of ACP device.				

In general, there were insufficient follow-up data to allow for disaggregated analysis and comparison of individual devices. It was not possible to determine if any device was associated with superior technical or procedural success as opened devices which were discarded before implantation were not recorded. For completeness, the EAC performed analysis comparing the two main device types (WATCHMAN vs. ACP/Amulet) in relation to efficacy in terms of death and neurological events, reported in Appendix 7. There was no statistical difference seen between devices. Additionally, there were no significant differences reported associated with device type and major or minor complications (*Supplementary Material - Table 5 and Table 6*).

There are only limited data comparing efficacy and safety of devices in the literature. The UK registry by Betts *et al.* (2016) [20] compared outcomes with patients undergoing LAAO with the WATCHMAN with ACP/Amulet. The authors found that the WATCHMAN device was associated with the use of significantly more peri-procedural anticoagulation (48.8%)

compared with ACP/Amulet (0.1%, p = 0.0001). There were no differences in terms of clinical outcomes.

The systematic review and meta-analysis by Wei *et al.* (2016) [24] compared pooled literature on the WATCHMAN, ACP, and PLAATO (discontinued) devices. The PLAATO device was associated with a significantly increased risk of all-cause death and cardiac or neurological death. The ACP device was associated with a significantly increased risk of thrombus formation on the device. Otherwise there were no significant differences detected between the WATCHMAN and ACP devices. A non-systematic review by Perotta *et al.* (2016) [45] reported on complications associated with LAAO devices. No significant differences between devices were reported.

Overall, the CtE registry and published data do not signal that there are differences in efficacy and safety between devices. A survey of European providers of LAAO found that around two thirds of centres exclusively use one type of device (principally WATCHMAN or ACP), with the remaining third using a mixture of devices [46]. In centres where a choice of devices is available, procedural safety and efficacy is likely to be confounded by patient selection.

Conclusion

There are insufficient data from the CtE registry to determine if the type of device used impacts on efficacy or safety. No evidence was identified in the EAC literature review that either WATCHMAN or ACP/Amulet is associated with superior clinical outcomes. Potential differences could be biased by patient selection, particularly in centres where a choice of devices is available (for instance allowing for anatomical matching).

3.4.7 Question Seven

> "Is the frequency of complications seen with the intervention clinically acceptable?"

The following recommendation (1.1) was made regarding LAAO in NICE IPG349 [47]:

> "Current evidence suggests that percutaneous occlusion of the left atrial appendage (LAA) is efficacious in reducing the risk of thromboembolic complications associated with non-valvular atrial fibrillation (AF). With regard to safety, there is a risk of life-threatening complications from the procedure, but the incidence of these is low. Therefore, this procedure may be used provided that normal arrangements are in place for clinical governance, consent and audit."

The CtE registry has not detected a safety signal that contradicts this recommendation (see Question One). The EAC has not identified additional clinical evidence published since IPG349 (June 2010) that flags a concern for the efficacy or safety of LAAO.

Conclusion

The frequency of complications seen with LAAO in the registry is consistent with previous studies. Data on complication rates from the CtE registry will help direct informed patient consent for future procedures.

3.4.8 Question Eight

> "Are clinical outcomes from left atrial appendage occlusion associated with particular patient characteristics (clinical or demographic)?"

Exploratory multivariate analysis was conducted on the CtE registry data, 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, LV ejection fraction, presence of LA thrombus, LA spontaneous echo contrast, LAAO morphology;
- In-hospital major and minor complications outcomes – covariates: procedure number (tertiles), gender, age, BMI, diabetes, eGFR, hypertension, medications, LV ejection fraction, presence of LA thrombus, LA spontaneous echo contrast, LAAO morphology and device used.

Therefore, a simpler set of covariates were tested for the CtE data and no significant association between age or sex and death was found (so being slightly older, younger, female, female and older, female and younger makes no difference to outcome in the CtE registry).

The PROTECT-AF trial [16] reported subgroup analysis on its primary endpoint (composite of stroke, cardiovascular or unexplained death, or systemic embolism at 18 months). It reported that there were no significant differences between the following subgroups: sex (male, female); age (<75 years, ≥ 75 Years); $CHADS_2$ score (1, ≥ 1); AF pattern (paroxysmal, persistent, and permanent); LAA ostium size (< median, ≥ median); LAA length (< median, ≥ median); left ventricular ejection fraction ([LVEF] < 60%, ≥ 60%).

The EWOLUTION registry [48], which focussed on procedural outcomes, did not find any relationship between subgroup type and procedural success. Additionally, risk of stroke, as measured by $CHADS_2$ and CHA_2DS_2-VASc scores, was not associated with increased risk of serious peri-procedural adverse events. However, an increased HAS-BLED score was associated with a significantly increased risk for adverse events, as was eligibility for anticoagulation. An observational study that included use of the WATCHMAN device (n=219) found that the presence of a device leak (measured using TOE) was not associated with an increased risk of thromboembolism [49].

Conclusion

No significant associations were found between age or gender and death in the CtE registry. There is limited evidence in the literature that increased bleeding risk may be associated with worse peri-procedural outcomes. However, the presence of residual leak after closure does not appear to be directly associated with worse longer-term clinical outcomes.

3.4.9 Question Nine

> "What are the full procedural costs of left atrial appendage occlusion to the NHS?"

Table 7 demonstrates that the forecast cost for an LAAO procedure ranges from about £9,600 to £13,600, with a central estimate of around £11,800 (2017/18 prices). The device cost included in each scenario is £[redacted] per patient (£[redacted] for one device) and it accounts for about [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. This also reported the devices used by manufacturer across centres. NHS Supply Chain provided the unit cost including VAT for each device for the main manufacturers. An additional 15% overhead was added to the NHS Supply Chain cost. These data enabled the EAC to calculate an average cost per device and per patient.

Under the central cost scenario the pre-operative pathway accounted for 7%, the procedure 77% and subsequent management 16% of total costs respectively.

3.4.10 Question Ten

> "What are the potential cost savings for the NHS through provision of left atrial appendage occlusion for appropriate patients?"

'Appropriate patients' has been construed as patients with non-valvular atrial fibrillation and an absolute or relative contraindication to anticoagulation therapy.

Cost consequences analyses were undertaken to compare the costs and clinical outcomes of LAAO plus medical therapy with medical therapy alone. This is reported in a separate output from the EAC [50]. Subsequently:

- All costs, except device costs, were updated to 2017/18 costs using the hospital & community health services index [14]. This was estimated to have increased by 1.8% in each of the two intervening years.
- The neurological event rates in the model were updated from CtE registry data inputs, using the preferred linked dataset.

This is a summary of the new analyses:

Where possible, linked data were used to inform the parameters in the economic model. The key costs modelled over a 15-year time horizon for each comparator were:

- LAAO procedure costs;
- NHS and social care costs to manage haemorrhagic and ischaemic strokes and TIAs;

- Costs of medication;
- Cost of bleeds for the events coded as such in the registry.

Total costs over the 15 years were reported from an NHS-only perspective and the wider NHS and social care perspective.

All patients entered the model aged 75 years, consistent with patients in the registry. In the LAAO arm, patients had a risk of strokes and bleeds at the rates observed at up to two years in the linked dataset (see event rates for ischaemic and haemorrhagic strokes in Table 11). These rates were extrapolated to 15 years. Patients in the comparator arm received medical therapy and were estimated to have stroke and bleeding risks in accordance with their baseline CHA_2DS_2-VASc and HAS-BLED risk scores. The estimated cost of the LAAO procedure was calculated using resource use data from the registry and a costing template completed by participating sites. Medication use was taken from registry data (see response to Question Nine). The medicines regimen prescribed to patients before the procedure was assumed to apply to those in the medical therapy arm, whilst the medicines prescribed at two years post-procedure were assumed to apply to patients after the LAAO procedure. NHS and social care costs associated with managing strokes were taken from a cost study conducted by the Sentinel Stroke National Audit Programme [53]. The study was based on patient-level health and social care costs for virtually all patients admitted to hospital with stroke in England and hence reflect current funding rules across the two sectors. Other costs were from national databases and updated to 2017/18 prices.

The model was run for a cohort of 1,000 people, with costs and patient outcomes aggregated for all patients for the 15-year time horizon (from 75 years to age 90 years). Costs were discounted at 3.5% per year.

The results from the base case are those which use the best point estimates for all the parameters that inform the model. Hence its results are the best estimate of the total costs.

Table 20 presents total costs for NHS components under the base case assumptions. The total NHS discounted cost of the LAAO pathway was estimated at £15,491 per patient. The procedure and bleeds recorded in the registry prior to discharge, accounted for 76% of these costs. Management of strokes and TIAs was the second largest component (15%), followed by medicines (8%), with subsequent bleeds accounting for the balance of 1%.

The total discounted cost of the medical therapy pathway was estimated at £8,694 per patient. Management of haemorrhagic and ischaemic strokes and TIAs was the largest component (76%), followed by medicines (18%), with bleeds accounting for the balance of 6%.

Hence the discounted NHS costs were £6,797 per person higher in the LAAO arm, a 78% increase on the cost of medical therapy only. The benefit from avoided stroke management and medication costs of almost £5,034 per patient with LAAO was insufficient to offset the initial procedure costs of about £11,800 per patient. The cost of the procedure would need to reduce by 58% to £5,000 before the NHS could achieve financial breakeven on the procedure.

If costs were not discounted then the additional cost per patient with LAAO was about £5,732, with a procedure cost reduction of 51% to £6,065 required before financial breakeven could be achieved.

Table 20: Total NHS costs per patient over a 15-year time horizon.

	Discounted costs per patient			Undiscounted costs per patient		
	LAAO	**MT**	**Difference**	**LAAO**	**MT**	**Difference**
Procedure & bleeds	£11,831	£0	£11,831	£11,831	£0	£11,831
Medication	£1,170	£1,617	-£447	£1,435	£1,963	-£528
Ischaemic stroke (NHS)	£1,717	£4,677	-£2,960	£2,099	£5,704	-£3,605
Haemorrhagic stroke (NHS)	£491	£1,729	-£1,238	£621	£2,125	-£1,504
TIA	£44	£166	-£122	£54	£200	-£146
Bleeds	£238	£505	-£267	£291	£606	-£316
Total	**£15,491**	**£8,694**	**£6,797**	**£16,330**	**£10,598**	**£5,732**

With the inclusion of social care costs both arms had similar costs, with the LAAO arm having total discounted costs of about £18,725 per patient and medical therapy £18,551 per patient, a higher cost of £174 per patient with LAAO. This is less than 1% of the pathway costs and indicates cost equivalence between the two technologies. Evidence from the Stroke Audit costs [53] shows that 60% of the costs to manage strokes are incurred in social care. Adopting an NHS perspective removed the majority of the stroke-related savings and switched the procedure from being cost-neutral to cost-incurring.

Sensitivity analyses identified that the model's results were sensitive to changes in the relative risk reduction ratios for stroke following an LAAO procedure, the costs to manage strokes and the cost of the LAAO procedure. Removing the 15% overhead on the device cost included within the procedure cost in the base case, reduced the incremental increase in the total cost of the LAAO procedure to £5,702 per patient, from £6,797. Changes in other parameters had little impact on the absolute saving from LAAO over medical therapy.

3.4.11 Question Eleven

> "Is left atrial appendage occlusion cost-effective from the perspective of the NHS?"

The response to Question Ten has identified that an economic model estimated an incremental cost to the NHS of about £6,800 per patient with an LAAO procedure compared with medical therapy only. When the wider health and social care perspective is adopted the model predicted that implementing LAAO will be cost neutral for NHS and social care providers.

The model also reported changes in clinical outcomes as identified in Table 21. Numbers are rounded, hence tables may not sum precisely.

Table 21: Comparison of clinical events per 1,000 patients over a 15-year horizon.

	LAAO	MT	Difference	Percentage change with LAAO
Ischaemic stroke	118	318	-201	-63%
Haemorrhagic stroke	30	97	-68	-70%
Subsequent strokes	32	91	-60	-65%
TIA	53	195	-142	-73%
Deaths	670	768	-98	-13%
Life years	11.1	9.9	1.2	13%

The model predicted that over 15 years the total number of strokes per 1,000 patients (ischaemic, haemorrhagic and subsequent strokes) may reduce from over 500 when patients are managed only on medical therapy to under 180 following an LAAO procedure, a reduction in strokes of about 330 or 65%. This is equivalent to a reduction in all-stroke risk from over 50% to 18%. Associated with this reduction were almost 100 forecast fewer deaths in the cohort receiving the LAAO procedure.

The reduction of 65% in the absolute risk of strokes is derived using the observed ischaemic and haemorrhagic stroke rates reported in the linked dataset (Table 11). The rate is reasonably consistent with the range of 66% to 87% reported in a number of clinical studies of LAAO compared with medical therapy (see Section 2 of the separate report [52]).

The key uncertainties with the clinical analyses are the validity of:

- Using the predicted stroke rates from the CHA_2DS_2-VASc tool for the medical therapy arm;
- Extrapolating the observed risk reduction in strokes from the registry at 2 years to 15 years;
- Extrapolating stroke costs over 15 years given the population are already aged 75 years.

In addition to the estimated life years gain of 1.2 years with LAAO compared with medical therapy over the 15 years, patients will receive a benefit from improved quality of life as a consequence of fewer strokes. This benefit was not measured in the CtE register although it did provide a measure of the procedure-related gain in quality of life (see response to Question 3).

The quality of life benefit associated with fewer strokes would be essential to inform a cost utility analysis where results are expressed as an incremental cost per quality adjusted life year. However, NICE advised the EAC that this form of analysis was not requested by NHS England.

With cost consequences analysis, the decision makers do not have a threshold-based decision rule to inform their decisions on cost effectiveness. Hence it is not possible for the EAC to advise from an NHS perspective, whether the additional cost to the NHS of about £6,800 is cost-effective, given the forecast savings in strokes and deaths.

Adopting the wider NHS and social care perspective, the EAC can conclude the LAAO procedure is cost-effective compared to medical therapy. Costs are broadly equivalent between the two arms and LAAO is associated with material clinical and patient benefits from avoided strokes and associated reduced mortality.

3.4.12 Summary of Answers to NHS England Questions

Answers to the NHS England questions are summarised in Table 22.

Table 22: Summary of NHS England answers

Final version of question, as amended by NICE following discussion with EAC	Summary answer
1. Can UK clinical teams reproduce the short and medium success rates for left atrial appendage occlusion reported in existing clinical trials, with equivalent or lower complication rates?	Procedural efficacy data reported from the registry are largely complete and consistent with published data from RCTs and observational studies. Approximately nine in ten LAAO procedures result in procedural success (closure of LAA without major complication). Medium term efficacy (measured as the rate of neurological events, ischaemic events and/or death) was higher in the linked dataset compared with published data (mainly from RCTs). However, interpretation is limited by issues with generalisability because the patients in the registry were at greater risk of neurological events compared with the patients enrolled in RCTs, and because they were in most cases not eligible for oral anticoagulation (see Table 12). The rate of major complications reported by the CtE registry appears to be consistent with that published in the literature.
2. Does left atrial appendage occlusion offer patients a lower risk of stroke or other embolic clinical events in the short and medium term compared with those that would have been predicted on the basis of validated risk scores?	Point estimate data reported from linked dataset on the incidence of post-procedural ischaemic events is consistent with LAAO conferring a protective effect. However, this effect cannot be validated statistically.
3. Is left atrial appendage occlusion associated with an improved quality of life?	CtE registry data showed no significant changes in individual quality of life (EQ-5D) components or utility scores over time. The median visual analogue scale (VAS) score at 6 weeks showed a statistically significant improvement compared to pre-procedure. One QoL study identified in the literature reported LAAO was associated with significant improvements in QoL in the physical domains after 1 year.
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)?	The registry did not follow-up patients for sufficiently long enough to answer this question.

Final version of question, as amended by NICE following discussion with EAC	Summary answer
5. How many patients with atrial fibrillation with a contra-indication to oral anticoagulants (including previous significant bleed), or who have had a thromboembolic event despite being on oral anticoagulants, are candidates for left atrial appendage occlusion?	This question could not be answered using data from the registry. Using published data, the EAC has estimated that the unmet need of LAAO could range from 19,500 to 127,700 people, with 1400 to 9400 patients over 65 years becoming eligible each year. This represents a crude estimate and is dependent on the precise indication definitions for LAAO.
6. Which devices are used to undertake LAAO and what are the device-specific efficacies and safety outcomes in CtE funded patients undergoing the procedure?	The CtE registry reported that the ACP/Amulet devices and WATCHMAN devices dominated the market with 54.6% and 38.1% usage respectively. An analysis of efficacy in terms of death and neurological event between WATCHMAN and ACP/Amulet devices showed no statistical differences between the two manufacturers. There was no significant difference reported in the proportion of major and minor complications.
7. Is the frequency of complications seen with the intervention clinically acceptable? (This question has already been considered by the NICE Interventional Procedures Advisory Committee when developing the IP guidance on this procedure. 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).	There was no safety flag identified from the registry data that would require an update of NICE IPG349.
8. Are clinical outcomes from left atrial appendage occlusion associated with particular patient characteristics (clinical or demographic)?	There were insufficient data reported in the registry to allow for subgroup analysis.
9. What are the full procedural costs of left atrial appendage occlusion to the NHS?	The central estimate of the cost of an LAAO procedure is about £11,800, range £9,600 to £13,600.
10. What are the potential cost savings for the NHS through provision of left atrial appendage occlusion for appropriate patients?	The LAAO procedure plus medical therapy is estimated to have higher NHS-related costs of about £6,800 per patient compared to medical therapy only over a 15-year time horizon from the date of the procedure.

Final version of question, as amended by NICE following discussion with EAC	Summary answer
11. Is left atrial appendage occlusion cost-effective from the perspective of the NHS?	In a cohort of 1,000 patients with similar characteristics to those in the registry, over a 15-year period, the LAAO procedure plus medical therapy was estimated to reduce strokes from over 500 when patients are managed only on medical therapy to about 180, a reduction in strokes of 328 or 65%. Associated with this reduction were almost 100 forecast fewer deaths in the cohort receiving the LAAO procedure, giving a life-year gain of 1.2 years. The EAC cannot advise whether the additional cost to the NHS of £6,800 per patient is cost-effective given the forecast savings in strokes and deaths.

Section 4: Discussion

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

The CtE registry enrolled a total of 571 patients, of which 525 were included (with 46 patients not meeting inclusion criteria). Included patients had a median age of 75 years, median CHA_2DS_2-VASc of 4, and median HAS-BLED score of 4. Five hundred and nine patients (97.0%) recorded both admission and discharge data, allowing for procedural analysis. Medium term safety and efficacy outcomes were reported in follow-up information in 82.4% procedures at 6 weeks, 80.9% at 6 months, 76.1% at 1 year and 70.2% at 2 years. There were no significant differences in clinical characteristics between patients who were followed up and all patients at baseline except for device used.

Most patients received either a WATCHMAN (38.1%) or AMPLATZER (Amulet/ACP) device (54.6%). Device implantation was technically successful in 93.6% of patients, and was regarded as a procedural success in 89.0% of cases (technical success in absence of major complication). The large majority of patients had one night stay in hospital. There was an in-hospital rate of major complications (defined as death, neurological event, pericardial effusion requiring intervention, embolization, surgical intervention, major vascular injury, major bleed, myocardial infarction, acute kidney injury at Stage 2 or 3 and endocarditis) of 5.5% and minor complication rate of 4.6%.

The primary efficacy outcome of the CtE registry, a composite measure of all-cause mortality and neurological events, was 9.8 (95% CI 7.0 to 13.4) events per 100 PY, over an aggregated follow-up period of almost 400 PY. Of the 19 neurological events reported, 10 were ischaemic and 4 were haemorrhagic in origin, with 4 of undetermined cause and 1 CVA/RIND reported. The crude event rate for ischaemic events was 2.6 (95% CI 1.3 to 4.8) events per 100 PY follow-up. Two deaths were attributed to ischaemic stroke. Data on the primary efficacy of LAAO in the registry has been superseded by linked data (Section 4.2).

The central estimate of the cost of the procedure was £11,800 (range £9,600 to £13,600). [redacted] the cost was associated with the device ([redacted]%), with additional costs being incurred by investigations ([redacted]%); staffing costs ([redacted]%); consumables (5%); hospital stay (5%); theatre time (4%), and outpatient follow-up (2%).

Analysis of limited EQ-5D data indicated that the use of LAAO had minimal impact on quality of life in any of the domains, as would be expected with a preventative intervention.

4.2 SUMMARY OF FINDINGS FROM PRIMARY DATA COLLECTION (DATA LINKAGE)

By linking the registry to HES APC and ONS routine datasets, a total of 45 'new' neurological events (30 ischaemic, 12 haemorrhagic, 3 unknown type) and 50 deaths were identified; however, given the extended length of follow-up at 817 PY, the total event rate of this composite outcome remained comparable at 9.9 (95%CI 7.9 to 12.3) events per 100 PY follow-up. By conducting data linkage we were able to identify 28 additional neurological events and 31 additional deaths which were not captured in the registry – demonstrating limited coverage of the registry. This was related to the poor completion of follow-up records in the registry, and also due to events occurring at different hospitals (and not identified by the LAAO treating centre completing the registry). It is important to note that as of 14th September 2018, only 13/45 neurological events have been externally validated.

Of the 50 reported deaths, 9 were reported as caused by a neurological event (6 haemorrhagic, 2 ischaemic, 1 unknown) and 12 were reported as caused by malignant neoplasm (3 of which were diagnosed pre-LAAO procedure). It is important to note that, 49/50 identified deaths were reported in ONS, with the remaining death being confirmed by registry and HES.

Additionally, there were also 5 new cases of vascular dementia reported post-LAAO procedure.

4.3 RESULTS IN THE CONTEXT OF OTHER STUDIES

The EAC performed a literature search which identified key studies published on percutaneous LAAO through the endocardial approach. Two RCTs and three observational studies were selected from the body of evidence as being most useful in providing data to contextualise the results of the CtE registry.

The CtE registry provided good data on the procedural efficacy and in-hospital safety of LAAO. These data were consistent with those reported in the literature, indicating that English centres participating in CtE were performing the procedure to an expected standard.

Medium-term efficacy data (neurological events and death) was available in 70% of patients at 2 years follow-up. There was some indication that the efficacy of LAAO in preventing these events, as measured directly by the registry and using linked data, was inferior to that seen for similar outcomes in the RCTs and observational registries, with the lower CI not overlapping with CIs or point estimates reported in the published literature (see Table 14). The neurological event rate also appeared to be substantially higher in the CtE registry compared with published studies. Two deaths were recorded in the registry as being due to ischaemic stroke. However, no firm conclusions could be drawn on the relative efficacy and safety of LAAO because patients enrolled in the registry were known to be at higher risk of ischaemic events than those reported in the RCTs and were, in the main, not receiving oral anti-coagulation.

Currently the only direct, comparative data published on LAAO is restricted to the PROTECT-AF [16] and PREVAIL [17] RCTs. These non-inferiority trials, discussed in the

EAC literature review [9], did not provide evidence of equivalence of the WATCHMAN device with oral anticoagulation. Furthermore, they did not investigate the efficacy and safety of LAAO in the population of interest, which are primarily people who are unable to take warfarin or DOACs. This gap in the evidence base has not been fully addressed by observational studies, which lack a control arm.

Recently, the protocol for a new RCT has been published which should provide clarity on the effectiveness of LAAO in patients unable to receive oral anticoagulation. The Assessment of the WATCHMAN Device in Patients Unsuitable for Oral Anticoagulation (ASAP-TOO) trial [51] will be a relatively large trial (n=888) with long-term outcomes (5 years) performed in patients (CHA_2DS_2-VASc ≥ 2) contraindicated to warfarin. The RCT will compare the safety and efficacy of the WATCHMAN device with the use of antiplatelet monotherapy or no treatment. This RCT should provide valuable data that may resolve the uncertainties discussed. However, the trial is not due for completion until 2023.

The EAC identified 15 economic studies, of which 1 was considered to have good internal and external validity [48]. This study, which used data from a UK hospital registry, reported that LAAO was potentially cost-saving over a time horizon of 10 years compared against other therapies such as anticoagulation. Other studies have also indicated LAAO may be cost-effective in the longer-term, but these studies are limited in generalisability due to the perspective, setting and application of clinical data (which were derived from the non-generalisable PROTECT-AF and PREVAIL trials of the WATCHMAN device).

In summary, the EAC has identified some concerns regarding the efficacy of LAAO 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 inferior in the registry compared with much of the published literature. The EAC considered that this was likely to be due to the limited generalisability of the published studies, particularly the RCTs which featured a different (lower risk) population and intervention (which included warfarin). However, if LAAO in the CtE setting is not as effective as predicted, this could also have consequences for the economic benefits of the procedure. Therefore, further research may be warranted.

4.4 LIMITATIONS AND STRENGTHS

4.4.1 Limitations of primary evidence

The CtE registry was a single armed study and thus comparisons had to be made implicitly with results published in the literature [52]. 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 drugs). Secondly, much of the published literature was not directly generalisable to the data collected from the CtE registry, thus inferences of equivalence (or not) are subject to considerable uncertainty.

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

- The registry was funded for a maximum follow-up of 2 years. 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 525 patients eligible for analysis (Appendix 1), only 121 (25.8%) had an LAAO device implanted, were still alive at the previous follow-up hospital visit and had reached 2 years since their date of procedure (*Supplementary Material – Table 3*). It is possible that this cohort of patients receiving treatment early in the project may not be representative of the overall cohort (e.g. because patients were prioritised on the waiting list due to pressing clinical needs, or because of the potential for learning curve issues);
- 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.

In conducting data linkage the following assumptions were also made:

- We assume that the identifiers and matching process matched were correct for the 460 patients who did not have a red flag (i.e. who had no conflicting data fields appearing across the 3 data sources to suggest otherwise).
- The proportion of patients with a "red flag" associated with their data linkage (35/495; 7%) is higher than we expected in a well-characterised cohort. In excluding these patients we have assumed that the remaining 460 are i) representative of all those successfully implanted and ii) have had their data successfully linked.
- ONS is regarded as the gold standard of death reporting; however, there is a delay in some deaths appearing in the ONS mortality dataset due to lack of death certification (i.e. those under investigation). Therefore 1 additional death recorded in the registry and confirmed in HES but not appearing in ONS was included in our total number of deaths.
- Long-term follow-up in the registry was poor, therefore long-term analysis (post-LAAO discharge) relied on HES/ONS data due to more comprehensive coverage.
- The total number of post-procedural neurological events from HES may have included events which were historic but mis-coded as "new" neurological events. To minimise the effect of this, we retrospectively created an additional set of validation rules, and highlighted all discrepancies with the registry developer. Six responses were received from the centres (4 indicating error in registry, 1 indicating error in HES and 1 unknown).This highlights a higher error rate in the registry than HES.
- Due to limitations with routine datasets (i.e. ONS only including registered deaths from England and Wales, HES APC only including NHS episodes of care conducted in hospitals in England) it is likely that the estimated event rates represent lower estimates, due to incomplete data coverage.
- All 50 deaths were validated by either ONS (49/50 deaths captured in ONS as gold standard of death reporting) or by registry and HES (1/50 deaths). However, only 13 of the 45 neurological events were validated following data linkage (10 confirmed by registry and HES/ONS, 3 identified only in HES and verified externally by treating centre) at the time of setting the validation rules for analysis (14th September 2018).

Responses from NICOR to the technical issue log (post-data analysis, 9th November 2018) confirm that:

- 1 neurological event (identified in the registry only) was confirmed as an error in reporting;
- a total of 22 out of the remaining 44 neurological events have been validated (10 reported in HES/ONS and registry, 7 in HES not registry but event was confirmed by centre, 4 in both HES and ONS but not registry, 1 in registry not captured in HES but centre confirmed event occurred in Wales which is not in HES catchment);
- in 7 cases the centre responded to state they were unable to validate the event as it occurred at a different organisation and not documented within their local records;
- centre responses were not available for the remaining 15 neurological events (5 identified by registry only, 9 identified by HES only and occurring at a different hospital, 1 identified by HES only and occurring at the same treating hospital).

Therefore at least 38 of the 45 neurological events have been either independently validated or conflicting information between the registry and HES data sources have been satisfactorily explained.

4.4.2 Strengths of primary evidence

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

Secondly, following an initial disappointing response from centres in providing follow-up data, this improved considerably such that there was about 400 PY follow-up available for analysis. This improved the precision and certainty of time-to-event analysis. Where follow-up was achieved (for 70.2% of eligible patients [n=121] at 2 years), the completion of individual data fields varied, but overall, data completeness was regarded as good. The number reporting results for each data field are presented in the *Supplementary Material* to this report.

Thirdly, patients from the CtE registry were linked with HES APC and ONS data, which provided a more comprehensive estimate of mortality and neurological event rates due to increased coverage and longer total duration of follow-up. Results from the linked dataset were relatively concordant with the CtE registry, lending some confidence that the results were accurate.

Finally, the CtE registry reported important clinical outcomes. In addition, the registry captured quality of life and medication data (not captured in HES APC) 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.

In addition to the strengths (and limitations) of the registry, it should be considered that it provided patients with access to treatment they might have otherwise forgone. This is important in the case of this population with AF, as LAAO represents the only treatment

modality (other than generally ineffectual antiplatelet treatment) available to them in the prevention of ischaemic stroke.

Section 5: Conclusions

The LAAO CtE registry included 525 patients who had AF and were at high risk of ischaemic stroke (median CHA_2DS_2-VASc of 4) and had a contraindication to oral anticoagulation (warfarin or DOAC). 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 a bespoke review [3], were made in order to answer 11 questions asked by NHS England.

The registry reported a technical success rate of 93.6% (91.1% to 95.6%) and a procedural success rate of 89.0% (86.0% to 91.6%), indicating the procedure was successful in about 9 out of 10 patients. There was an in-hospital major complication rate of 5.5% (3.7 to 7.8%). These short-term results were consistent with values reported in the literature.

The CtE registry reported a total of 10 ischaemic events over the course of about 400 PY, giving a rate of 2.6 (95% CI 1.3 to 4.8) per 100 PY. The linked dataset, with more comprehensive coverage, reported a total of 30 ischaemic events, at a rate of 3.5 (95% CI 2.3 to 4.9) per 100 PY. Both estimates are numerically lower than that observed in epidemiological studies of patients receiving no treatment, but statistical analyses could not performed to test this (due to data heterogeneity and lack of patient level reporting).

Twenty five deaths were reported in total in the registry, five of which occurred in hospital. The CtE registry reported a composite of (all-cause) death or neurological event rate of 9.8 (95% CI 7.0 to 13.4) per 100 PY. The linked dataset reported all-cause mortality or neurological events in a total of 81 patients (50 deaths, 45 neurological events – with 14 fatal neurological events) but a similar rate of 9.9 (95% CI 7.9 to 12.3) per 100 PY. These event rates were substantially higher than those reported in RCTs in patients receiving LAAO [16, 17]. However, an important limitation of this comparison was that the registry and RCT populations, and to a lesser extent interventions, were not generalisable. That is, it has been shown that patients enrolled into the CtE registry had a greater underlying risk of stroke compared with those enrolled in the RCTs.

The registry did not report important changes in quality of life associated with LAAO, and was not designed to detect long-term adverse events beyond the 2 year time horizon. Although it was not possible to directly estimate the amount of people who may benefit from the intervention in England, it is likely to number in the thousands. An additional survey performed by the EAC indicated the overall cost per procedure was on average £11,800, with a range of £9,600 to £13,600.

It is known that the risk of thromboembolic stroke in people with AF can be significantly reduced using oral anticoagulation in the form of warfarin or DOACs. For people with genuine contraindications to these drugs, LAAO may be the only viable treatment option. The CtE registry has demonstrated that LAAO may reduce stroke risk compared to historical controls; however, it has not demonstrated equivalence of efficacy compared with patients participating in RCTs who were not contraindicated to warfarin. At present, there are no comparative studies that demonstrate the efficacy of LAAO in the population represented by the CtE. This issue should be resolved with the publication of the ASAP-TOO trial [51], but

this is some years away. In the meantime, the evidence for the use of LAAO in patients contraindicated to oral anticoagulation, including evidence generated from this registry, is restricted to uncontrolled observational studies, and as such is somewhat equivocal.

Economic modelling suggests that the procedure will increase costs to the NHS by about £6,800 but would be financially neutral if a wider NHS and social care perspective is adopted. Based on the registry data only (linked data not used in economic modelling) recorded stroke event rates at two years, extrapolated over 15 years, the procedure is forecast to deliver large reductions in the potential number of strokes and deaths compared with medical therapy. With cost consequences analysis, decision makers do not adopt a threshold-based decision rule to inform their decisions on cost effectiveness. Hence it is not possible for the EAC to advise from an NHS perspective, whether the additional cost to the NHS of £6,800 is cost-effective given the forecast savings in strokes and deaths. If the wider NHS and social care perspective is adopted the EAC can advise the procedure is cost-effective, having similar costs to current practice but material clinical benefits.

Section 6: Acknowledgements

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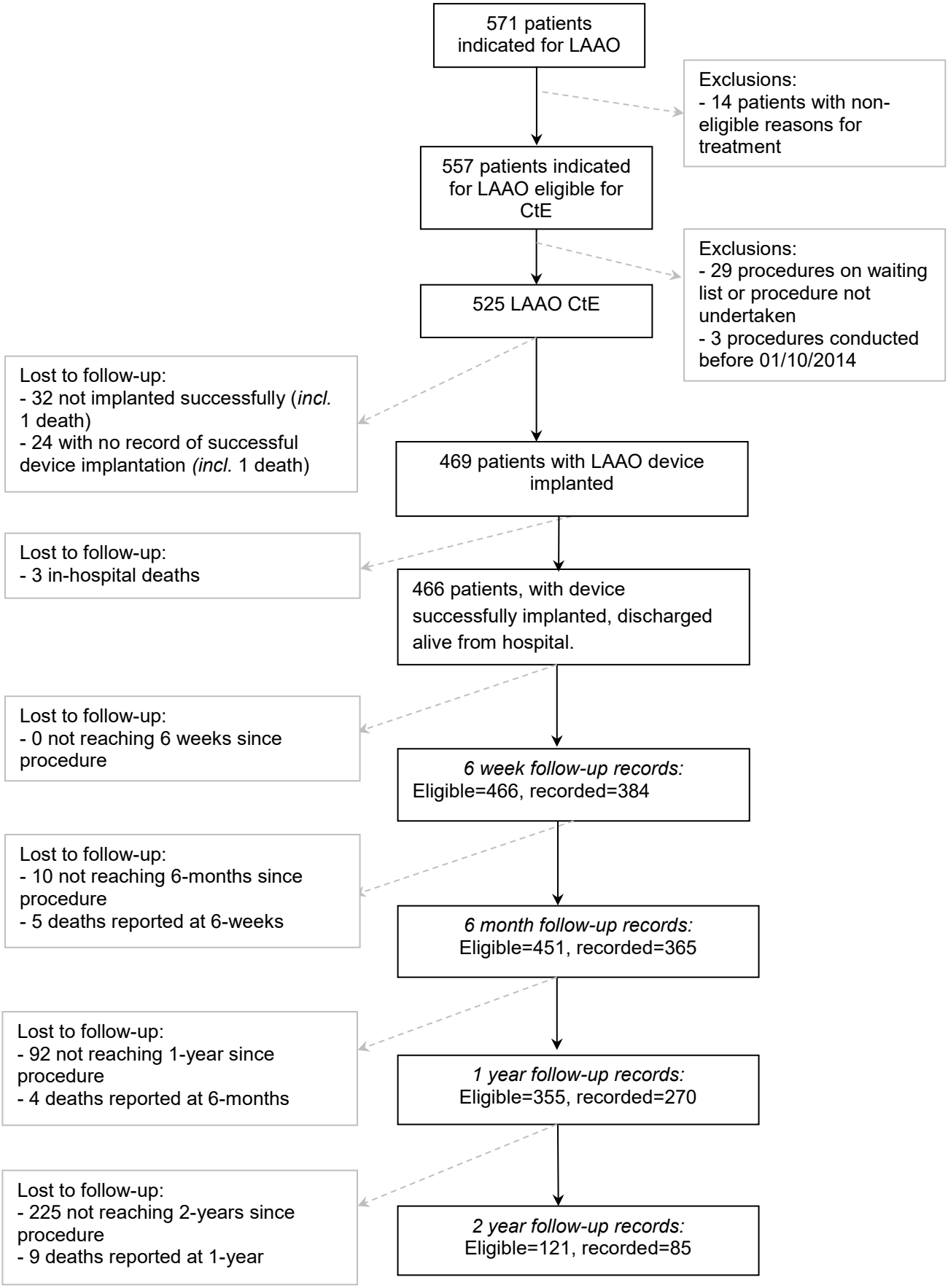
Appendix 1 – Data Flow Diagram – CtE Registry



Appendix 2 – Patient Characteristics – CtE Registry

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

Patient characteristic†	All eligible LAAO patients (n=525)	All patients with follow-up (n=440)	p-value
Female	164 (31.3%)	139 (31.7%)	0.94
Age, years median (Q1,Q3) [range]	75 (70,80) [43-92]	75 (70,80) [43-92]	0.76
BMI, kg/m^2 median (Q1,Q3) [range]	27.1 (24.3,31.1) [10.1-46.1]	27.6 (24.5,31.2) [10.0-46.1]	0.50
Ethnic origin:			0.85
Caucasian	501 (96.5%)	422 (97.0%)	
Black	6 (1.2%)	5 (1.1%)	
Asian	8 (1.5%)	4 (0.9%)	
Other	4 (0.8%)	4 (0.9%)	
Diabetes:			0.97
No	382 (73.6%)	325 (74.0%)	
Yes (not insulin)	120 (23.1%)	101 (23.0%)	
Yes (insulin)	17 (3.3%)	13 (3.0%)	
eGFR median (Q1,Q3) [range]	68 (54,82) [6-274]	69 (55,82) [6-262]	0.64
$CHADS_2$ median (Q1,Q3) [range]	3 (2,4) [0-6]	3 (2,4) [0-6]	0.97
CHA_2DS_2-VASc median (Q1,Q3) [range]	4 (3,5) [0-9]	4 (3,5) [0-8]	0.97
HAS-BLED median (Q1,Q3) [range]	4 (3,5) [1-6]	4 (3,5) [1-6]	0.92
NYHA			0.99
No limitation of physical activity	186 (42.4%)	153 (41.9%)	
Slight limitation of ordinary physical activity	194 (44.2%)	164 (44.9%)	
Marked limitation of ordinary physical activity	54 (12.3%)	445 (12.1%)	
Symptoms at rest or minimal activity	5 (1.1%)	4 (1.1%)	
EHRA AF			1.00
No AF-related symptoms	218 (52.0%)	183 (52.0%)	
Mild symptoms; normal daily activity not affected	184 (43.9%)	155 (44.0%)	
Severe symptoms; normal daily activities affected	15 (3.6%)	13 (3.7%)	
Disabling symptoms; normal daily activity discontinued	2 (0.5%)	1 (0.3%)	
Smoking status:			0.86
Never smoked	255 (54.3%)	221 (55.1%)	

Patient characteristic†	All eligible LAAO patients (n=525)	All patients with follow-up (n=440)	p-value
Ex-smoker	202 (43.0%)	167 (41.6%)	
Current smoker	13 (2.8%)	13 (3.2%)	
Dialysis status:			1.00
No	505 (99.0%)	430 (99.1%)	
Acute	1 (0.2%)	0 (0.0%)	
Chronic	4 (0.8%)	4 (0.9%)	
Rhythm history:			0.99
No arrhythmias	5 (1.0%)	4 (0.9%)	
Paroxysmal AF/flutter	143 (27.4%)	115 (26.3%)	
Persistent AF/flutter	83 (15.9%)	69 (15.8%)	
Permanent AF/flutter	288 (55.3%)	247 (56.5%)	
Atrial tachycardia	1 (0.2%)	1 (0.2%)	
Other symptomatic arrhythmia	1 (0.2%)	1 (0.2%)	
Pre-op heart rhythm:			0.97
Arrhythmia	417 (80.5%)	355 (81.1%)	
Sinus	94 (18.1%)	77 (17.6%)	
Paced	7 (1.4%)	6 (1.4%)	
Hypertension:			0.72
No	157 (30.3%)	128 (29.2%)	
Yes	355 (68.4%)	304 (69.2%)	
Yes, systolic BP > 160 mmHg	7 (1.3%)	7 (1.6%)	
CCF (heart failure)	56 (10.9%)	45 (10.3%)	0.83
MI	101 (19.5%)	84 (19.2%)	0.93
Peripheral vascular disease	34 (6.7%)	29 (6.8%)	1.00
Significant liver disease	8 (1.6%)	5 (1.2%)	0.78
Neurological disease:			0.98
Yes, CVA	258 (49.7%)	220 (50.1%)	
Yes, other	87 (16.8%)	74 (16.9%)	
No	174 (33.5%)	145 (33.0%)	
Significant valve disease	38 (7.5%)	33 (7.7%)	1.00
Asymptomatic carotid disease:			0.96
Carotid disease excluded	180 (48.4%)	151 (48.7%)	
Carotid disease (<50% stenosis)	19 (5.1%)	18 (5.8%)	
Carotid disease (≥50% stenosis)	6 (1.6%)	4 (1.3%)	
No carotid imaging done	167 (44.9%)	137 (44.2%)	
Previous significant bleed:			0.99
No	63 (12.4%)	51 (11.8%)	
Yes (life threatening/disabling)	211 (41.5%)	179 (41.5%)	
Yes (major)	200 (39.3%)	173 (40.1%)	
Yes (minor)	35 (6.9%)	28 (6.5%)	
Previous peripheral embolism	9 (1.8%)	7 (1.6%)	1.00
Medications (pre-op):			0.99
Single antiplatelet	137 (26.6%)	111 (25.8%)	
Dual antiplatelet	28 (5.4%)	26 (6.0%)	
Anticoagulant alone	75 (14.5%)	67 (15.5%)	
Antiplatelet(s) & Anticoagulant(s)	6 (1.2%)	6 (1.4%)	
Other	56 (10.9%)	46 (10.7%)	
None	214 (41.5%)	175 (40.6%)	
Concomitant NSAID use	30 (6.1%)	29 (6.9%)	0.69

Patient characteristic†	All eligible LAAO patients (n=525)	All patients with follow-up (n=440)	p-value
Previous interventions:			
Coronary revascularisation	93 (18.1%)	77 (17.7%)	0.93
MV surgery	12 (2.3%)	9 (2.1%)	0.82
AV procedure	20 (3.9%)	15 (3.5%)	0.86
LAA procedure	18 (3.6%)	11 (2.6%)	0.45
CRM device therapy	74 (14.5%)	63 (14.6%)	1.00
Ablation therapy	36 (7.0%)	30 (6.9%)	1.00
DC cardio-/atrio-version(s)	55 (11.7%)	47 (11.8%)	1.00
Atrial septal procedure	2 (0.4%)	1 (0.2%)	1.00
LV ejection fraction:			0.96
Good (>50%)	403 (80.4%)	164 (80.8%)	
Moderate (30-50%)	75 (15.0%)	30 (14.8%)	
Poor (<30%)	23 (4.6%)	9 (4.4%)	
LA thrombus	19 (3.8%)	1 (0.5%)	0.11
LA spont. echo contrast (SEC):			1.00
None	346 (69.2%)	297 (69.9%)	
Yes – only in LA appendage	71 (14.2%)	59 (13.9%)	
Yes – elsewhere in LA	26 (5.2%)	21 (4.9%)	
Yes – LAA and elsewhere	57 (11.4%)	48 (11.3%)	
Aortic atheroma in arch:			0.98
Not imaged	391 (77.4%)	330 (76.7%)	
Grade 1	101 (20.0%)	87 (20.2%)	
Grade 2	11 (2.2%)	11 (2.6%)	
Grade 3	1 (0.2%)	1 (0.2%)	
Grade 4	1 (0.2%)	1 (0.2%)	
LAAO morphology:			1.00
Single straight windsock	193 (40.0%)	165 (39.9%)	
Single chicken wing	87 (18.0%)	75 (18.1%)	
Bilobe	128 (26.5%)	112 (27.1%)	
Trilobe	10 (2.1%)	8 (1.9%)	
Retroverted	19 (3.9%)	17 (4.1%)	
Broccoli	41 (8.5%)	33 (8.0%)	
Other	5 (1.0%)	4 (1.0%)	

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.

Appendix 3 – Procedural Characteristics – CtE Registry

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

Procedural characteristic†	All eligible LAAO patients (n=525)	All patients with follow-up (n=440)	p-value
Treating Hospital			1.00
Liverpool Heart & Chest Hospital NHS Foundation Trust	86 (16.4%)	81 (18.4%)	
University Hospital of North Staffordshire NHS Trust	63 (12.0%)	54 (12.3%)	
Oxford University Hospitals NHS Trust	66 (12.6%)	61 (13.9%)	
Brighton & Sussex University Hospitals NHS Trust	58 (11.0%)	44 (10.0%)	
University Hospitals Leicester NHS Trust	47 (9.0%)	34 (7.7%)	
Leeds Teaching Hospitals NHS Trust	41 (7.8%)	33 (7.5%)	
Barts Health NHS Trust	39 (7.4%)	32 (7.3%)	
The Newcastle upon Tyne Hospitals NHS Foundation Trust	31 (5.9%)	24 (5.5%)	
Guy's and St Thomas' NHS Foundation Trust	31 (5.9%)	29 (6.6%)	
University Hospital Birmingham NHS Foundation Trust	19 (3.6%)	14 (3.2%)	
Kings College Hospital NHS Foundation Trust	25 (4.8%)	18 (4.1%)	
South Tees Hospitals NHS Foundation Trust	15 (2.9%)	13 (3.0%)	
The Heart Hospital	1 (0.2%)	1 (0.2%)	
Elective procedure	507 (99.6%)	428 (99.5%)	1.00
General anaesthesia	514 (99.4%)	431 (99.8%)	0.63
Intra-operative echo imaging‡:			0.82
3D TOE	372 (58.4%)	311 (57.3%)	
2D TOE	256 (40.2%)	227 (41.8%)	
ICE	6 (0.9%)	4 (0.7%)	
None	3 (0.5%)	1 (0.2%)	
Cerebral protection device used	2 (0.4%)	0 (0.0%)	0.50
No. of devices opened for use:			0.50
0	16 (3.1%)	-	
1	436 (85.0%)	387 (89.4%)	
2	54 (10.5%)	42 (9.7%)	
3	5 (1.0%)	4 (0.9%)	
4	2 (0.4%)	0 (0.0%)	
Device used:			<0.0001*
WATCHMAN	172 (38.1%)	156 (41.7%)	

Procedural characteristic†	All eligible LAAO patients (n=525)	All patients with follow-up (n=440)	p-value
Amulet	212 (46.9%)	189 (50.5%)	
ACP	35 (7.7%)	26 (7.0%)	
Coherex - WaveCrest	3 (0.7%)	3 (0.8%)	
None	30 (6.6%)	-	
Device size, mm median (Q1,Q3) [range]	25 (22,27) [14-35]	25 (22,27) [14-35]	0.81
Fluoroscopy time, mins median (Q1:Q3) [range]	10 (7,15) [5-120]	10 (7,15) [5-120]	0.62
X-ray dose, mGray.cm^2 median (Q1:Q3) [range]	1655 (576,3000) [0-20,000]	1690 (604.5,3000) [10-20,000]	0.82
Contrast dose, ml median (Q1:Q3) [range]	70 (40,110) [10-350]	70 (40,110) [10-300]	0.93
Procedural duration, mins median (Q1:Q3) [range]	75 (57,110) [0-300]	77 (60,108) [0-300]	0.84

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.
‡ multiple choices permitted
* p-value with significant difference in variable found between those with follow-up and the whole cohort after Bonferroni corrections applied for multiple comparisons

Appendix 4 – Outcomes – CtE Registry

Outcomes for all eligible LAAO patients.

	In-hospital (n=525)		After discharge (6w,6m,1y,2y FU combined) (n=440)	
	Total No. of patients	% [95% CI]	Total No. of patients	% [95% CI]
Major complications:	**29**	**5.5 [3.7:7.8]**	**42**	**9.5 [7.0:12.7]**
Death	5	1.0 [0.3:2.2]	20	4.5 [2.8:6.9]
Neurological event	4	0.8 [0.2:1.9]	15	3.4 [1.9:5.6]
Pericardial effusion (requiring intervention)	11	2.1 [1.1:3.7]	-	-
Embolisation	4	0.8 [0.2:1.9]	0	0.0 [0.0:0.8]
Surgical intervention	10	1.9 [0.9:3.5]	0	0.0 [0.0:0.8]
Major vascular injury	5	1.0 [0.3:2.2]	-	-
Major bleed	10	1.9 [0.9:3.5]	11	2.5 [1.3:4.4]
MI	2	0.4 [0.0:1.4]	2	0.5 [0.1:1.6]
AKI (Stage 2 or 3)	3	0.6 [0.1:1.7]	-	-
Endocarditis	2	0.4 [0.0:1.4]	1	0.2 [0.0:1.3]
Minor complications:	**24**	**4.6 [3.0:6.7]**	**72**	**16.4 [13.0:20.2]**
Device malfunction	1	0.2 [0.0:1.1]	-	-
Malposition	0	0.0 [0.0:0.7]	54	12.3 [9.4:15.7]
Minor vascular injury	3	0.6 [0.1:1.7]	-	-
Pericardial effusion (conservative treatment)	6	1.1 [0.4:2.5]	-	-
Oesophageal damage (without death/further intervention)	0	0.0 [0.0:0.7]	-	-
Procedure-related arrhythmia	5	1.0 [0.3:2.2]	-	-
Minor bleed	8	1.5 [0.7:3.0]	20	4.5 [2.8:6.9]
Peripheral embolism	0	0.0 [0.0:0.7]	0	0.0 [0.0:0.8]
AKI (Stage 1)	1	0.2 [0.0:1.1]	-	-
Any complication (minor & major combined)	**49**	**9.3 [7.0:12.2]**	**109**	**24.8 [20.8:29.1]**
Device implanted	**469**	**93.6 [91.1:95.6]**	**-**	**-**
Yes, no leak	434	86.6 [83.3:89.5]	**-**	**-**
Yes, minor leak	32	6.4 [4.4:8.9]	**-**	**-**
Yes, moderate leak	1	0.2 [0.0:1.1]	**-**	**-**
Yes, major leak	2	0.4 [0.0:1.4]	**-**	**-**
Procedural success†	**446**	**89.0 [86.0:91.6]**	**-**	**-**
Extended length of stay‡	**114**	**22.4 [18.8:26.3]**	**-**	**-**
Clinical failure	**-**	**-**	**40**	**9.1 [6.6:12.2]**
Device not in situ	**-**	**-**	26	5.9 [3.9:8.5]
LAA not sealed – large leak (≥3mm)	**-**	**-**	7	1.6 [0.6:3.3]
Neurological event	**-**	**-**	8	1.8 [0.8:3.6]

Note:
† device implanted in absence of major complications
‡ >1 night

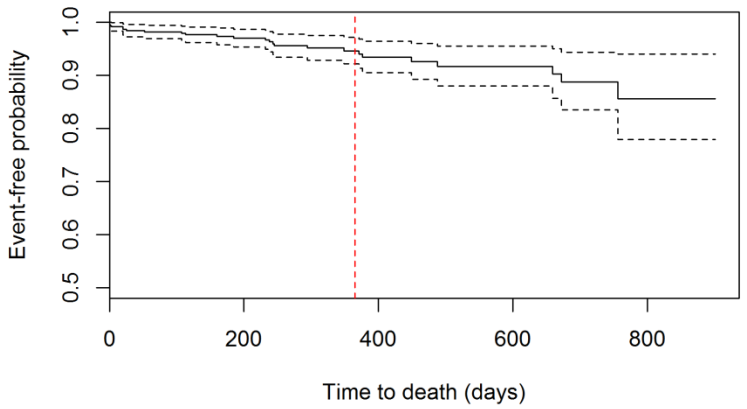
Appendix 5 – Outcomes (Time to Event Analysis) – CtE Registry

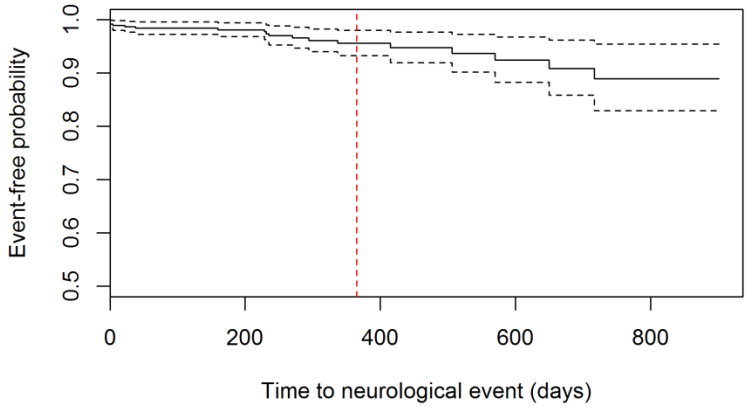
Patient outcomes (in-hospital and after discharge as reported at any follow-up combined) for all eligible LAAO patients.

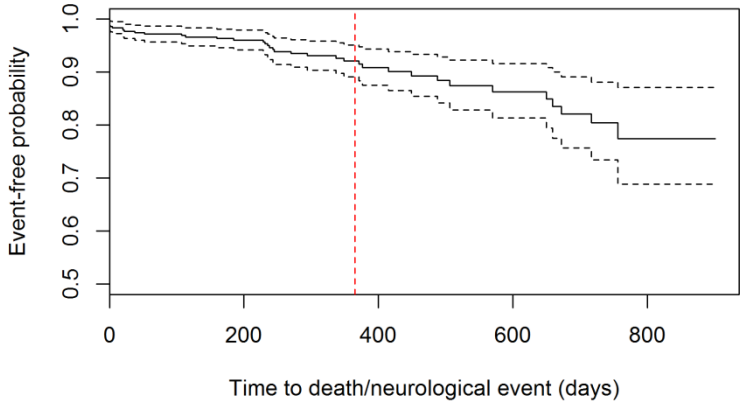
	No. of patients with event	Total follow-up (person-years)	Event rate (per 100 person-years follow-up) [95% CI]	No. of patients at risk at 1-year	1-year event-free probability (95% CI)
Major complications:					
Death	25 (4.8%)	401.9	6.2 [4.0:9.2]	167	0.947 (0.922 to 0.972)
Neurological event	19 (3.6%)	382.0	5.0 [3.0:7.8]	157	0.956 (0.933 to 0.980)
Ischaemic events only	*10 (1.9%)*	*383.4*	*2.6 [1.3:4.8]*	*159*	*0.979 (0.961 to 0.996)*
Death or neurological event	39 (7.4%)	396.6	9.8 [7.0:13.4]	164	0.921 (0.891 to 0.952)
Minor complications:					
Malposition	60 (11.4%)	373.8	16.1 [12.3:20.7]	152	0.843 (0.801 to 0.887)
Peripheral embolism	0 (0.0%)	-	-	-	-

Appendix 6 – Kaplan-Meier Curves – CtE Registry

Kaplan-Meier curve for death (top panel), neurological event (middle panel) and death or neurological event (bottom panel): 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 – Event by Device Manufacturer – CtE Registry

Deaths (a) and neurological events (b) by device manufacturer for all eligible LAAO CtE patients.

a)

Device Manufacturer	Death	No event	TOTAL
Boston Scientific (WATCHMAN)	8	164	**172**
St. Jude Medical (Amulet / ACP)	15	232	**247**
Coherex (WaveCrest)	0	3	**3**
Not specified	1	29	**30**
TOTAL	**24**	**428**	**452**

b)

Device Manufacturer	Neurological event	No event	TOTAL
Boston Scientific (WATCHMAN)	6	166	**172**
St. Jude Medical (Amulet / ACP)	12	235	**247**
Coherex (WaveCrest)	0	3	**3**
Not specified	1	29	**30**
TOTAL	**19**	**433**	**452**

Appendix 8 – Cost of an LAAO Procedure

Table A.8.1 identifies all the inputs and sources used to calculate the central cost. Table A.8.2 provides information on the sensitivity analyses conducted to provide high and low cost ranges. These are stated at 2015/16 price levels. Subsequently the costs were increased to 2017/18 costs using the hospital & community health services index [14]. This was estimated to have increased by 1.8% in each of the two intervening years. This increase was not applied to the cost of the device, the price of which was agreed with manufacturers for the duration of the registry. Both tables report the unit costs at 2015/16 prices to enable readers to track the unit cost back to the original source.

Table A.8.1: Cost of pathway for an LAAO procedure (2015/16 prices)

Parameter	Usage	Unit cost	% patients	Total cost	Source
LAAO 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 [13]
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 [12]
ECG	1	£40.35	100%	£40.35	
ToE (day case)	1	£506.30	100%	£506.30	
Blood gases	1	£6.42 - £9.84	100%	£8.13	Tests from clinical experts; costs from 'Preoperative tests' by National Clinical Guideline Centre [53]
Haemostasis of prothrombin time	1	£29.42	5%	£1.56	Tests from clinical experts; warfarin use from database and costs from 'Preoperative tests' by National Clinical Guideline Centre [53]
FBC	1	£3.00	100%	£3.00	Tests from clinical experts; costs from NHS Reference costs [12]
U&E	1	£3.00	100%	£3.00	
Sub-total pre-operative assessment costs				**£792**	All costs include overheads
Peri-operative costs:					
Cardiologist	[redacted] for 95 mins	£[redacted] per hr	[redacted]%	£[redacted]	Operators from database, cost PSSRU [13]
Registrar	[redacted] for 95 mins	£[redacted] per hr	[redacted]%	£[redacted]	
Anaesthetist	[redacted] for 85 mins	£[redacted] per hr	[redacted]%	£[redacted]	Staffing structure from clinical experts; cost PSSRU [13]
Cath lab assistant band 3	[redacted] for 85 mins	£[redacted] per hr	[redacted]%	£[redacted]	
Echocardiographer	[redacted] for 85 mins	All band 6, nurse £[redacted] per hr; rest	[redacted]%	£[redacted]	
Nurse	[redacted]		[redacted]%	£[redacted]	

Parameter	Usage	Unit cost	% patients	Total cost	Source
	for 85 mins	£xxx per hr			
Cardiac physiologist	[redacted] for 85 mins		[redacted]%	£[redacted]	
Radiographer	[redacted] for 85 mins		[redacted]%	£[redacted]	
Procedural time in theatre	85 mins	£299 per hr	100%	£423.13	Time from database; cost from Information Services Division (ISD) cost of theatres excluding staff and consumables costs [14]
ToE or ICE	[redacted]	£[redacted]	[redacted]%	£[redacted]	Use from database; costed as EY502 complex echocardiogram for an elective inpatient from NHS Reference costs [12]
Anaesthetic Drugs - Desflurane & Remifentanil	1	£82.18	100%	£82.18	Drugs agreed with clinical experts; price from a submitted template
Heparin 2 hrs per surgery and 8/12 hrs after.	1	£5.80	100%	£5.80	Drugs from clinical experts; costs from BNF [54]
Cefuroxime X 2 1.5 g, 8 hours apart	1	£10.10	100%	£10.10	
Consumables	1	£500	100%	£500	One well-completed template summed to a total cost £424. A second template summed to £686 for a General Cath Lab Instrument Set at £418 and PCI consumables at £268. The experts judged this too high and we agreed to use £500 per procedure
Devices opened per patient	[redacted]	£[redacted]	[redacted]%	£[redacted]	Number and mix of devices from dataset; cost of device from NHS Supply Chain and include VAT. An overhead of 15% was added for overheads associated with procurement and finance costs within NHS trusts. The rate was calculated from an analysis of property-related, management and admin overheads within the Scottish NHS (see ISD http://www.isdscotland.org/Health-Topics/Finance/Costbook/Speciality-Costs/Overhead.asp). These represent an estimate of costs to a trust to re-order, store, deliver to theatre and finance costs. Results are presented with and without this overhead.
Sub-total peri-operative costs				**£8,933**	All costs include overheads
Post-operative management					
Inpatient stay	1.5 days	£356 per day	100%	£567	Stay mean value from dataset; costed using mean cost for codes

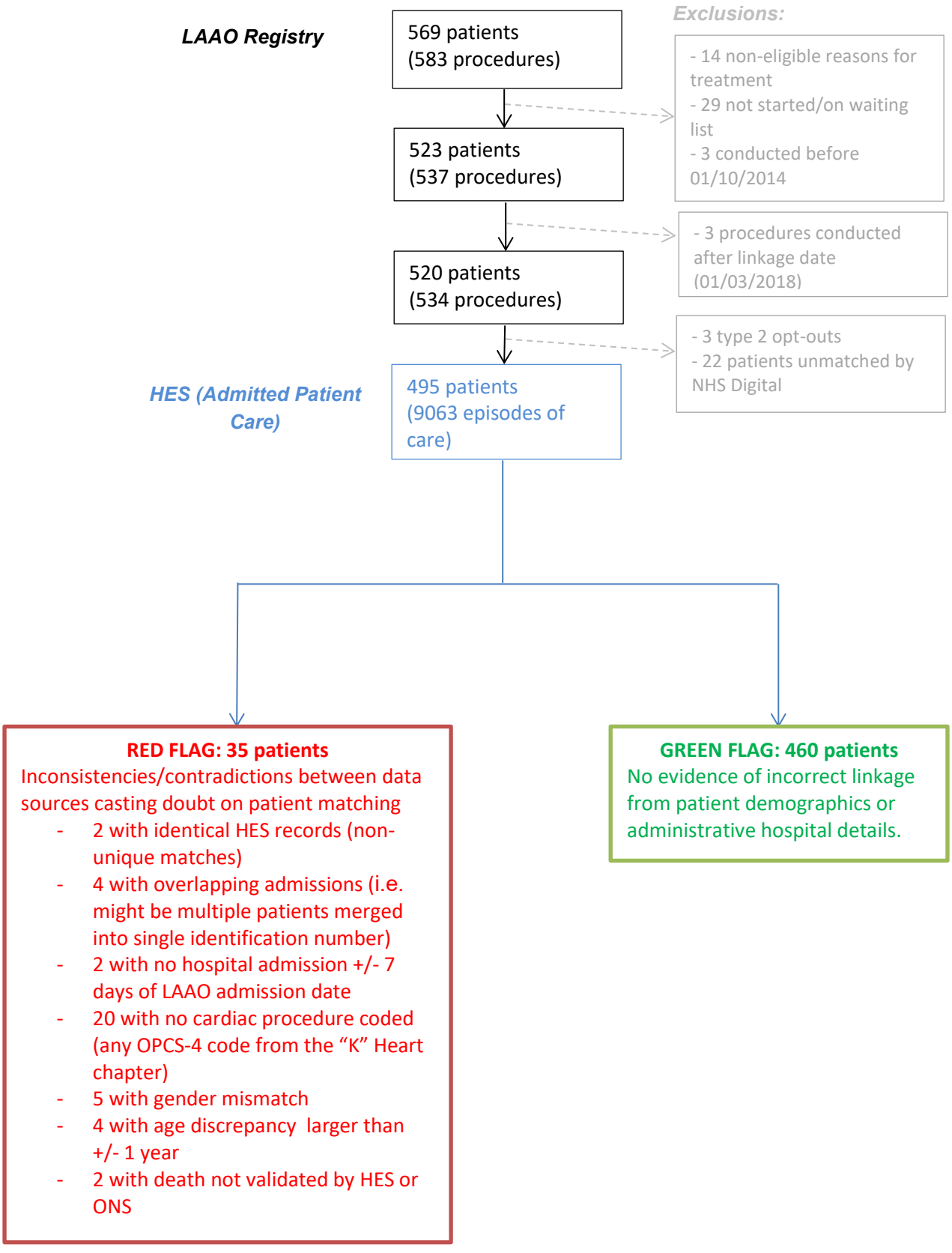
Parameter	Usage	Unit cost	% patients	Total cost	Source
					EY23A to C for Standard Other Percutaneous Transluminal Repair of Acquired Defect of Heart. Reference costs [12]
Transthoracic Echocardiogram	1	£1,437	0.77	£1,106	Use from database; costed as EY502 complex echocardiogram for an inpatient from NHS Reference costs [12]
Out-patient follow-up	1	£191	100%	£191	Use from clinical experts; cost Cardiac Surgery consultant-led outpatients. Reference costs [12]
Sub-total post-operative management				**£1,864**	All costs include overheads
GRAND TOTAL				**£11,589 (2015/16 prices)** **£11,798 (2017/18 prices)**	

Table A.8.2: Low and high cost scenarios for pathway for an LAAO procedure 2015/16 prices

Scenarios	Changes from central case	New cost
Pre-operative assessment central cost £792		
Low cost	Use first quartile cost for ToE (£185 vs central value £506) and 20% decrese in all other costs.	£413
High cost	Use third quartile cost for ToE (£657 vs central value £506) and 20% increase in all other costs.	£1,000
Peri-operative costs central cost £8,933		
Low cost	Use first quartile reported for procedure time and 20% decrease in all other costs except device.	£8,162
High cost	Use third quartile reported for procedure time and 20% increase in all other costs except device.	£9,668
Post-operative management central cost £1,864		
Low cost	Use length of stay time of 0.5 days and tariff cost for Complex Echocardiogram for Congenital Heart Disease elective patient.	£913
High cost	Use 2 days length of stay and 20% increase in all other costs.	£2,666
Total cost central case and % accounted for by device		**£11,589 ([redacted]%)**
Total case low cost and % accounted for by device		**£9,488 ([redacted]%)**
Total cost high cost and % accounted for by device		**£13,334 ([redacted]%)**

When updated for inflation to 2017/18 prices, the forecast cost for an LAAO procedure ranges from about £9,600 to £13,600 with the device cost (£[redacted] per patient; £[redacted] per device) accounting for about [redacted]% to [redacted]% of the total cost.

Appendix 9 – Data Flow Diagram –Linked Data



Appendix 10 – Linked Data reported in-hospital complications

Complication recorded*	CtE Registry
Air embolism	1
AKI (within 72 hours of procedure)	2
Procedure related arrhythmia (self-terminating)	4
Procedure related arrhythmia (pharmacological intervention, cardioversion or pacing)	1
Cerebrovascular event	4
- haemorrhagic	1
- CVA/RIND	1
- undetermined	2
Clinical bleed	15
- minor	5
- major	2
- life-threatening or disabling	8
Death	4
New or worsening effusion without tamponade (conservative treatment)	6
Endocarditis	2
MI (within 72 hours of procedure)	1
Pseudoaneurysm	1
Retrieval of embolised/unstable device	5
- percutaneous – successful	1
- surgical – successful	4
Sepsis	1
Surgical intervention for any other reason	8
Tamponade	9
- percutaneouse drainage	3
- surgical drainage	6
Vascular stent or other percutaneous procedure	3
AV fistula	1

Complication recorded*	HES
† E03.2: Hypothyroidism due to medicaments and other exogenous substances	1
† E13.9: Other specified diabetes mellitus – without complications [Drugs, medicaments and biological substances causing adverse effects in therapeutic use]	1
† I20.9: Angina pectoris	1
† I31.3: Pericardial effusion (noninflammatory)	3
† I47.2: Ventricular tachycardia	1
† I50.1: Left ventricular failure	1
† I72.4: Aneurysm and dissection of artery of lower extremity	1

Complication recorded*	HES
† J18.1: Lobar pneumonia, unspecified	1
† R00.1: Bradycardia, unspecified	2
† R22.1: Localized swelling, mass and lump, neck	1
† R33X: Retention of urine	3
T81.0: Haemorrhage and haematoma complicating a procedure, not elsewhere classified	25
T81.2: Accidental puncture and laceration during a procedure, not elsewhere classified	3
T81.3: Disruption of operation wound, not elsewhere classified	2
T81.7: Vascular complications following a procedure, not elsewhere classified (air embolism following procedure NEC)	2
T82.3: Mechanical complication of other vascular grafts	1
T82.5: Mechanical complication of other cardiac and vascular devices and implants	2
T82.8: Other specified complications of cardiac and vascular prosthetic devices, implants and grafts	1
T88.4: Failed or difficult intubation	1
Death	2

**Note patients can experience multiple complications*

†qualified by a supplementary ICD-10 code indicating complication