Implantable cardiac monitors (BioMonitor 2-AF, Confirm Rx insertable cardiac monitor and Reveal LINQ Insertable Cardiac Monitoring System) to detect atrial fibrillation after cryptogenic stroke

DAR PROTOCOL

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Rider on responsibility for protocol
The views expressed in this report are those of the protocol and not necessarily those of the NIHR HTA Programme. Any errors are the responsibility of the authors.

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TABLE OF ABBREVIATIONS

Abbreviation	In full
AF	Atrial fibrillation
CASP	Critical Appraisal Skills Programme
CDSR	Cochrane Database of Systematic Reviews
CRD	Centre for Reviews and Dissemination
DARE	Database of Abstracts and Reviews of Effects
EAG	Evidence assessment group
ECG	Electrocardiogram
ECHO	Echocardiogram
ESUS	Embolic stroke of undetermined stroke
HSUV	Health state utility values
HTA	Health technology assessment
ICER	Incremental cost-effectiveness ratio
ICM	Implantable cardiac monitor
NHS	National Health Service
NHS EED	NHS Economic Evaluation Database
NICE	National Institute for Health and Care Excellence
PCN	Patient care network
PCS	Patient care system
PSA	Probabilistic sensitivity analysis
QALY	Quality-adjusted life year
QUADAS-2	Quality Assessment of Diagnostic Accuracy Studies tool – 2
RCT	Randomised controlled trial
ROBINS-I	Risk Of Bias In Non-randomised Studies – of Interventions
SLR	Systematic literature review
SMS	Short messaging service
TIA	Transient ischemic attack
UK	United Kingdom

1 PLAIN ENGLISH SUMMARY

Ischaemic strokes are blockages in blood vessels in the brain that lead to the death of brain tissue, resulting in clinical signs and symptoms such as weakness or loss of function in the arms or legs, slurred speech or drooping of part of the face. Cryptogenic ischaemic strokes are strokes that have no clearly identifiable cause despite standard medical investigations such as blood tests, a heart tracing (electrocardiogram [ECG]), and a scan of the heart (echocardiogram [ECHO]). Cryptogenic transient ischaemic attacks (TIAs) are like strokes only the symptoms resolve within 24 hours.

Atrial fibrillation (AF) is an irregular heart rhythm that can occur intermittently or permanently and is associated with an increased risk of stroke and TIA. It is thought that undiagnosed AF may be the cause of some cryptogenic strokes and TIAs. Patients with a cryptogenic stroke or TIA may benefit from further tests to investigate for the presence of AF, as there are treatments that can be given to reduce the risk of stroke in patients diagnosed with AF.

AF is diagnosed as an irregular heart rhythm seen using inpatient or outpatient ECGs, or heart rhythm monitors that are worn at home by a patient as part of a test known as "external ambulatory ECG monitoring". External ambulatory ECG monitoring is typically done for between 24 hours and two weeks depending on the device used. However, the intermittent nature of AF in some patients can make it difficult to diagnose AF using ECG or external ambulatory ECG monitoring and so longer-term heart rhythm monitoring may be beneficial.

Reveal LINQ™, Confirm RX™ and BioMonitor 2-AF™ are implantable cardiac monitors (ICMs), which can be put inside patients with cryptogenic strokes or TIAs, to monitor their heart for AF on a longer-term basis (typically for 2 to 4 years depending on the battery life of the device). ICMs may help in identifying patients with cryptogenic stroke or TIA who have AF that has not already been diagnosed using external ambulatory ECG monitoring.

The aim of this project is to review the clinical scientific evidence, and to assess the costs and benefits associated with the use of ICMs to detect AF in people with cryptogenic strokes and TIAs.

2 DECISION PROBLEM

2.1 Aim of the assessment

The aim of this diagnostic assessment review is to assess whether the use of implantable cardiac monitors to assess for suspected paroxysmal atrial fibrillation in people who have had a cryptogenic stroke represents a cost-effective use of National Health Service (NHS) resources compared to no further testing after outpatient external ambulatory electrocardiogram (ECG) monitoring.

2.2 Population and target condition

2.2.1 Population: Cryptogenic stroke or TIA

Strokes and TIAs are caused by the interruption of the blood supply to the brain, either due to the blockage of a blood vessel by a blood clot or due to a bleed from a blood vessel in the brain. In a stroke or TIA, the blood supply to an area of the brain is impaired resulting in damage to the brain tissue. The main difference between a stroke and a TIA is that the symptoms associated with a TIA resolve within 24 hours, whereas in an untreated stroke the symptoms last for longer than 24 hours.

Cryptogenic strokes and TIAs are strokes and TIAs that have no known cause. There is no formal consensus definition on what criteria are required to be met for the formal diagnosis of a cryptogenic stroke or TIA.[1] The evidence assessment group's (EAG's) clinical experts reported that in UK clinical practice, patients will generally undergo a series of blood tests, an inpatient ECG, an echocardiogram (ECHO) and a doppler ultrasound scan of their carotid arteries to exclude the common causes of ischaemic stroke and TIA before arriving at the diagnosis of a cryptogenic stroke or TIA.

2.2.2 Target condition: Atrial fibrillation

Atrial fibrillation (AF) is an irregular heart rhythm; in some patients it is intermittent, whereas in others it occurs on a permanent basis. In patients where it occurs intermittently, it is known as paroxysmal AF. AF is known to be associated with an increased risk of stroke and TIAs.[2] This is because the irregular heart rhythm can result in the heart not emptying properly and the remaining blood forming a blood clot. If this blood clot in the heart then travels via the bloodstream to the brain, it can result in a blockage in the blood flow to an area of the brain which presents clinically as a stroke or TIA. There are drugs that can be given to patients with AF to reduce the risk of blood clots forming and, therefore, in cryptogenic stroke or TIA patients with AF this would help to reduce the risk of them developing a further stroke or TIA.

2.2.3 Epidemiology

It is estimated that 1.4 million people in England have AF, which is approximately 2.5% of the population.[3] According to data from Public Health England, it is estimated that 425,000 people are also living with undiagnosed AF across England.[3] The prevalence of AF is higher in men than in women (2.9% versus 2.0%) and also increases with increasing age, with the majority of cases of AF in people aged over 65 years (80.5%).[3, 4]

People with AF have a five-fold higher risk of having a stroke or TIA compared to people without AF.[4] Published data on cryptogenic stroke are limited but the National Stroke Association report that, "roughly 30-40% of first time strokes are cryptogenic, or due to unknown cause".[5] The National Stroke Association also highlights the importance of establishing the cause of a stroke to decrease the risk of future strokes, and select appropriate preventative care.[5] Published data suggest that the recurrence rate of stroke is around 30% and people are at highest risk of a subsequent stroke in the first year with associated higher mortality rates.[6]

2.2.4 Current diagnostic and treatment pathways

The EAG's clinical experts reported that there is no standard guideline on the diagnostic tests required in the UK, either in patients with cryptogenic stroke or TIA, to further investigate patients with cryptogenic stroke or TIA for underlying AF.[7] The NICE guideline on stroke and transient ischaemic attack in over 16s: diagnosis and initial management is currently undergoing review for updating but the current NICE guideline on stroke provides no specific recommendations on the diagnosis of AF in people with acute stroke.[7]

The NICE guideline on atrial fibrillation recommends that people with asymptomatic suspected paroxysmal AF undetected by standard ECG recording have a 24‑hour ambulatory ECG monitor, although this recommendation is not specific for cryptogenic stroke or TIA patients.[8] The European Society of Cardiology Guidelines for the management of AF recommend that patients with ischaemic stroke or TIA are investigated for AF using a short-term ECG recording and then continuous ECG monitoring for a minimum of 72 hours.[9]

The EAG's clinical experts reported that patients with a cryptogenic stroke or TIA diagnosis will typically have a short-term ECG as an inpatient to rule out cardiac arrhythmias such as AF as part of the diagnostic work-up to reach the diagnosis of a cryptogenic stroke or TIA. These patients diagnosed with cryptogenic stroke or TIA will then often go on to receive outpatient external ambulatory ECG monitoring for a minimum of 24 hours to detect undiagnosed AF. Clinical experts reported that patients will typically receive 24 to 48-hour external ambulatory ECG monitoring (for example using a Holter monitor) although in some areas this may be extended to 2 weeks or even 30 days of monitoring

depending on local practices and patient–clinician preferences. Clinical experts reported that ICMs are not routinely used in UK clinical practice for AF detection after cryptogenic stroke or TIA and that they are likely to only be used in the NHS after patients have received an initial period of at least 24-hours external ambulatory monitoring.

2.3 Interventions

The interventions to be assessed are implantable cardiac monitors (ICMs). ICMs are also known as insertable cardiac monitors and implantable loop recorders. A small incision is made in the skin of the chest and the ICM is inserted in a pocket beneath the skin. ICMs allow long-term monitoring of heart rhythm and can be used to detect intermittent or paroxysmal AF (i.e., AF that is not present all the time). The devices may improve detection of intermittent AF in people who have had a cryptogenic stroke, and who are at increased risk of a further stroke. If AF is diagnosed, anticoagulant therapy can be a treatment option to reduce the risk of experiencing another stroke or TIA. ICMs continuously capture subcutaneous electrocardiograms (ECGs) for up to several years and automatically record information if the device detects an arrhythmia, or if a person activates the device (because they have symptoms that may suggest an arrhythmia is happening). These recorded ECGs are remotely transmitted to clinicians for review to determine if AF has occurred.

Three different ICMs are included in the NICE scope: BioMonitor 2-AF;[10] Confirm RX;[11] Reveal LINQ.[12]

2.3.1 BioMonitor 2-AF

The BioMonitor 2-AF™ ICM (BIOTRONIK) is supplied with programmer and software specific to the device, together with a tool designed to facilitate insertion of the ICM.[10] An optional extra accessory is the Remote Assistant, which enables the patient to trigger recording of heart rhythm. The BioMonitor 2-AF comprises a solid housing section and a flexible component, which is the lead body and carries the antenna for Home Monitoring.

During implantation, the standard program is activated in the BioMonitor 2-AF via the programmer, which is used to set parameter combinations, and for interrogation and saving of data from the device. The programmer's ECG display must not be used for diagnostics, because it does not meet all the standard requirements for diagnostic ECG devices.

With Home Monitoring, diagnostic information, as well as technical data of the ICM, are automatically and wirelessly sent to a stationary or mobile transmitter via the antenna in the lead body. The data are encrypted and sent from the transmitter to the BIOTRONIK Home Monitoring Service Centre via the cellular phone network. The received data are deciphered and evaluated. Clinicians can set the criteria for evaluation to be used for each patient and can configure the time of notification via e-mail, SMS or

fax. An overview of the results of the analysis is displayed on the protected Internet platform Home Monitoring Service Centre. Data are transmitted with a daily device message. Messages that indicate special events in the heart or in the device are forwarded at a pre-set time. A test message can be initiated at any time using the programmer to immediately check the Home Monitoring function.

The parameters in the sensing settings, such as high pass filter, target sensing threshold, or noise window, can be adjusted to individual patients. The sensing parameters are subsumed in one program (SensingConsult ™). In addition to the possible individual program, there are preconfigured programs for PVC detection, for T-wave suppression, and for management of variable amplitudes. The signals are automatically recorded and stored once a detection type is activated and the detection occurs. Multiple detection types can be activated simultaneously. A total of 55 individual episodes with a length of at least 40 s each can be stored automatically. The maximum storage period for an individual episode is 60 s. The device can store four recordings triggered by the patient with a duration of at least 7.5 min. The recording includes 7 min of pre-episode history and 0.5 min of post-episode history relative to the time of triggering. The maximum recording duration for an individual episode is 10 min. The BioMonitor 2-AF can store episodes of subcutaneous ECGs with a total length of at least 60 min. When performing in-office follow-ups using the programmer, the subcutaneous ECG is indicated with markers after applying the programming head.

2.3.2 Confirm RX

The Confirm RX™ (St Jude Medical) is designed to detect arrhythmias and wirelessly transmit data to the Merlin.net™ Patient Care Network (PCN).[11] The ICM constitutes the inserted portion of the ICM system. The Merlin™ Patient Care System (PCS) with software version 23.0 (or greater), magnet, myMerlin™ mobile application (app), and Merlin.net PCN comprise the external components of the system. The Merlin PCS and magnet are used to interrogate and program the device in the clinic. Remote transmissions are performed using the app. The app also allows patients to record and send EGMs of symptomatic events to the clinic. All remotely transmitted data is made available on Merlin.net where clinicians can log in, review data, and make a diagnosis. Additional accessories include specialised tools for incision and insertion of the device.

2.3.3 Reveal LINQ

The Reveal LINQ™ Insertable Cardiac Monitoring System (Medtronic) consists of:

- a Reveal LINQ ICM;
- Reveal Patient Assistant;
- MyCareLink Programmer;

- remote monitoring system (MyCareLink Patient Monitor and MyCareLink network).

The Reveal LINQ ICM kit comes with tools tailored to facilitate insertion of the device. The incision tool makes a small opening in the skin (less than 1 cm) and the insertion tool is used to make a small pocket for the ICM and insert the device under the skin. In most cases the procedure can be done using local anaesthetic. The Reveal LINQ could be implanted by healthcare professionals other than cardiologists (e.g., cardiac physiologists, nurses, neurologists or stroke physicians) and clinical experts at the scoping workshop reported that it is not necessary to carry out insertion of the device in a catheterisation laboratory setting, as with some of the other ICMs. Training in inserting the device is provided by the Medtronic field team and is also available on-line. The battery life of the device is estimated as 3 years (assuming an average of 1 auto-detected episode per day and 1 patient-activated episode per month). While the device does not need to be removed, the company suggests removal when it is no longer required. The ICM is for single-patient use only.

The Medtronic CareLink™ programmer is used to program the device settings by placing the programming head over the device. Programmable parameters include those that determine when an episode of arrhythmia is recorded by the device; for example, 'AF detection sensitivity' and recording threshold (the length of episode required before it is recorded by the device).

The Reveal LINQ ICM identifies and records potential AF episodes using the Reveal LINQ AF algorithm. An ECG trace is assessed in 2 minute 'windows', which are considered as positive if AF is present for longer than a programmable threshold. The device can also be programmed to only store episodes that persist for a set period of time (6, 10, 20, 30 or 60 minutes). A total AF burden is also calculated, consisting of all 2-minute windows during which AF was present for longer than threshold value. In addition to AF, the Reveal LINQ ICM can also detect tachyarrhythmia, bradyarrhythmia or pause episodes. The device also contains an accelerometer to allow changes in patient activity over time to be monitored.

The Patient Assistant device is a hand-held battery-operated piece of equipment that the patient can use to record their heart rhythm when, or immediately after, they experience symptoms that may indicate that they are in AF (e.g., loss of consciousness or palpitations). Operating the Patient Assistant involves pressing a button on the device and holding it over the ICM.

The ICM can store up to 27 minutes of ECG from arrhythmias detected automatically and up to 30 minutes from patient-activated episodes.

Rhythm abnormalities recorded by the Reveal LINQ ICM are wirelessly transmitted to the MyCareLink Patient Monitor and then sent to a CareLink server in the Netherlands using a cellular telephone connection network. Transmitted and stored data are encrypted. A care alert is sent to clinicians when

the device detects a rhythm abnormality, and clinicians can access the data through the CareLink website using a password protected log-in. Alternatively, daily notifications of cardiac activity can be sent. The device will also send alerts if the battery charge is low. If the device is unable to communicate with CareLink it will register as 'disconnected'. The company also offers a triage and monitoring service (FOCUSON) for ECG recordings made by the device.

2.4 Place of the intervention in the treatment pathway

The intended place of use of the interventions in the treatment pathway of patients diagnosed with cryptogenic stroke or TIA is following a minimum of 24 hours of external ECG cardiac monitoring.

2.5 Relevant comparators

The relevant comparators are each of the interventions versus each other or versus no further testing after outpatient external ambulatory ECG monitoring for a minimum of 24-hours.

2.6 Reference standard

The interventions will be compared to the results of a reference standard for the purposes of assessment of diagnostic accuracy. The reference standard is used to verify the presence or absence of atrial fibrillation, the target condition. The reference standard for this assessment is 24-hour external ambulatory ECG monitoring. However, papers that include a reference standard of other commonly used ECG monitoring such as 7-day external ECG monitoring will also be considered so far as the evidence allows. One issue with the reference standard compared with ICMs is that they potentially cannot be used for extended periods of time.

3 REPORT METHODS FOR ASSESSING THE OUTCOMES ARISING FROM THE USE OF THE INTERVENTIONS

A systematic literature review will be conducted to evaluate the clinical effectiveness of the Reveal LINQ insertable cardiac monitor[13], the BioMonitor 2-AF ICM[10] and the Confirm RX ICM[11] for detecting suspected asymptomatic atrial fibrillation (AF) after cryptogenic stroke, and the diagnostic accuracy of these three ICMs for the diagnosis of AF using 24-hour external ECG monitoring (e.g. Holter monitor) as the reference standard (studies that include a reference standard of other commonly used ECG monitoring such as 7-day external ECG monitoring will also be considered so far as the evidence allows).

The systematic review methods will follow the general principles outlined in the Centre for Reviews and Dissemination (CRD) guidance for conducting reviews in healthcare,[14] NICE's Diagnostics Assessment Programme manual[15] and the Cochrane Handbook for Systematic Reviews of Diagnostic Test Accuracy.[16]

3.1 Review eligibility criteria

The eligibility criteria required for studies to be included in the review of the clinical effectiveness evidence are described in the following subsections.

3.1.1 Population

Study populations eligible for inclusion will be those comprising of people with a cryptogenic embolic stroke or cryptogenic transient ischaemic attack (TIA) for whom there is a suspicion of paroxysmal atrial fibrillation, and who have had at least 24 hours of outpatient external ambulatory ECG monitoring that has not detected AF.

It is also anticipated that the relevant setting will be secondary or tertiary care although study setting will not be used to determine study eligibility.

3.1.2 Interventions

The interventions under investigation are:

- Reveal LINQ[13];
- BioMonitor 2-AF[10];
- Confirm RX[11].

Data from earlier versions of each of the devices will be included as deemed necessary.

3.1.3 Comparators

The comparators will be each of the interventions versus each other or versus no further testing after outpatient external ambulatory ECG monitoring.

3.1.4 Reference standard

The reference standard for the assessment of diagnostic accuracy will be 24-hour external ambulatory ECG monitoring. However, papers that include a reference standard of other commonly used ECG monitoring such as 7-day external ECG monitoring will also be considered so far as the evidence allows.

3.1.5 Outcomes

If the evidence permits the following outcomes will considered:

- Diagnostic accuracy (sensitivity and specificity, and/ or if raw data are available, the numbers of true positive, true negative, false positive and false negative test results);
- Diagnostic yield (number of atrial fibrillation diagnoses);
- Detection of other cardiac pathologies or incidental findings (non-atrial fibrillation)
- Time to diagnosis of atrial fibrillation;
- Time to initiation of anticoagulants;
- Uptake of anticoagulants;
- Incidences of device failure (such as inability to transmit data or unexpectedly short battery life) and device removal because of failure or adverse events;
- Hospitalisations caused by atrial fibrillation;
- Number of outpatient visits related to monitoring for atrial fibrillation;
- Ease of use of devices for clinicians (including insertion);
- Mortality;
- Morbidity (including further strokes or TIAs, other thromboembolisms and heart failure, any complications arising from preventative treatment, such as adverse effects of anticoagulation treatment, and any adverse events related to implanting or removing the devices, such as infection or inflammation);

- Health-related quality of life;
- Acceptability of the devices to patients.

3.1.6 Study design

The following types of studies will be included:

- Randomised controlled trials or observational studies, where participants are assigned to a minimum of 24-hours external ECG monitoring plus ICM or a minimum of 24-hours external ECG monitoring for diagnosis of AF, and where outcomes are compared at follow-up.
- Test accuracy studies assessing the test accuracy of Reveal LINQ/BioMonitor 2-AF/Confirm RX and/or 24-hours external ECG monitoring with 24-hours external ECG monitoring as the reference standard. In addition, papers that include a reference standard of other commonly used ECG monitoring such as 7-day external ECG monitoring will also be considered so far as the evidence allows.

If insufficient studies are identified for the ICMs following a minimum of 24-hours external ECG monitoring, then studies of ICMs following shorter durations or no external ECG monitoring will be considered for inclusion.

The following study/publication types will be excluded:

- Pre-clinical and animal studies;
- Reviews, editorials, and opinion pieces;
- Case reports;
- Non-English language studies.

3.2 Search strategy

The searches will combine terms for the condition (AF) and terms for the technology being assessed. For the technology we will use both generic terms (e.g. ICM) and terms for the specific product (e.g. Reveal LINQ). The search strategy will be refined by scanning key papers identified during the review, through discussion with the review team, clinical experts and information specialists.

Electronic sources to include: MEDLINE (Ovid), EMBASE (Ovid), and the Cochrane Library (including the Cochrane Database of Systematic Reviews [CDSR], the Database of Abstracts of Reviews of Effects [DARE], the Health Technology Assessment [HTA] Database and CENTRAL).

The electronic databases will be searched from inception until the latest available version. A draft Medline search strategy will be provided in the final protocol as Appendix 9.1.

Ongoing and unpublished studies will be searched for using: clinicaltrials.gov, controlled-trials.com, clinicaltrialsregister.eu.

Relevant reviews and guidelines will be identified through consultation with clinical experts and searching the National Institute for Health and Care Excellence (NICE) website to identify further potentially relevant studies.

Reference lists of included papers will be assessed and the abstracts from key conference proceedings from the last 2 years, of conferences identified in consultation with clinical experts, will be screened, where possible, for additional relevant studies.

3.3 Study selection

The titles and abstracts of all identified studies from the electronic database searches will be independently assessed for inclusion by two reviewers to identify the potentially relevant full-text articles to be retrieved. Full-text copies of the selected studies agreed for inclusion after title and abstract screening will be obtained and all full-texts will be assessed independently by two reviewers for inclusion using the eligibility criteria outlined in Section 3.1. Any disagreements will be resolved by discussion, and, if necessary, a third reviewer will be consulted.

3.4 Data extraction strategy

Data will be extracted by one reviewer using a standardised data extraction form, and independently checked for accuracy by another. Information extracted will include details of the study's design and methodology, intervention and comparator tests, reference standard, baseline characteristics of participants, and outcome measures, including clinical outcome efficacy and any adverse events. Where there is incomplete information, if time constraints allow, attempts will be made to contact authors with a request for further details. Discrepancies will be resolved by discussion, with involvement of a third reviewer if necessary.

3.5 Quality assessment strategy

The quality of included studies will be assessed by one reviewer and independently checked by another. Any disagreements will be resolved by consensus and if necessary a third reviewer will be consulted. The quality of diagnostic studies will be assessed using the QUality Assessment of Diagnostic Accuracy Studies - 2 (QUADAS-2) tool,[17] according to recommendations by the *Cochrane Handbook for Diagnostic Test Accuracy Reviews*.[16] The quality of clinical effectiveness studies will be assessed according to their study design; randomised controlled trials will be assessed according to

recommendations by the CRD[14] and the Cochrane Handbook for Systematic Reviews of Interventions[18] and recorded using the Cochrane Risk of Bias Tool[18], non-randomised studies will be assessed using the Risk Of Bias In Non-randomized Studies - of Interventions (ROBINS-I) tool[19] and qualitative studies will be assessed using the Critical Appraisal Skills Programme (CASP) tool.[20]

The results of the quality assessments may be used to inform sensitivity analyses to explore the impact of study quality upon the findings of the review in sensitivity analyses (where evidence permits).

3.6 Methods of analysis/synthesis

Details of results on clinical effectiveness and quality assessment for each included study will be presented in structured tables and as a narrative summary. Where sufficient clinically and methodologically homogenous data are available, data will be pooled using appropriate meta-analytic techniques. Clinical, methodological and statistical heterogeneity will be investigated.

For test accuracy data, absolute numbers of true positive, false negative, false positive and true negative test results, as well as sensitivity and specificity values, with 95% confidence intervals will be presented for each study. In addition, positive predictive values (PPV) and negative predictive values (NPV) for each device will be calculated.

3.6.1 Potential subgroup analyses

If there are sufficient data, then the following subgroups will be investigated:

- People with varying lengths of previous outpatient external ambulatory ECG monitoring that has not detected atrial fibrillation (for example 1, 2, 7, 14 or 30 days);
- People with a cryptogenic TIA;
- People with a cryptogenic stroke (excluding TIA).

3.6.2 Sensitivity analyses

Sensitivity analyses will be conducted to include studies deemed to be high risk of bias as they will have been excluded from the primary analyses.

4 REPORT METHODS FOR SYNTHESISING EVIDENCE OF COST EFFECTIVENESS

The economic evaluation will assess the cost-effectiveness of an implantable cardiac monitors (ICMs) compared with no further monitoring, to detect atrial fibrillation (AF) in people who have had a cryptogenic stroke, including TIAs, and have received at least 24 hours of non-invasive external cardiac monitoring. A systematic literature review (SLR) of existing economic evaluations will be undertaken to inform the concept and development of a *de novo* economic model.

4.1 Identifying and systematically reviewing published cost-effectiveness studies

A SLR will be undertaken to identify published full economic evaluations of implantable monitors to detect AF in people with cryptogenic stroke. A search filter to identify economic evaluations will be applied to the search strategies and the electronic databases will be searched from inception until the latest available version.

The following databases will be searched for relevant studies:

- Ovid MEDLINE® In-Process & Other Non-Indexed Citations (Ovid);
- Ovid MEDLINE® ePub Ahead of Print (Ovid);
- Embase (Ovid);
- EconLit (Ovid);
- NHS Economic Evaluation Database (NHS EED);
- Cochrane Database of Systematic Reviews (CDSR) (Cochrane);
- Cochrane Central Database of Controlled Trials (CENTRAL) (Cochrane);
- Database of Abstracts of Reviews of Effects (DARE) (Cochrane);
- Health Technology Assessment Database (HTA) (Cochrane).

The methodological quality of the full economic evaluations identified in the review will be assessed using the Drummond checklist.

Separate searches will be carried out for supporting information on costs and resource use, as well as on utility data. Study selection and data extraction will be carried out as described in Sections 3.3 and 3.4 respectively.

The search strategy will combine terms capturing the interventions or comparators (Section 3.1.2 and 3.1.3) of interest and the target population (Section 3.1.1). Health economic and quality of life search terms will be applied to capture the study designs of interest (cost-effectiveness, cost and quality of life, health state utility values [HSUVs]). Searches will be restricted to studies published in the English language; however, no restriction by setting or geographical location will be applied to the search strategy. If sufficient data is available from a UK setting, data from non-UK based studies will not be extracted.

In addition, clinical experts in the field will be contacted with a request for details of published and unpublished studies of which they may have knowledge. Furthermore, identified systematic reviews and companies' submissions will be searched for additional references.

Main findings from the studies identified from the SLR will presented with a narrative synthesis and structured tables.

4.2 Development of a health economic model

A *de novo* economic model using Microsoft® Excel will be developed following the completion of the SLR and discussion with clinical experts. The model will assess the cost effectiveness of implantable cardiac monitors compared with no further monitoring to detect atrial fibrillation in people who have had a cryptogenic stroke, including TIAs, and have received at least 24 hours of outpatient external ambulatory ECG monitoring that has not detected atrial fibrillation.

Model parameters (e.g. utilities, cost data) will be populated from the results of the economic and outcome searches and combined with unit costs from NHS reference costs and other relevant publications of UK health care costs as appropriate. The Evidence Assessment Group (EAG) will elicit expert opinion if published data are not available to inform all model parameters. All evidence will be evaluated according to the recommendations of the NICE Diagnostics Assessment Programme manual.[15]

4.2.1 Model structure

The structure of the model will take into consideration previous economic models in the area of diagnostic monitoring for AF. The model structure will be dependent on the data that is identified through both the clinical and economic SLR, as it could be based on outcomes identified through randomised controlled trial (RCT) evidence or require the use of diagnostic accuracy data (such as

sensitivity and specificity). Furthermore, if the clinical SLR identifies outcomes for detection of other cardiac pathologies or incidental findings (non-atrial fibrillation), narrative consideration will be given to the potential impacts on cost-effectiveness of these outcomes.

It is anticipated that event pathways may be modelled by using a hybrid model (a decision tree for the period of monitoring followed by a state transition cohort structure, e.g. Markov) to estimate long-term costs and benefits. However, depending on the clinical data available for the devices, the model structure described here is subject to change and alternative model structures may need to be explored. The economic model will incorporate the pathways of care that individuals follow under standard practice in the UK NHS and for which credible evidence is available. The EAG will review previous economic models and seek expert clinical advice to help structure the diagnostic and care pathways.

It is expected that a linked-evidence modelling approach may be required, as the results of initial scoping searches indicate that studies assessing ICMs often focus on diagnostic accuracy, duration of AF and number of AF events detected rather than on long-term clinical outcomes (such as stroke events) resulting from the use of these devices.

The patient population considered in the model will be people with a cryptogenic stroke, including TIAs, who have received at least 24 hours of outpatient external ambulatory ECG monitoring that has not detected atrial fibrillation. The economic assessment will be undertaken from the perspective of the NHS and Personal Social Services. The model time horizon will be set to patient lifetime and both costs and benefits will be discounted at 3.5% per annum.

The output of the economic model will be incremental cost effectiveness ratios (ICERs), using quality-adjusted life-years (QALYs) as the measure of effectiveness. Various sensitivity analyses will be conducted to test the robustness of the model to changes in parameter assumptions and potentially also to alternative data sources. In particular, the NICE final scope specifies exploring the impact of company triage services on the ICER, the inclusion of which is dependent on the data available. To assess the overall uncertainty in the model estimates, a probabilistic sensitivity analysis (PSA) will be conducted using appropriately sampled values for all relevant parameters in the model.

5 HANDLING INFORMATION FROM THE COMPANIES

Data submitted by the manufacturers/sponsors will only be considered if received by the EAG no later than 30/09/2018. Data arriving after this date will not be considered. Any data that meet the inclusion criteria for the review will be extracted and quality assessed as stated in the methods section of this protocol.

Any 'commercial in confidence' data provided by manufacturers, and specified as such, will be highlighted in blue and underlined in the assessment report (followed by company name in parentheses). Any 'academic in confidence' data provided by manufacturers, and specified as such, will be highlighted in yellow and underlined in the assessment report. An executable model will be supplied, with any confidential data used in the cost effectiveness model replaced with dummy data.

6 COMPETING INTERESTS OF AUTHORS

None of the authors have any relevant competing interests to declare.

7 TIMETABLE/MILESTONES

Milestone	Date to be completed
Draft protocol	31/07/2018
Final protocol	24/08/2018
Progress report	22/11/2018
Draft assessment report	25/01/2019
Final assessment report	22/02/2019

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9 APPENDICES

9.1 Appendix 1 Draft search strategy (MEDLINE)

1 (Reveal adj2 LINQ*).mp.

2 (Reveal adj2 XT*).mp.

3 BioMonitor*.mp.

4 (Confirm adj2 RX*).mp.

5 (SJM adj2 Confirm*).mp.

6 (insertable adj4 cardiac adj4 monitor*).mp.

7 (implantable adj4 cardiac adj4 monitor*).mp.

8 (insertable adj4 loop adj4 recorder*).mp.

9 (implantable adj4 loop adj4 recorder*).mp.

10 ICM.mp.

11 or/1-10

12 exp STROKE/

13 exp "Intracranial Embolism and Thrombosis"/ or Embolism/

14 exp Brain Ischemia/

15 (stroke* or apoplexy* or CVA or CVAS or cryptogenic* or TIA or TIA*).mp.

16 ((cerebrovascular or cerebral vascular or cerebrum vascular or cerebrumvascular or cerebral or vascular or brain) adj4 (accident* or arrest* or failure* or injury or insult* or event* or insufficiency)).mp. (117154)

17 ((ischemi* or ischaemi*) adj4 (attack* or cerebral or transient or brain or cerebral or cerebri* or neural or seizure*)).mp.

18 ((cerebrum or brain or cerebral or cortical or hemisphere*) adj4 (infarct* or necro* or insult*)).mp.

19 or/12-18

20 11 and 19

21 animals/ not humans/

22 20 not 21

23 limit 22 to english language