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

DIAGNOSTIC ASSESSMENT REPORT

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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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Peter Cain	Development of the economic model; carried out the economic analysis and report writing.
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ABSTRACT

Background

Cryptogenic stroke (CS) is where no known stroke cause is identified after diagnostic tests. Implantable cardiac monitors (ICMs) can be used to diagnose AF over several years and risk of stroke recurrence can be reduced with AF treatment.

Objectives

To assess the diagnostic test accuracy (DTA), and clinical and cost-effectiveness of BioMonitor 2-AF, Confirm RX, and Reveal LINQ for detecting AF after 24 hours of external ECG monitoring in CS patients.

Methods

A systematic review was undertaken; MEDLINE, EMBASE, CENTRAL, DARE and the HTA databases were searched from inception until September 2018. Two reviewers agreed studies for inclusion and quality assessed the included comparative study using the Cochrane risk of bias 2 tool. There were insufficient data for synthesis, so results were discussed narratively.

A two-stage *de novo* economic model was developed. The first stage was a short-term patient flow model to identify CS patients with AF who have been detected and prescribed anticoagulation treatment, with those who are undetected remaining on antiplatelet treatment. The second stage was a long-term Markov model which captures the lifetime costs and benefits of patients on either anticoagulation or antiplatelet treatment.

Results

One randomised controlled trial (CRYSTAL-AF) in CS was included and no DTA studies. CRYSTAL-AF assessed Reveal XT (Reveal LINQ predecessor) compared with standard of care monitoring (SoC). Twenty-six single-arm observational studies for the Reveal devices were included after widening the eligibility criteria to include non-comparative studies. The only data included for BioMonitor 2-AF or Confirm RX were from mixed population studies supplied by the companies.

AF detection in CRYSTAL-AF was higher with the Reveal XT than SoC at all timepoints and by 36 months, 19% of patients with ICM were detected with AF and 2.3% with conventional follow-up. The 26 observational studies demonstrate that even within a CS population AF detection rates are highly variable and all or most AF detected was asymptomatic so would not likely have been picked up without ICM. Device-related adverse events such as pain and infection were low in CRYSTAL-AF, the single-arm observational studies and the mixed population studies.

The *de novo* economic model produced incremental cost effectiveness ratios (ICERs) comparing ICMs with SoC to detect AF in CS patients. The results of the pairwise analysis, that is each ICM device compared with SoC, demonstrate ICMs could be considered cost-effective at a £20,000 – £30,000 threshold compared with SoC. When each device is compared incrementally, BioMonitor 2-AF dominates Reveal LINQ and Confirm RX. However, BioMonitor 2-AF and Confirm RX could only be included in the analysis by making a strong assumption of equivalence with Reveal LINQ.

Conclusions

The evidence suggests that the Reveal LINQ is more effective in detecting AF than SoC but there is insufficient clinical data in a CS population to draw conclusions for the Confirm RX and BioMonitor 2-AF. The cost-effectiveness results indicate that ICMs could be considered a cost-effective use of NHS resources compared with SoC for patients who have had a CS and no AF has been detected after 24 hours of external ECG monitoring.

Study registration

The protocol for this review is registered on PROSPERO as CRD42018109216.

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TABLE OF ABBREVIATIONS

Abbreviation	In full
AE	**Adverse event**
AF	Atrial fibrillation
BNF	British National Formulary
CASP	Critical Appraisal Skills Programme
CDSR	Cochrane Database of Systematic Reviews
CEAC	Cost-effectiveness acceptability curve
CENTRAL	Cochrane Central Register of Controlled Trials
CI	Confidence interval
CIS	Cryptogenic ischemic stroke
CRB	Clinically relevant extracranial bleed
CRD	Centre for Reviews and Dissemination
CRNMB	Clinically relevant non-major bleed
CRT	Cardiac resynchronisation therapy
CS	Cryptogenic stroke
CT	Computed tomography
CTA	Computed tomography angiogram
CVE	Cardiovascular events
DAR	Diagnostics assessment review
DARE	Database of Abstracts and Reviews of Effects
DOAC	Directly acting oral anticoagulant
DVT	Deep vein thrombosis
DWI	Diffusion-weighted imaging
EAG	Evidence Assessment Group
ECG	Electrocardiogram
ECH	Extracranial haemorrhage
ECHO	Echocardiogram
ESO	European Stroke Organisation
ESUS	Embolic stroke of undetermined stroke
EQ-5D	EuroQol 5-dimensions
HR	Hazard ratio
HRQoL	Health-related quality of life
HS	Haemorrhagic stroke
HSUV	Health state utility values
HTA	Health technology assessment
HUI	Health Utilities Index
ICD	Implantable cardioverter defibrillator
ICER	Incremental cost-effectiveness ratio
ICH	Intracranial haemorrhage
ICM	Implantable cardiac monitor
INB	Incremental net benefit
IQR	Interquartile range
IS	Ischemic stroke
ITT	Intention-to-treat
KM	Kaplan–Meier

LA	Left atrium
LV	Left ventricle
MI	Myocardial infarction
MPP	Manual pulse palpation
MRA	Magnetic resonance angiogram
MRI	Magnetic resonance imaging
NHS	National Health Service
NHS EED	NHS Economic Evaluation Database
NICE	National Institute for Health and Care Excellence
NMA	Network meta-analysis
NPV	Negative predictive value
OAC	Oral anticoagulant
OECD	Organisation for Economic Co-operation and Development
ONS	Office for National Statistics
OX-VASC	Oxford Vascular Study
PAC	Premature atrial contractions
PCN	Patient care network (Merlin.net, Abbott)
PCS	Patient care system (Merlin, Abbott)
PE	Pulmonary embolism
PFO	Patent foramen ovale
PICO	Population, intervention, comparator and outcome
PPV	Positive predictive value
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
SAE	Serious adverse event
SD	Standard deviation
SE	Standard error
SF-36	Short-Form Health Survey (36 items)
SF-6D	Short-Form-Six Dimensions
SLR	Systematic literature review
SMS	Short message service
SoC	Standard of care monitoring
TIA	Transient ischemic attack
TOE	Trans-oesophageal echocardiogram
UK	United Kingdom
VAS	Visual analogue scale

GLOSSARY

Accuracy	The ability of a diagnostic test to identify positive and negative cases correctly. Calculated as the proportion of true positives and true negatives in all evaluated cases.
Atrial fibrillation (AF)	Heart condition that causes an irregular and often abnormally fast heart rate. AF may be intermittent (paroxysmal) or continuous, and symptomatic (dizziness, shortness of breath, tiredness) or asymptomatic.
Cost effectiveness analysis	An economic analysis that converts effects into health terms and describes the costs per additional health gain
Cryptogenic stroke (CS)	A stroke of undetermined cause or origin. Classification of CS depends on the system used and may include strokes that have more than one identifiable cause, or those that have not been investigated fully.
False negative	An incorrect negative test result for an affected individual.
False positive	An incorrect positive test result for an unaffected individual.
Implantable cardiac monitor	Small electrocardiogram (EGC) devices for long-term monitoring of a patient's heart electrical activity. The device is implanted via a small incision under the skin of the patient's chest to record and transmit detected arrhythmia episodes.
Incremental cost-effectiveness ratio	The difference in the mean costs of two interventions in the population of interest divided by the difference in the mean outcomes in the population of interest.
Markov model	An analytical method particularly suited to modelling repeated events or the progression of a chronic disease over time
Meta-analysis	Statistical techniques used to combine the results of two or more studies and obtain a combined estimate of effect
Negative predictive value	Probability that people with a negative test result truly do not have the target condition (AF).
Opportunity costs	The cost of forgone outcomes that could have been achieved through alternative investments
Positive predictive value	Probability that people with a positive test result truly have the target condition (AF).
Probabilistic sensitivity analysis	A method of quantifying uncertainty in a mathematical model, such as a cost-effectiveness model
Reference standard	The best currently available diagnostic test against which the index test is compared
Sensitivity	Proportion of people with the target condition (AF) who test positive.
Specificity	Proportion of people without the target condition (AF) who test negative.
Transient ischemic attack	A brief episode of neurological dysfunction caused by loss of blood flow in the brain, without an identifiable lesion on imaging. TIAs have the same underlying mechanism as ischemic strokes, and symptoms resolve within 24 hours.
True negative	A correct negative test result for an unaffected individual
True positive	A correct positive test result for an affected individual

PLAIN ENGLISH SUMMARY

Cryptogenic strokes (CS) are strokes where there is no known cause identified. Atrial fibrillation (AF) is an abnormal heart beat associated with an increased risk of stroke and so people who have had a stroke are investigated for AF. However, AF may not be identified with standard tests after a stroke, which include a minimum of 24 hours of outpatient monitoring with an external electrocardiogram (ECG). Implantable cardiac monitors (ICMs) are small devices placed just beneath the skin of the chest that can monitor for AF over a long period of time (up to 4 years). If AF is detected, a person's risk of another stroke can be reduced by treatment with oral anticoagulants. This study aimed to compare three different ICMs (BioMonitor 2-AF, Confirm RX, and Reveal LINQ) to see how effective they are at detecting AF in people who have had a CS and to see whether they offer any benefit compared to the standard monitoring people currently receive. In addition, this review assesses the cost-effectiveness of the ICMs in terms of their value for money. We found no evidence which compared the three ICMs in CS patients. The limited clinical data available suggest all three ICMs are associated with few side effects but only one device (Reveal LINQ) had evidence that it was better at finding AF than standard monitoring in people with CS. We found that using ICMs offers value for money when compared with standard monitoring for people who have had a CS and no AF has been detected with standard tests after a stroke.

SCIENTIFIC SUMMARY

Background

Up to a third of first strokes are termed cryptogenic stroke (CS) because no known cause is identified. Atrial fibrillation (AF) is a common arrhythmia associated with a five-fold increased risk of stroke. Patients who have had a stroke are investigated for AF although it can be intermittent and asymptomatic, so may be undetected by standard post-stroke investigations. Implantable cardiac monitors (ICMs) are small devices inserted under local anaesthetic via a small incision in the chest and they capture and transmit electrocardiograms (ECGs) over a period of up to 4 years. The devices vary in size, cost, battery life, programming of parameters to detect arrhythmias, and the way data are transmitted and reviewed by clinicians; however, if they detect AF, a patient's risk of subsequent stroke can be reduced by treatment with oral anticoagulants.

Objectives

To assess the clinical- and cost-effectiveness of the BioMonitor 2-AF™ (BIOTRONIK, Berlin, Germany), Confirm RX™ (Abbott, Illinois, USA), and Reveal LINQ™ (Medtronic, Minneapolis, USA) to detect suspected paroxysmal AF in people who have had a CS. The review considers the diagnostic accuracy, clinical effectiveness and cost effectiveness of the three ICMs compared with no further testing after at least 24-hours of outpatient external ambulatory ECG.

Methods

Clinical effectiveness methods

A systematic review was conducted to identify diagnostic test accuracy (DTA) and clinical effectiveness studies on the use of ICMs and their earlier models. The comparators were each of the ICMs versus each other or versus no further testing after outpatient external ambulatory ECG monitoring. Electronic database searches in MEDLINE, EMBASE, the Cochrane Database of Systematic Reviews, the Cochrane Central Register of Controlled Trials, the Database of Abstracts of Reviews of Effects and the Health Technology Assessment Database were run in September 2018. A single RCT (CRYSTAL-AF) assessing an earlier Medtronic Reveal model (XT rather than LINQ) met the eligibility criteria, so the criteria were widened to find evidence for the BioMonitor 2-AF, Confirm RX and Reveal LINQ. First, non-comparative observational studies were sought within the CS population, and then evidence was considered from studies of mixed populations submitted by each company. Only CRYSTAL-AF falls within the eligibility criteria outlined in the original published protocol for this diagnostics assessment review (DAR), so the additional evidence should be interpreted with caution. It should also be noted that[11111111111] AF detection rates in ICM devices are dependent on the patient population, as is the incidence of the other clinical outcomes of interest in this DAR. The

results from non-cryptogenic stroke populations may not be representative of the ICM device performance in CS patients.

The titles and abstracts of all identified studies from the electronic database searches were independently assessed for inclusion by two reviewers. The Cochrane Risk of Bias 2.0 Tool was used for quality assessment of the RCT and extracted data was validated by a second reviewer. There was insufficient clinically and methodologically homogenous data available to enable data to be pooled and meta-analysed and so data from the RCT, observational CS studies and mixed population studies were tabulated and discussed narratively.

Cost-effectiveness methods

A systematic review was performed to identify published economic evaluations of ICMs for the detection of AF in a CS population. Electronic databases searches in MEDLINE, MEDLINE Ahead of Print and MEDLINE In-Process, EMBASE, EconLit, NHS Economic Evaluation Database, Cochrane Database of Systematic Reviews, Cochrane Central Database of Controlled Trials, Database of Abstracts of Reviews of Effects and Health Technology Assessment Database were run in September 2018. Additional searches were carried out in September 2018 to identify data on relevant costs and health state utilities.

A two-stage *de novo* economic model was developed to assess the cost-effectiveness of Reveal LINQ, BioMonitor 2-AF and Confirm RX compared with standard of care monitoring (SoC) to detect AF in patients who have had a CS. The first stage of the model was a short-term patient flow model to identify CS patients with AF who have been detected, and prescribed anticoagulation treatment, and those who are undetected will remain on antiplatelet treatment. The second stage of the model was a long-term Markov model which captures the lifetime costs and benefits of patients on either anticoagulation or antiplatelet treatment. Data on AF detection rates for all three ICMs are based on results from CRYSTAL-AF. A probabilistic sensitivity analysis (PSA) was conducted to establish the level of uncertainty in the model parameters. In addition, deterministic one-way sensitivity analysis and various scenario analyses were performed to assess the uncertainty in the assumptions used in the model. Total costs and quality adjusted life years (QALYs), as well as incremental costs and QALYs and incremental cost effectiveness ratios are reported. Costs and outcomes over the lifetime horizon were discounted at an annual rate of 3.5%.

Results

Summary of clinical effectiveness results

No DTA studies were identified exclusively in the CS population irrespective of the comparator selected and only one RCT was identified in a CS population (CRYSTAL-AF, n = 441). CRYSTAL-AF was an open-label RCT that compared the Reveal XT with conventional follow-up.

Twenty-six single-arm observational studies were identified after widening the eligibility criteria to include non-comparative studies. The studies all assessed the Reveal XT and Reveal LINQ; none provided evidence suitable to assess the efficacy of BioMonitor 2-AF or Confirm RX. Therefore, one study for Confirm DM2102, five studies of the BioMonitor 2 and five studies of the Reveal LINQ or XT in mixed populations were included from company submissions. The mixed population studies were all single-arm observational studies or DTA studies using Holter monitoring as the reference standard.

AF detection in CRYSTAL-AF was higher with the Reveal XT than conventional follow-up at all timepoints and by 36 months, 19% of ICM patients were detected with AF compared to 2.3% with conventional follow-up. Time to AF detection was significantly shorter for patients with the Reveal XT compared with conventional follow-up at 36 months (HR 8.8, 95% CI: 3.5 to 22.2, p<0.001) and more than 90% of patients diagnosed with AF in the ICM arm started an oral anticoagulant. The observational studies demonstrated that even within a CS population AF detection rates are highly variable, but results were broadly consistent with CRYSTAL-AF.

In CRYSTAL-AF, incident stroke or TIA rates were 5.0% with ICM versus 8.2% with conventional follow-up at 6 months, 6.8% vs 8.6% at 12-months and 9.0% vs 10.9%, at 36-months (all p>0.05). [redacted]

Device-related adverse events (AEs) such as pain and infection were low in CRYSTAL-AF, the single-arm observational studies and the mixed population studies. In CRYSTAL-AF, the rate of serious AEs was similar between groups (around 25–30%) but more ICM patients had non-serious AEs compared with conventional follow-up (18.6% vs 4.1%, respectively). At 12 months follow-up, 3.4% of ICMs had been removed in CRYSTAL-AF.

The results of the mixed population studies suggest that enhancements over time to the AF diagnosis algorithm in the Reveal ICMs has improved their DTA. A naïve comparison of the mixed population DTA studies of the Confirm DM2102 and Reveal LINQ suggests they both have 100% sensitivity for AF detection although specificity varies (85.7% and 99.0%, respectively). The BioMonitor 2 [redacted] However, this comparison is subject to clinical heterogeneity (patient populations, interventions and study designs) and the data are not necessarily reflective of CS patients or the ICM models of interest.

Summary of cost-effectiveness results

One study was identified that assessed the cost-effectiveness of the Reveal XT ICM (a predecessor of the Reveal LINQ) compared with SoC in a CS population. The economic evaluation was reviewed to determine the viability of using the model for the purposes of this DAR, but it was considered that the results produced by the model are potentially unreliable as there is significant uncertainty and potential flaws in the estimation of the clinical parameters in the model, particularly around the estimation of treatment effects by indirect comparison, AF incidence and detection rates used in the analysis.

However, the initial health states of the Reveal XT model to determine AF status were considered appropriate to inform a *de novo* short-term model, where the time horizon is linked to the battery life of an ICM device. From the short-term model, patients with AF (whether detected or undetected) will then feed into a long-term (lifetime) model, assessing the costs and benefits of anticoagulation therapy. A published long-term model assessing the cost-effectiveness of directly acting oral anticoagulants (DOACs) compared with warfarin and also assessed outcomes for antiplatelet treatment. It was deemed suitable to use for the long-term modelling of costs and benefits of CS patients who have AF (whether detected or undetected). The following clinical outcomes were included in the model: ischaemic stroke; myocardial infarction; clinically relevant (extracranial) bleeding (CRB); ICH; systemic embolism; TIA; and death.

Based on the studies identified in the systematic review, a two-stage *de novo* economic model was developed in Microsoft Excel® (Microsoft Corporation, Redmond, WA, USA). The first stage of the model was a short-term patient flow model to identify CS patients with AF who have been detected and are prescribed anticoagulation treatment and those who are undetected and remain on antiplatelet treatment. The second stage of the model utilises the long-term DOAC model which captures the lifetime costs and benefits of patients on either anticoagulation or antiplatelet treatment.

The *de novo* economic model produced incremental cost effectiveness ratios (ICERs) comparing implantable cardiac monitors (ICMs) with standard of care monitoring (SoC) to detect AF in CS patients. The monitors assessed were Reveal LINQ, BioMonitor 2-AF and Confirm RX. The results of the pairwise analysis, that is each ICM device compared with SoC, demonstrate ICMs are cost-effective at a standard £20,000 – £30,000 threshold compared with SoC. When each device is compared incrementally, BioMonitor 2-AF dominates Reveal LINQ and Confirm RX. However, the results for BioMonitor 2-AF and Confirm RX should be viewed with caution, as no data were available for any version of these devices in the CS population and as such there is substantial uncertainty in the results.

Discussion

Clinical discussion

There is extremely limited DTA or comparative clinical effectiveness evidence for the use of ICMs in the detection of AF, particularly in the CS population. There is also evidence to suggest that AF detection in ICM devices, is dependent on various factors including the patient population and incidence rate of AF, thus limiting the use of data in non-CS populations to draw meaningful conclusions. CRYSTAL-AF provides the most robust evidence on which to base conclusions of ICM efficacy, although its open-label design introduces potential bias; e.g. the outcome assessor was aware of the intervention assignment and was able to influence the assessment of AF. However, the AF detection rate from CRYSTAL-AF is potentially a conservative estimate for the Reveal LINQ as the mixed population DTA studies suggest the Reveal LINQ has fewer false positives and fewer false positives than the Reveal XT and so it is likely to be as effective if not better at detecting AF compared to the Reveal XT.

No studies were identified for the BioMonitor 2-AF or Confirm RX devices in CS populations and so evidence for these devices is limited to mixed population DTA and single-arm observational studies submitted by the companies. No evidence was found for any device for several outcomes (mortality, hospital and outpatient care for AF, related morbidities, AEs related to anticoagulation) and information about clinician ease of use and ICM acceptability to patients was limited. Nevertheless, they suggest the newer models of the ICMs (e.g. Reveal LINQ and Confirm RX) are easier to insert, associated with fewer AEs and suitable for insertion by trained nurses and cardiac physiologists. There is also evidence that the ICMs detected some non-AF cardiac arrhythmias although the potential benefit of this is unclear.

Cost-effectiveness discussion

The results of the pairwise analysis, demonstrate ICMs could be considered cost-effective at a £20,000 – £30,000 threshold compared with SoC. These results are comparable with the economic analysis produced by Diamantopoulos *et al*. 2016 which also used data from CRYSTAL-AF to compare ICMs with SoC.

Furthermore, clinical expert opinion suggests that an additional benefit of ICMs devices is the ability to detect non-AF arrhythmias, potentially preventing other events. However, data on incidental findings from ICMs was only found in observational studies, as previously mentioned and are of poor quality. As such, it is unclear how detection of other non-AF arrhythmias differs between standard care and ICMs and furthermore how a patient's treatment pathway changes. Therefore, understanding the differences in costs and benefits for incidental findings for ICMs is problematic. However, if without an ICM some of these arrhythmias remain undetected, then the impact on the cost-effectiveness estimates would be favourable towards ICMs, but the size of the impact is difficult to determine.

Conclusions

The evidence suggests that the Reveal LINQ is more effective in detecting AF than conventional follow-up and is associated with low AE rates. However, there is insufficient clinical data available for the Confirm RX and BioMonitor 2-AF in a CS population and so it is not possible to draw conclusions on their clinical efficacy or how any of the ICMs might compare with each other.

Based on a strong assumption of clinical equivalency between all the devices, the economic analysis found ICMs could be considered cost-effective at a £20,000 – £30,000 threshold compared with SoC. When each device is compared incrementally, BioMonitor 2-AF dominates Reveal LINQ and Confirm RX.

Study registration

The protocol for this review is registered on PROSPERO as CRD42018109216.

Funding

This Diagnostics Assessment Report was commissioned by the NIHR HTA Programme on behalf of the National Institute for Health and Care Excellence as project number 18/13/01.

1 BACKGROUND AND DEFINITION OF THE DECISION PROBLEM

The scope of this diagnostic assessment review (DAR) is to assess the cost-effectiveness of implantable cardiac monitors (ICM) to detect suspected paroxysmal atrial fibrillation (AF) in people who have had a cryptogenic stroke (CS, Table 1).[2] The review considers the diagnostic accuracy, clinical outcomes and costs of three types of ICM compared with no further testing after at least 24-hours of outpatient external ambulatory electrocardiogram (ECG), the alternative AF monitoring strategy in UK clinical practice.

Table 1. Scope of the assessment (reproduced from NICE final scope[2])

Decision question	**Does the use of implantable cardiac monitors to assess for suspected paroxysmal atrial fibrillation in people who have had a cryptogenic stroke represent a cost-effective use of NHS resources?**
Populations	People with a cryptogenic stroke (which includes cryptogenic 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 atrial fibrillation. Potential subgroups o 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) o People with a cryptogenic TIA o People with a cryptogenic stroke (excluding TIA)
Interventions	o BioMonitor 2-AF o Confirm RX o Reveal LINQ
Comparator	No further monitoring for atrial fibrillation (after at least 24 hours of outpatient external ambulatory ECG monitoring that has not detected atrial fibrillation)
Healthcare setting	Secondary and tertiary care
Outcomes	Intermediate measures for consideration may include: o Diagnostic accuracy o Diagnostic yield (number of atrial fibrillation diagnoses) o Detection of other cardiac pathologies or incidental findings (non-atrial fibrillation) o Time to diagnosis of atrial fibrillation o Time to initiation of anticoagulants o Uptake of anticoagulants o Incidences of device failure (such as inability to transmit data or unexpectedly short battery life) and device removal because of failure or adverse events o Hospitalisations caused by atrial fibrillation o Number of outpatient visits related to monitoring for atrial fibrillation o Ease of use of devices for clinicians (including insertion)
	Clinical outcomes for consideration may include: o Mortality o 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)
	Patient-reported outcomes for consideration may include: o Health-related quality of life o Acceptability of the devices to patients
	Costs will be considered from an NHS and Personal Social Services perspective. Costs for consideration may include:

	○ Costs related to implanting and removing the devices including staff and infrastructure costs ○ Costs related to the implantable cardiac monitor technologies (including training and consumable costs) ○ Costs related to maintenance of devices and ongoing monitoring (such as staff time to review and interpret ECGs recorded by the devices) ○ Costs related to preventative treatments, such as anticoagulants or antiplatelet therapies, and appointments required for changes of medication ○ Costs related to treatment for conditions related to atrial fibrillation (such as stroke and heart failure) ○ Costs related to adverse events caused by anticoagulation therapies or implanting/removing the devices
	The cost-effectiveness of interventions should be expressed in terms of incremental cost per quality-adjusted life year.
Time horizon	The time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes, including the risk of a further stroke, between the technologies being compared.
Abbreviations: ECG, electrocardiogram; NHS, National Health Service; NICE, National Institute for Health and Care Excellence; TIA, transient ischemic attack.	

1.1 Description of the health condition and aetiology

1.1.1 Population: Cryptogenic stroke or TIA

Stroke is the third most common cause of premature death in the UK[3] and a major cause of preventable disability.[4] Improvements in care have greatly improved mortality and morbidity over the last two decades, but there are still around 30,000[3] stroke related deaths each year in England, and around a quarter of patients leave hospital with moderate to severe disability.[5]

Strokes and transient ischemic attacks (TIAs) are caused by the interruption of the blood supply to part of the brain, either due to the narrowing or blockage of a blood vessel by a blood clot (ischemic stroke), or due to a bleed from a blood vessel in the brain (haemorrhagic stroke). The main difference between a stroke and a TIA is that the symptoms caused by damage to brain tissue from a TIA resolve within 24 hours, whereas in an untreated stroke the symptoms last for longer. Common symptoms of stroke include numbness, weakness or paralysis, slurred speech, blurred vision, confusion and severe headache.[6]

Causes of stroke are manifold and include the build-up of plaque in the artery supplying the ischemic region (atherosclerosis), AF, blood clots or tumours in the heart, heart abnormalities, recent myocardial infarction, migraine, and drug misuse.[7] However, up to a third of first time strokes are cryptogenic, meaning no known cause can be identified, which is most common in younger patients.[7] The Evidence Assessment Group's (EAG's) clinical experts reported that patients in the UK who have had a stroke will generally undergo a series of tests to identify a cause before the event is classed as cryptogenic, although some definitions include insufficient testing or identification of more than one cause.[7, 8] Diagnostic tests to identify cause of stroke generally include blood tests, inpatient ECG, echocardiogram (ECHO) and doppler ultrasound scan of the carotid arteries.

The recurrence rate of stroke is around 30% and people are at highest risk of a subsequent stroke in the first year, when mortality rates are also at their highest.[9] Establishing the cause of a stroke is paramount to decrease the risk of recurrence by selecting appropriate preventative care.[10]

1.1.2 Target condition: Atrial fibrillation

Atrial fibrillation (AF) is an irregular, rapid heart rhythm that can be intermittent or continuous. People with AF may experience heart palpitations, fatigue, dizziness and shortness of breath, but many people do not experience symptoms.[11] An estimated 1.4 million people in England have AF (approximately 2.5% of the population), and it is estimated that 425,000 are undiagnosed, making it the most common arrhythmia.[12] The prevalence of AF is higher in men than in women (2.9% versus 2.0%) and increases with age, with 80.5% of cases in people aged over 65 years.[12, 13]

The intermittent nature of paroxysmal AF can make diagnosis with short-term electrocardiogram (ECG) monitoring problematic because patients having infrequent episodes may not experience one during the monitoring. Asymptomatic AF can also remain undiagnosed unless a patient develops symptoms or is monitored incidentally for another reason or during a hospital stay. If AF is suspected, the likelihood of detecting asymptomatic paroxysmal AF increases with duration of monitoring or with repeated monitoring strategies.[14, 15]

People with AF have a five-fold higher risk of having a stroke or TIA compared to people without AF.[13, 16] The irregular heart rhythm means the heart can fail to empty properly and the remaining blood can form a clot. Stroke or TIA can occur if the clot moves and narrows or blocks the arteries supplying blood flow to the brain. While the relationship between AF and stroke is established, there has been some debate regarding the temporal relationship between them, with some studies suggesting AF acts as a marker of atrial dysfunction rather than a direct cause stroke.[7, 17, 18] The EAG's clinical experts advised that AF detected more than two year's post stroke may not be related to the index event although its management is still likely to be the same and the patient would be considered for treatment with a long-term oral anticoagulant (OAC). Clinical experts also reported that it is thought that up to half of all recurrent strokes may be due to an unrelated mechanism to that of the index event. Clinical experts also reported that there is no consensus on the duration of AF required prior to the commencement of an OAC and that the ICM devices have varying programmable thresholds for the detection of AF; e.g. 30 seconds, 2 minutes, 6 minutes, etc. Clinical experts suggested that treatment for AF of any duration in a CS patient should be considered due to the risk of recurrent stroke.

1.2 Current pathway of care

The EAG's clinical experts reported that there is no standard guideline on the diagnostic tests required in the UK to further investigate patients with CS or TIA for underlying AF and there is no consensus

on the duration or mode of monitoring for AF. The National Institute for Health and Care Excellence (NICE) guideline on stroke and TIA in over 16s: diagnosis and initial management (CG68) 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.[6]

The NICE guideline on AF 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 patients with CS or TIA.[19] 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.[20]

The EAG's clinical experts reported that patients with a CS or TIA diagnosis will typically have a short-term ECG as an inpatient to detect cardiac arrhythmias such as AF as part of the standard suite of diagnostic tests to identify the cause of stroke or TIA. Patients with no AF during inpatient monitoring will often receive outpatient external ambulatory ECG monitoring for 24 to 48-hours (for example using a Holter monitor). Clinical experts reported that 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 CS or TIA and that they are likely to only be used in the National Health Service (NHS) after patients have received an initial period of at least 24-hours external ambulatory monitoring.

Patients with AF detected after stroke or TIA can be treated to reduce the risk of a further stroke. NICE recommendations for stroke prevention therapy include rate or rhythm control and anticoagulation based on bleeding risk and CHA_2DS_2-VASc score.[19] CHA_2DS_2-VASc is measure of stroke risk in patients with AF based on age, sex, and history of congestive heart failure, stroke or TIA, vascular disease and diabetes.[21] Patients with prior stroke or TIA have a minimum CHA_2DS_2-VASc of 2 and automatically qualify for anticoagulation according to current NICE guidance (CG180), regardless of the presence of other stroke risk factors.[19] The NICE pathway for preventing stroke in people with AF[22] recommends anticoagulation with apixaban, dabigatran etexilate, edoxaban, rivaroxaban or a vitamin K antagonist, and the NICE guideline for AF management (CG180)[19] recommends review at least annually, and recommends against aspirin monotherapy. If anticoagulation is contraindicated due to bleeding risk, NICE recommends rate or rhythm control measures, annual review to assess stroke and bleeding risk, and consideration for left atrial appendage occlusion.[19] Clinical experts reported that patients with CS diagnosed with AF during follow-up with an ICM are most likely to have paroxysmal AF and the management would usually be anticoagulation. Clinical experts also reported that patients identified in advance as being unsuitable for anticoagulation, for example due to their risk of bleeding,

may not receive an ICM. However, clinical experts also reported that some patients diagnosed with AF may receive a left atrial appendage occlusion device as an alternative to oral anticoagulation therapy.

1.3 Description of the technologies under assessment

Implantable cardiac monitors (ICMs), also known as insertable cardiac monitors or implantable loop recorders, are small devices inserted beneath the skin of the chest. The devices allow extended monitoring and automatic recording of heart rhythm. The devices are inserted under local anaesthetic via a small incision and capture continuous ECG to detect various arrhythmias, including AF. ICMs are currently used in the NHS primarily as a method of monitoring patients experiencing syncope (fainting) to detect and treat underlying arrhythmias. The devices offer the possibility of continuous rhythm monitoring of people who have had a CS or TIA to increase the detection of intermittent or paroxysmal AF to help guide appropriate treatment for secondary stroke prevention.

The devices are usually inserted by cardiologists, cardiac physiologists and nursing staff in a sterile environment such as a catheterisation laboratory (hereafter, cath lab), but clinical experts report that there is variation across devices and with the ICM experience of the service in which the patient is being treated. Devices can be explanted once an arrhythmia has been detected or at the end of the battery life but can also be left *in situ*. Adverse events (AEs) are rare but can include infection or reaction at the insertion site, bleeding, excessive fibrotic tissue growth, extrusion, hematomas or cysts, keloid formation, and erosion or migration of the device.

Once implanted, the devices automatically capture continuous ECG, and record and transmit detected arrhythmia episodes for clinical review. Recording of episodes can also be activated manually by the patient if symptoms occur using optional external handheld patient devices or smartphone apps depending on the ICM. Detection parameters, data storage, method of data transmission and notification settings vary by device (see Table 2), but all have capabilities to recognise a range of arrhythmias and alert clinicians when an episode is detected. Data are transmitted via internet or cellular networks and encrypted for online storage. Clinical experts reported that programming of ICMs in relation to use of inbuilt automatic programmes varies depending on the patient characteristics and clinician preference. The clinical experts reported that often the ICMs standard setting for arrhythmia detection in CS patients is used to start with and this is then adjusted as necessary. The clinical experts also reported that the patient activator device is generally of little benefit if used in CS patients as they are generally asymptomatic in terms of AF and other cardiac arrhythmias.

Characteristics of the three ICMs included in the NICE scope[2] – BioMonitor 2-AF (BIOTRONIK, Berlin, Germany),[23] Confirm RX (Abbott, Illinois, USA),[24] and Reveal LINQ (Medtronic, Minneapolis, USA)[25] – are summarised in Table 2. The EAG has also included information about the Reveal XT device which is an earlier Medtronic model, because it was the device used in the only RCT identified

in the clinical evidence search. Earlier BIOTRONIK and Abbott ICM models are also available but have not been included because no relevant evidence in the CS or TIA population was submitted by the companies, and their capabilities were not considered relevant to the decision problem. However, it should be noted that some data on the Confirm DM202 in a non-CS population is discussed in Section 3.4.1 in the absence of data on the Confirm RX in a CS or non-CS population.

Table 2. Overview of the technologies under assessment

	In scope[2]			Not in scope
	BioMonitor 2-AF	**Confirm RX**	**Reveal LINQ**	**Reveal XT**
Standard components	•BioMonitor 2-AF device with flexible lead body •Insertion tools (FIT1 and FIT2) •SensingConsult™ programmer and software •Optional Remote Assistant	•Confirm RX device •Insertion tools •Merlin™ PCS and software •myMerlin™ mobile app •Merlin.net PCN •Mobile device with Bluetooth® wireless technology connection*	•Reveal LINQ device •Reveal Patient Assistant device •MyCareLink Programmer •MyCareLink Patient Monitor and network •Insertion tools	•Reveal XT device •Reveal Patient Assistant Device •CareLink Programmer •Vector Check positioning tool
Cost of device	£1,030	£1,6[illegible]	[illegible]	N/A
ICM dimensions	88.4 x 15.2 x 6[illegible] (weight 10.1 g)	[illegible] x 9.4 x 3[illegible] (weight 3.0 g)	4[illegible].8 x [illegible] x [illegible].0 mm (weight 2.5 ± 0.5 g)	95 x 62 x 8 mm (weight 15 g)
Insertion procedure	Commonly by cardiologist (± assistant) in cath lab; nurse- or physician-led insertion increasing	Commonly by cardiologists, cardiac physiologists and nursing staff in a cath lab.	By cardiologists, cardiac physiologists and nursing staff in a cath lab although company submission reported that 'out-of-lab' procedures are possible.	By cardiologists, cardiac physiologists and nursing staff in cath lab.
Patient activation	Optional hand-held patient assistant available	Integrated™ in myMerlin app	Patient assistant device as standard	Patient assistant device – 1- and 2-button models available
Detection and sensing parameters	Adjustable or pre-set functions to detect various AF characteristics, high ventricular rate, bradycardia, sudden rate drop and asystole	AF (regularity, R-R variance and sudden onset), brady arrhythmias, tachy arrhythmias, pauses, tloc conditions, epilepsy exclusion.	Standard and adjustable AF settings, tachyarrhythmia, bradyarrhythmia, pause episodes.	Atrial tachyarrhythmia/ atrial fibrillation (exclusive algorithm), bradyarrhythmia, asystole, ventricular tachyarrhythmia
Device storage	55 automatically detected episodes and 4 patient activated episodes (total 60 minutes)	Up to 250 AF episodes plus [illegible]50 auto-activated and patient-activated episodes (total 60 mins)	27 mins of automatic detections and 30 mins of patient-activation	27 mins of automatic detections and 22.5 mins of patient-activation
Telemetry	Daily message to Home Monitoring Service Centre via cellular phone network	Via app to Merlin.net™ PCN, accessed by clinicians	Via myCareLink Patient Monitor to a CareLink server using a cellular telephone connection network.	Via CareLink programmer to CareLink server
Clinician notification	Alerts via email, SMS or fax	Email/SMS alerts through website. Auto follow-up via app monthly.	Alerts via cellular telephone connection network	Follow-up via the Programmer at pre-set intervals or programmable notification on detection
Estimated battery life	4 years	2 years	3 years	3 years

	In scope[2]			Not in scope
	BioMonitor 2-AF	**Confirm RX**	**Reveal LINQ**	**Reveal XT**
Additional features	-	Symptom annotator via app Free technical support available via helpline or local staff	Patient activity accelerometer Triage and monitoring service (FocusOn)	-
Abbreviations: cath lab, catherisation laboratory; PCN, patient care network; PCS, patient care system; SMS, short messaging service. *provided free by Abbott if required				

1.3.1 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.[23] 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. Only the BioMonitor 2-AF is included in the scope of this review because information provided by the company indicate that other models, such as the BioMonitor 2-S, do not have functionality for AF detection.

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 parameters in the sensing settings, such as high pass filter, target sensing threshold, or noise window, can be adjusted to individual patients. Alternatively, standard and preconfigured settings are available, all contained within the SensingConsult™ program. The signals are automatically recorded and stored once a detection type is activated and the detection occurs, and multiple detection types can be activated simultaneously.

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, short message service (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 an arrhythmia episode or a problem with the device are forwarded to the patient's clinician at a pre-set time, and a test message can be initiated by the programmer at any time to check the Home Monitoring function.

A total of 55 individual episodes with a length of at least 40 s each can be stored automatically. The device can store four recordings triggered by the patient (using the optional patient remote assistant device) 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. It is reported by BIOTRONIK that the BioMonitor 2-AF has a battery life of 4-years, which is the longest out of the three ICMs under review in this DAR.

1.3.2 Confirm RX

The Confirm RX™ (developed by St Jude Medical which was acquired by Abbott) is designed to detect arrhythmias and wirelessly transmit data to the Merlin.net™ Patient Care Network (PCN).[24] The Confirm RX ICM comprises of internal and external components. 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, and remote transmissions are performed using the associated smartphone app. The app also allows patients to record and send ECGs of symptomatic events to the clinic without the need for an additional patient activator device that is required with some other ICM devices (e.g. Reveal LINQ and BioMonitor 2-AF).

The ICM has a CS programmable setting in which certain device parameters are automatically programmed to detect and record arrhythmias in CS patients. The detection algorithms combine regulatory, variance and sudden onset measures to recognise and trigger an alert for AF. Clinicians can choose fixed settings or programme parameters including episode duration threshold, AF burden alerts and storage of pre- and post-AF recordings. 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. The company reports the battery life of the Confirm RX to be two years; although this is based on the assumption of an average of one auto detected episode per day, one patient activated symptom episode per month and up to 6-months shelf storage time prior to implantation.[26]

Information provided by the company included physical specifications and a list of warnings and precautions, including physician training and insertion procedures. Additional information about the detection capabilities were provided by the company upon request (Table 2).

The EAG notes from literature available on the company website[27] that there were two earlier models of ICM released by St Jude Medical, the SJM Confirm™ DM2100 and the SJM Confirm™ DM2102. The model under review in this DAR is the Confirm RX™ DM3500 and the EAG is unclear how this differs to the earlier models. The EAG requested clarification from the company who reported that the DM2102 is a pacemaker-sized device that requires a larger incision and cath lab or pacing suite facilities for insertion by a cardiologist. The company also reported that the DM3500 is the Confirm Rx, and that this is a much smaller device that is injectable and only requires clean facilities, such as side room, and can be inserted by a specialist nurse or cardiac physiologist. Due to the absence of clinical data on the Confirm RX DM3500 the EAG reports some data in Section 3.4.1 from a clinical study relating to the SJM Confirm DM2102.

1.3.3 Reveal LINQ

The Reveal LINQ™ Insertable Cardiac Monitoring System (Medtronic) consists of a Reveal LINQ ICM, Patient Assistant, MyCareLink Programmer and remote monitoring system (MyCareLink Patient Monitor and MyCareLink network. The Reveal LINQ ICM kit also includes tools tailored to facilitate insertion of the device. The Reveal XT is an earlier and larger Medtronic ICM model that has AF detection functionality for patients with CS. Clinical expert opinion and evidence from a mixed population suggest that the Reveal LINQ has better specificity than the XT (Section 3.4.3), is easier to implant and leads to fewer complications due to its size, and that AF detection accuracy between the devices is similar.[28]

Medtronic highlighted that size of Reveal LINQ differentiates it from other devices and means a smaller incision in the skin is required (less than 1 cm). Clinical experts at the NICE scoping workshop reported that the procedure can be done by healthcare professionals other than cardiologists (e.g., cardiac physiologists, nurses, neurologists or stroke physicians) and in a procedure room rather than a cath lab. Training in inserting the device is provided by the Medtronic field team and is also available on-line. Medtronic also offer a monitoring service (FOCUSON) to interpret and triage ECG recordings made by the device before the patient's clinician is notified.

The device can be programmed by placing the Medtronic CareLink™ programmer head over the device and there are pre-programmed settings that the EAG's clinical experts reported are generally used for patients with CS. ECG recordings for episodes of AF are stored although the device uses a detection window of 2 minutes in its algorithm for AF detection; the ICM therefore cannot reliably detect AF episodes of less than 2 minutes. The ICM can be programmed to only store episodes of AF exceeding a set threshold (all episodes, 6, 10, 20, 30 or 60 minutes) although the default setting in CS would be to store all detected episodes of AF. Total AF burden can be calculated, and tachyarrhythmia, bradyarrhythmia and pause episodes can also be detected. The battery-operated and hand-held Patient Assistant device allows the patient to press a button to trigger a recording in the event of symptoms (e.g., onset of loss of consciousness or palpitations).

The battery life of the device is estimated by the company to be 3 years with average use assumptions (1 auto-detected episode per day and 1 patient-activated episode per month). As for the other devices, it is for single patient use and, while it does not need to be removed, the company recommend doing so if it is no longer needed. The ICM can store up to 27 minutes of ECG from arrhythmias detected automatically and up to 30 minutes from patient-activated episodes. The device also contains an accelerometer to allow changes in patient activity over time to be monitored.

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, and the device will register as 'disconnected' if it is unable to communicate with CareLink.

1.4 Comparators and the reference standard

The diagnostic accuracy and clinical outcomes of ICMs are considered for patients with CS or TIA in whom no AF has been detected following a minimum of 24 hours of external ECG cardiac monitoring. The clinical outcomes for ICMs (after a minimum of 24 hours of external ECG monitoring) will be compared to no further monitoring (also after a minimum period of 24 hours of external ECG monitoring). The diagnostic test accuracy (DTA) of the ICMs will be compared to 24-hour external ambulatory ECG monitoring or other commonly used ECG monitoring regimens such as 7-day Holter monitoring; the reference standard. External ECG monitoring is most commonly conducted with a Holter monitor, a portable battery-operated device that records continuous ECG, usually for 24 to 48 hours via electrodes that attach to the skin.

2 METHODS FOR ASSESSING CLINICAL EFFECTIVENESS

A systematic literature review was conducted to evaluate the clinical effectiveness of the Reveal LINQ insertable cardiac monitor,[25] the BioMonitor 2-AF ICM[23] and the Confirm RX ICM[24] for detecting suspected asymptomatic atrial fibrillation (AF) after cryptogenic stroke (CS), and the diagnostic accuracy of these three implantable cardiac monitors (ICMs) for the diagnosis of AF.

The systematic review methods follow the general principles outlined in the Centre for Reviews and Dissemination (CRD) guidance for conducting reviews in healthcare,[29] the NICE Diagnostics Assessment Programme manual[30] and the Cochrane Handbook for Systematic Reviews of Diagnostic Test Accuracy.[31] The protocol for this review is registered on PROSPERO as CRD42018109216 and also available at: https://www.nice.org.uk/guidance/gid-dg10023/documents/final-protocol.

2.1 Eligibility criteria

Study populations eligible for inclusion in the review of clinical effectiveness were those comprising of people with a cryptogenic embolic stroke or cryptogenic transient ischaemic attack (TIA) for whom there is a suspicion of paroxysmal AF. In the protocol it was specified that, if possible, patients were to have had at least 24 hours of outpatient external ambulatory electrocardiogram (ECG) monitoring that has not detected AF although this was not applied as an inclusion criterion in the final review due to the small number of eligible studies identified. Based on the available evidence, and in line with the protocol, this eligibility criteria was not applied and study defined CS or TIA was permitted. The study definitions and inclusion criteria are discussed alongside the results in Section 3.

Study setting (as planned in the protocol) was not used to determine study eligibility. However, in the protocol it was anticipated that the relevant study setting would be secondary or tertiary care which was consistent with the studies included.

The interventions under investigation in this diagnostic assessment report are:

- Reveal LINQ;[25]
- BioMonitor 2-AF; [23]
- Confirm RX. [24]

Data from earlier versions of each of the devices were included as deemed necessary; in particular data from an earlier model of the Reveal LINQ, known as the Reveal XT, were included. The comparators

for included studies were each of the interventions versus each other or versus no further testing after outpatient external ambulatory ECG monitoring.

The anticipated comparator for the assessment of diagnostic accuracy was 24-hour external ambulatory ECG monitoring with the reference standard being clinical validation of ICM detected AF or ECG validation. In addition, papers that included other commonly used ECG monitoring methods as the comparator such as 7-day external ECG monitoring were considered although no diagnostic accuracy studies were identified that met the population inclusion criteria (CS) irrespective of the comparator selected.

The following outcomes were considered in the review:

- Diagnostic accuracy (sensitivity, specificity, and the numbers of true positive, true negative, false positive and false negative test results);
- Diagnostic yield in terms of number of AF diagnoses;
- Diagnostic yield in terms of the detection of other cardiac pathologies or incidental findings (i.e. non-AF)
- Time to diagnosis of AF;
- 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 (AEs);
- Hospitalisations caused by AF;
- Number of outpatient visits related to monitoring for AF;
- 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 AEs of anticoagulation treatment, and any AE related to implanting or removing the devices, such as infection or inflammation);
- Health-related quality of life (HRQoL);

- Acceptability of the devices to patients.

The following types of studies were planned to 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 included a reference standard of other commonly used ECG monitoring such as 7-day external ECG monitoring were considered.

As insufficient studies were identified for the ICMs following a minimum of 24-hours external ECG monitoring, studies of ICMs following shorter durations or no external ECG monitoring were also considered for inclusion. However, there was still insufficient data for the Reveal LINQ and no suitable comparative studies identified for the Confirm RX or BioMonitor 2-AF in the CS population. The study design inclusion criteria were therefore relaxed to also allow inclusion of single-arm observational studies for any of the three ICM devices and their earlier models and the review protocol was amended.[32] The rationale for choosing to amend the study design inclusion criteria rather than another part of the population, intervention, comparator and outcomes (PICO) inclusion criteria was that the current searches only limited studies by their population and interventions. The interventions are already unrestricted in terms of the model of the devices specified in the NICE final scope for the review[2] and so no further changes could be made to broaden the included interventions. The population inclusion criteria were also considered unsuitable for extending further, as the definition of CS was unrestricted and the AF detection rates in ICM devices are dependent on the patient population, as is the incidence of the other clinical outcomes of interest in this diagnostics assessment review (DAR).[1] Therefore, allowing the inclusion of studies in non-cryptogenic stroke patients was deemed to be unsuitable as they are likely to have different incidence rates of AF, and the other clinical outcomes of relevance to this DAR.[1] It was therefore considered that data from non-cryptogenic stroke populations would not be representative of the respective ICM device performance in cryptogenic stroke or TIA (hereafter referred to as CS) patients.

The following study/publication types were excluded:

- Pre-clinical and animal studies;

- Reviews, editorials, and opinion pieces;

- Case reports or studies of fewer than 10 patients;
- Non-English language studies.

2.2 Search strategy

The electronic database searches combined terms for the condition (AF) and terms for the technology being assessed. For the technology, generic terms (e.g. ICM) and terms for the specific product (e.g. Reveal LINQ) were used. There were no study design filters applied although animal and non-English language articles were excluded using search syntax. The search strategy was refined by scanning key papers identified during the review, and through discussion with the review team, clinical experts and information specialists.

Electronic sources that were searched were as follows: MEDLINE (Ovid), EMBASE (Ovid), the Cochrane Library (including the Cochrane Database of Systematic Reviews [CDSR] and the Cochrane Central Register of Controlled Trials [CENTRAL]), and the CRD database for the Database of Abstracts of Reviews of Effects (DARE] and the Health Technology Assessment [HTA] Database.

The electronic databases were all searched from inception until the latest available version. A copy of the final search strategies is provided in Appendix 9.3.

Ongoing and unpublished studies were also searched and identified using:

- clinicaltrials.gov;
- controlled-trials.com;
- clinicaltrialsregister.eu;
- company submissions from Abbott, BIOTRONIK, and Medtronic; and
- the clinical effectiveness electronic database search results.

Relevant reviews and guidelines were identified through electronic database searches, consultation with clinical experts and searching the National Institute for Health and Care Excellence (NICE) website and the reviews were used to identify further potentially relevant studies.

Reference lists of included papers have also been assessed for additional relevant studies. It was planned to hand search the European Stroke Organisation Conference, International Stroke Conference and UK stroke forum conference proceedings for the last 2 years, but this was deemed unnecessary as abstracts

from those conferences were identified in the literature searches and supplemented by the submissions from companies.

2.2.1 Handling information from the companies

Data submitted by companies was originally only going to be considered if received by the Evidence Assessment Group (EAG) no later than 30/09/2018. However, all data submitted by companies during the writing of the report has been considered for inclusion and additional information has also been requested and provided by each of the three companies involved. Data that met the inclusion criteria for the review have been extracted and quality assessed as stated in the methods section of this protocol.

Any 'commercial in confidence' data provided by companies, and specified as such, has been highlighted in [redacted] in the assessment report (followed by the company name in parentheses). Any 'academic in confidence' data provided by companies, and specified as such, has been highlighted in [redacted] in the assessment report.

2.3 Study selection and data extraction

The titles and abstracts of all identified studies from the electronic database searches were 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 were obtained and all full-texts were again assessed independently by two reviewers for inclusion using the eligibility criteria outlined in Section 2.1. Any disagreements were resolved by discussion, and, it was not necessary to consult with the third reviewer.

Data for the comparative studies were extracted independently by two reviewers using a standardised data extraction form. Data for five of the single-arm and observational studies were extracted independently by two reviewers to pilot the data extraction form. After agreeing the final data extraction form, one reviewer completed the data extraction for the remaining studies and the second reviewer validated 25% of the included studies. Information extracted included 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 AEs. Where there was incomplete information, attempts were made to contact authors with a request for further details. Discrepancies in the data extraction were resolved by discussion, and a third reviewer was available if necessary, although they were not required.

2.4 Quality assessment

The quality of included comparatives studies has been independently assessed by two reviewers and any differences were resolved by consensus with a third reviewer consulted if necessary. The included

randomised controlled trial was 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 2.0 Tool.[33] The observational studies were not quality assessed as the majority of them were single-arm studies and there is no standardised quality assessment tool suitable for assessing single-arm clinical effectiveness studies. It should also be noted that their results are only reported narratively or in tables (no evidence synthesis conducted using them). There were no diagnostic accuracy studies in CS patients included and so quality assessment with the QUality Assessment of Diagnostic Accuracy Studies - 2 (QUADAS-2) tool[34] was not required.

2.5 Methods of analysis and evidence synthesis

Details of results on clinical effectiveness and quality assessment for each included study are presented in structured tables and as a narrative summary. There was insufficient clinically and methodologically homogenous data available to enable data to be pooled and meta-analysed. Clinical and methodological heterogeneity were investigated and discussed narratively.

For test accuracy data, positive predictive values (PPV), negative predictive values (NPV), sensitivity values and specificity values, with 95% confidence intervals are presented for each study where available.

2.5.1 Potential subgroup analyses

The subgroups which were investigated where evidence allowed were as follows:

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

2.5.2 Sensitivity analyses

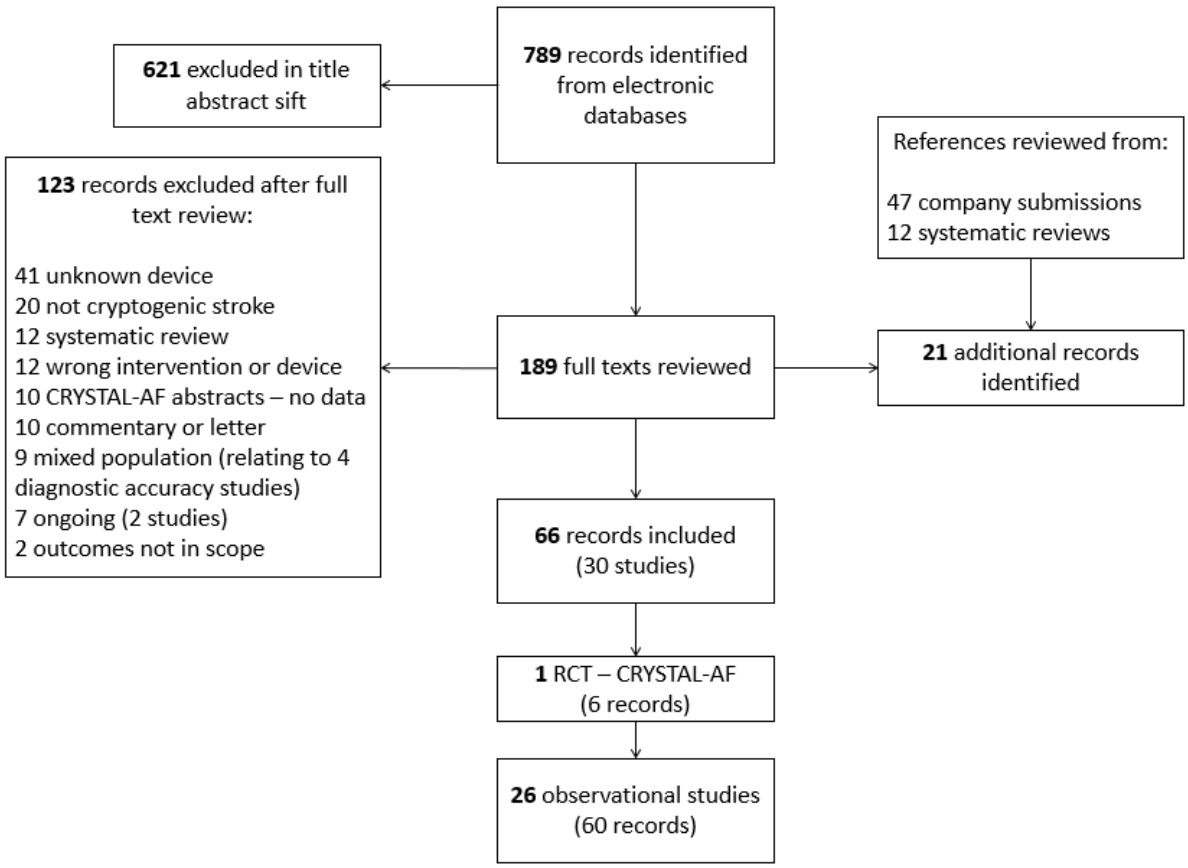
The planned sensitivity analyses were to include studies deemed to be high risk of bias that were excluded from the primary analyses. Sensitivity analyses were not conducted as there was insufficient data for any data synthesis to be conducted.

3 RESULTS OF CLINICAL EFFECTIVENESS REVIEW

3.1 Quantity and quality of the available evidence

The electronic database searches were run on 13 September 2018. The results of the electronic database searches are summarised in Figure 1. There were 72 references identified in the Cochrane database searches (Cochrane Database of Systematic Reviews [CDSR] and Cochrane Central Register of Trials [CENTRAL]), 1 reference from resources searched through the CRD (Database of Abstracts of Reviews of Effects [DARE] and the Health Technology Assessment [HTA] database), 758 references from EMBASE (via OVID) and 123 references from Medline (via OVID). The 954 results from the electronic database searches were all imported into EndNote and de-duplicated. Following de-duplication, there were 789 articles from electronic database searches that were assessed for eligibility in the review through title and abstract screening. The reference lists of 12 systematic reviews identified in the database searches were also screened for potentially relevant studies along with 47 documents supplied by the companies of the three implantable cardiac monitors (ICM devices (Confirm RX, Abbott; BioMonitor 2-AF, BIOTRONIK; and Reveal LINQ, Medtronic).

Figure 1. PRISMA diagram for the review of clinical effectiveness



As discussed in the methods section (Section 2.1), initially the results were screened for comparative studies, but comparative data was only available for one device albeit for a different model (Reveal

LINQ rather than XT). As comparative studies proved to be unavailable for two of the devices (Confirm RX and BioMonitor 2-AF), single arm observational studies were also reviewed for the following:

- to identify any useful information that could be obtained for Confirm RX, BioMonitor 2-AF and Reveal LINQ;
- in addition, to:
    - find confirmatory evidence for the outcome data identified for the Reveal XT;
    - inform any outcomes in the National Institute for Health and Care Excellence (NICE) final scope[2] not covered by the comparative study identified for REVEAL XT.

This protocol amendment affected only the screening of the results and was implemented following the first sift of the title and abstracts. The results are therefore presented for the revised inclusion criteria to avoid double counting of articles that met the original and the revised inclusion criteria. In total 189 full texts were screened and 66 of these (relating to 27 studies) were included in the diagnostics assessment review (DAR). A list of excluded studies along with the reasons for exclusion is provided in Appendix 9.4.

The 66 included articles relate to 1 randomised controlled trial (RCT; 6 publications), and 26 observational studies (60 publications). The RCT relates to a study known hereafter as CRYSTAL-AF.[35] which compared the Reveal XT ICM with conventional follow-up for AF in patients with a CS or cryptogenic transient ischemic attack (TIA; hereafter referred to together as CS). The results of CRYSTAL-AF are discussed separately to the observational studies below. The rationale for discussing the CRYSTAL-AF RCT data separately is that it was deemed to be the most robust clinical evidence for the Reveal LINQ ICM despite it relating to an earlier model, the Reveal XT. In addition, the evidence assessment group (EAG) noted that all the included observational studies related to the Reveal LINQ or its earlier model, the Reveal XT, with one study also including a small proportion of patients with the BioMonitor (an earlier model of the BioMonitor 2-AF) but reporting no data by device. The observational studies, therefore, do not provide clinical data for the other ICM devices under review in this DAR (BioMonitor 2-AF or Confirm RX) but they do supplement the evidence from CRYSTAL-AF by providing data for an additional outcome from the NICE scope and providing a larger data set to reflect the generalisability of the results from the RCT. The observational studies provide additional outcome data for all of the outcomes for which data were obtained from CRYSTAL-AF with the exception of health-related quality of life (HRQoL). In addition, the observational studies provided data for the outcome of diagnostic yield of cardiac pathologies other than atrial fibrillation (AF).

Company submission data on non-CS populations were therefore included to enable some discussion on the clinical effectiveness of BioMonitor 2-AF and Confirm RX.

Eight ongoing studies were identified from the registry searches (n = 4), the electronic database searches (n = 1, plus 1 duplicate), and from material submitted by the companies (n = 3). Seven records were excluded from the registry searches for having the wrong populations and two were already included in the review (Pedersen 2018 and the LINQ registry reported in Ziegler 2017; NCT02011256 and NCT2746471, respectively). In addition to studies already reviewed in the registry searches, STROKE-AF (NCT02700945) was excluded from the company submission lists because it recruited people with stroke of known origin.

SAFFO (the Silent Atrial Fibrillation aFter Ischemic StrOke trial; NCT02684825) is a prospective, multicentre, randomised, controlled, open-label trial based in Italy. The study aimed to randomise 424 patients with thrombotic or lacunar stroke to receive a Reveal LINQ ICM or standard monitoring for AF detection. The primary outcome is AF or flutter within 12 months to be assessed by blinded reviewers. The study began in October 2015 and planned to recruit 424 patients. The estimated primary completion listed on clinicaltrials.gov is June 2018 but no results have yet been reported.

NOR-FIB (NCT02937077) is a multi-centre prospective observational trial of the Reveal LINQ ICM based in Norway. The study is designed to evaluate AF detection and identify biomarkers in 500 patients with CS or TIA over 12 months and is due to report in 2019. NCT03720639 plans to recruit a mixed diagnosis cohort of 500 patients to compare the transmission capabilities of the Confirm RX and Reveal LINQ, which is due to complete in 2020. Two further ongoing studies identified in the registry searches have no status, results, or associated publications; CRYPTONITE (NCT001025947) is listed as an Italian observational study of the Reveal XT with a planned enrolment of 100 patients with CS but no update since 2013, and NCT02216370 is a Slovakian case-control study with planned enrolment of 125 patients with CS.

Relevant ongoing studies outlined in the company submissions were the SMART registry (Confirm RX), the SCARF active non-comparative observational study of 50 CS patients with unspecified ICMs that was due to complete in April 2017 (NCT01550042), and a Canadian RCT comparing the clinical and cost-effectiveness of the Reveal LINQ ICM with external loop recording in 300 CS patients due to complete in December 2019 (PERDIEM; NCT02428140). Abbott outlined that the SMART registry is a post-approval study planning to recruit at least 2,000 patients with Confirm RX (NCT03505801) across multiple indications, but with a planned subgroup analysis for CS; completion is expected during 2019.

As discussed above, there were no published or ongoing studies identified that assess the diagnostic accuracy of any of the three ICM devices exclusively in a CS population. However, this is not altogether unsurprising given that the incidence of AF is very low in the CS patient population and, therefore, a very large study with long-term follow-up consistent with the battery life of the ICM device would be required to have enough patients detected with AF on a short-term Holter monitor in order to assess the diagnostic test accuracy (DTA) of an ICM. As such, it is unsurprising that DTA data were not identified for any of the three ICMs under review in the CS population. As discussed in the Section 2.1, it was decided not to widen the population inclusion criteria for the review despite the small number of relevant studies in the CS population; this is because the performance (e.g. positive predictive value [PPV] and negative predictive value [NPV]) of AF detection in ICM devices, is dependent on the patient population, incidence rate of AF, the duration of monitoring and the type of AF.[1] However, the EAG noted that the companies of the three ICMs under review also submitted evidence from non-CS populations for their devices and so in the absence of data in the CS population the EAG decided to narratively review these data. Test accuracy data from the applicable ICM models of each of the three devices under review are discussed in Section 3.3 but it should be noted that the populations from which these data are generated are likely to be heterogenous and, the devices and software to which these test accuracy data relate are not necessarily the most up to date. These results should be interpreted with caution as the performance (e.g. PPV and NPV) of AF detection in ICM devices, is dependent on the patient population, incidence rate of AF, the duration of monitoring and the type of AF.[1] The data reported in Section 3.3 are not necessarily representative of the respective ICM device performance in CS patients and they are not directly comparable between the devices.

3.2 CRYSTAL-AF

3.2.1 CRYSTAL-AF: study details

CRYSTAL-AF[35] was an open label parallel-group RCT sponsored by the company, Medtronic. There were various conflicts of interest relating to the authors of the different publications of the study, including employment, grants and personal fees from Medtronic. The EAG also noted that CRYSTAL-AF formed the basis of the clinical data in the company submission from Medtronic for this DAR despite CRYSTAL-AF being a study of the Reveal XT, a predecessor model of the Reveal LINQ, the model under review in this DAR. The differences between the two models are discussed in Section 1.3.3 and data provided by the company on the DTA of the two devices (albeit not from an exclusively CS population) is discussed in Section 3.4.3.

In CRYSTAL-AF patients were randomised 1:1 to receive the Reveal XT ICM or conventional follow-up care. Details of the follow-up received by both groups is reported in Table 4. Randomisation was stratified within the study groups according to the type of index event (stroke or TIA) and the presence or absence of a patent foramen ovale (PFO). The EAG's clinical experts reported that the rationale for

stratification by PFO is likely to be because its presence is associated with AF. There is no known difference in the incidence of AF in patients with TIA compared to in those with stroke as their index event although clinical experts considered it reasonable for it to also be applied as a stratification factor.

Patients were enrolled to CRYSTAL-AF between June 2009 and April 2012 from 55 centres in 14 countries across Europe, Canada and the USA. The study closure was planned to be at 12-months after the last patient was randomised, with the primary study follow-ups scheduled at 6 and 12 months. The study inclusion criteria were as follows:

1. Recent episode of cryptogenic symptomatic TIA or recent episode of cryptogenic ischemic stroke which was defined in a protocol amendment as from <60 days to <90 days. TIAs were required to have a visible lesion on magnetic resonance imaging (MRI) or computed tomography (CT) that fits the symptoms of the TIA and associated speech problems, or weakness of arm or leg, or hemianopia;

2. The patient or their legally authorised representative willing to sign a patient consent form; and

3. The patient is aged ≥40 years old.

The definition of a CS in CRYSTAL -AF was that no possible cause could be determined despite extensive workup according to the standard protocol of the participating study centre. Before randomisation, the following clinical tests were required to establish the diagnosis of CS:

- MRI or CT;
- 12-lead ECG for AF detection;
- 24-h ECG monitoring for AF detection and premature atrial contractions (PAC) analysis (e.g. Holter);
- trans-oesophageal echocardiogram (TOE);
- Computed Tomography Angiography (CTA) or Magnetic Resonance Angiography (MRA) of the head and neck to rule out other causes of stroke pathologies. A later protocol amendment allowed ultrasonography of cervical arteries and transcranial Doppler ultrasonography of intracranial vessels, in place of MRA or CTA of the head and neck in patients older than 55 years of age.

The EAG's clinical experts reported that the tests required in CRYSTAL-AF to define CS were broadly consistent with the tests expected to be conducted in England. The clinical experts also reported that

there are standard blood tests that would be required as part of the diagnostic work-up, and that all patients should receive transthoracic echocardiography prior to TOE; a small minority of patients may not receive TOE due to its invasive nature, but they may still be classified as CS and go on to have an ICM.

The actual pre-enrolment screening for AF consisted of Holter monitoring with a median duration of 23 hours (interquartile range, 21 to 24) in 71.2% of patients (n=314, mean 31.0 +/–66.7 hours [assume standard deviation (SD) although not specified in paper]) and inpatient telemetry monitoring with a median duration of 68 hours (interquartile range, 40 to 96) in 29.7% of patients (n=131, mean 74.6 +/–51.4 hours [assume SD although not specified in paper]) in CRYSTAL-AF. The EAG considers it important to highlight that in the CRYSTAL-AF protocol it was specified that patients were required to have a minimum of 24-hours of outpatient external ECG monitoring to be diagnosed with a CS. The EAG notes that 29.7% of patients in CRYSTAL-AF did not receive outpatient ECG monitoring and that even the patients that did receive the outpatient Holter monitoring did not necessarily receive it for a full 24 hours (median 23 hours).

The main exclusion criteria for CRYSTAL-AF were a history of AF or atrial flutter, an indication or contraindication for permanent oral anticoagulant (OAC) therapy at enrolment, or an indication for a pacemaker or implantable cardioverter defibrillator (full exclusion criteria presented in Table 1Table 3). The EAG's clinical expert reported that these exclusion criteria are as expected for a clinical trial and in keeping with what would be expected in clinical practice in England and Wales with the exception of a recent history of myocardial infarction (MI) where if left ventricular (LV) function remained good then it would not necessarily be a reason for not implanting an ICM device in CS patients in clinical practice in England and Wales.

Table 3. CRYSTAL-AF exclusion criteria

Exclusion criteria
1. Patient has known etiology of the TIA or stroke (based on neuro-/cardiac/vascular imaging), such as:
• Angiographic signs of large-artery atherosclerosis (MRA, CTA, or digital subtraction angiography) in the artery feeding the acute ischemic territory
• Radiographic appearance consistent with acute small-artery occlusion, with lesion <1 cm in diameter (DWI or CT).
• Evidence of a high-risk cardiac or aortic arch source of embolism (LV or LA thrombus or "smoke," emboligenic valvular lesion or tumor, PFO with extant
source of venous thromboembolism, aortic arch plaque >3 mm thick or with mobile components or any other high-risk lesion)
• History of spontaneous deep vein thrombosis
• Stroke of other determined cause such as presence of nonatherosclerotic vasculopathies, hypercoagulable states (must be tested in patients <55 y old) and
hematologic disorders
2. Patient has untreated hyperthyroidism.
3. Patients had myocardial infarction <1 m before stroke/TIA.
4. Patient had coronary bypass grafting <1 m before stroke/TIA.
5. Patient has valvular disease requiring immediate surgical intervention.
6. Patient has documented history of AF or atrial flutter.

7. Patient has presence of a PFO, and PFO is/was an indication to start OAC in the patient according to the ESO guidelines. 8. Patient has permanent indication for anticoagulation at enrolment. 9. Patient has permanent OAC contraindication. 10. Patient is already included in another clinical trial that will affect the objectives of this study. 11. Patient's life expectancy is <1 y. 12. Patient is pregnant. 13. Patient is indicated for implant with a pacemaker, ICD, CRT device, or an implantable hemodynamic monitoring system 14. Patient is not fit or is unable or unwilling to follow the required procedures of the Clinical Investigation Plan.
Abbreviations: CRT, cardiac resynchronisation therapy; CTA, computed tomography angiogram; DWI, diffusion-weighted imaging; ESO, European Stroke Organisation; ICD, implantable cardioverter defibrillator; LA, left atrium; LV, left ventricle; MRA, magnetic resonance angiogram; OAC, oral anticoagulant; PFO, patent foramen ovale; TIA, transient ischemic attack.

In total, 447 patients were enrolled to CRYSTAL-AF although only 441 underwent randomisation with 221 randomised to the ICM study arm and 220 to the conventional follow-up arm. Only 208 randomised patients (94.1%) in the ICM arm received the ICM device and 5.4% of these had withdrawn from the study by the 6-month follow-up assessment. Reasons for withdrawals are presented in Table 4, and with the exception of cross-over, there were similar numbers of withdrawals between the two study arms. In relation to cross-over, 2.7% of patients in the conventional follow-up arm received an ICM whereas 5.4% of patients in the ICM arm received conventional follow-up. In addition, there was an issue relating to delayed implantation of the ICM device in 11.5% of patients which may have impacted on the AF-detection results of Reveal XT in CRYSTAL-AF. The likely impact of the withdrawals and delayed ICM implantation on the results is discussed further in the quality assessment of CRYSTAL-AF in Section 3.2.1.1.

The standard scheduled follow-up for patients in both of the study arms of CRYSTAL-AF was follow-up visits at 1, 6, and 12 months and every 6 months thereafter until study closure, with unscheduled visits in the event of symptom occurrence or after the transmission of ICM data, if advised by the investigator. If patients reported an episode of AF since the previous visit, then information was collected, and source documentation was acquired for adjudication, where possible. As reported in Table 4, the number of patients who reached 36 months follow-up was low in both study arms although the numbers were balanced across the two arms (24 patients in each study arm).

Table 4. CRYSTAL-AF duration of follow-up and withdrawals

Treatment	**ICM - continuous monitoring**	**Conventional follow-up**
Randomised, N	221 [208 received device]	220
Withdrawals, n (%) At 6 months	12 (5.4%) Crossed over to control 12 (5.4%) Exited the study ● 3 Died ● 1 Was lost to follow-up ● 5 Withdrew ● 3 Were withdrawn by investigator	6 (2.7%) Crossed over to ICM 13 (5.9%) Exited the study ● 2 Died ● 1 Was lost to follow-up ● 7 Withdrew ● 3 Were withdrawn by investigator

Details of follow-up for AF detection	Patients assigned to the ICM group were scheduled to have the device inserted within 10 days after randomization. ICM settings were programmed in a standardized fashion. The ICM that was used (REVEAL XT, Medtronic) automatically detects and records AF irrespective of heart rate or symptoms. The Medtronic CareLink Network was used to remotely transmit the device data.	Patients assigned to the control group underwent assessment at scheduled and unscheduled visits, with ECG monitoring performed at the discretion of the site investigator. Monitoring type, duration, and all results were recorded.
Mean days from index event	To randomisation (SD): 38.1 (27.6)	
	To insertion of device: 184/208 (88.5%) within 10 days. Scheduling delays (22 patients) or medical justification 2 patients) accounted for delayed insertions (median delay, 6 days; interquartile range, 1 to 32).	N/A
Mean duration/length of follow-up for AF detection Number of patients completing follow-up: • 6-month • 12-month • 24-month • 36-month	20.3 +/- 9.4 months (407.4 patient-years) 205 194 88 24	19.2 +/-9.9 months (patient-years not reported) 208 185 89 24
Abbreviations: AF, atrial fibrillation; ECG, electrocardiogram; ICM, implantable cardiac monitor; n, number of patients; SD, standard deviation.		

The primary efficacy outcome in CRYSTAL-AF was the time to first detection of AF (lasting >30 seconds) at 6 months follow-up and the secondary outcome was AF detection at 12 months of follow-up. The rate of AF detection was estimated with the use of the Kaplan–Meier (KM) method and compared between groups on an intention-to-treat basis with the use of a log-rank test. Patients were censored in the primary analysis at the time of death, study exit, or completion of 6 months of follow-up. Pre-planned subgroup analyses were age, sex, race or ethnic group, type of index event, presence or absence of PFO, and $CHADS_2$ score. However, as only the type of index event was relevant to the NICE final scope[2] the results for the other subgroups are not discussed in detail in this report, however, they are summarised in the results for the primary outcome.

The baseline characteristics of the patients enrolled who underwent randomisation in CRYSTAL-AF are presented in Table 5. The EAG notes that while there were no significant differences between the study arms at baseline ($p<0.05$), there were some small baseline differences including in the distribution of patients with PFO and history of prior stroke. These differences were small and unlikely to be a result of any systematic issues with randomisation.

In terms of applicability of the patients in CRYSTAL-AF to the equivalent patients in the UK who may be eligible for an ICM for AF detection following a CS, the EAG's clinical experts reported that as expected in a clinical trial the patients in CRYSTAL-AF were slightly younger compared to those likely to be eligible for an ICM for CS in the UK. In addition, clinical experts reported that using the CRYSTAL-AF criteria for cryptogenic TIA then possibly a higher proportion of TIAs would be expected in clinical practice and estimated to be closer to 20% of the total ICM eligible CS population. In addition, all patients would be expected to be on an antiplatelet agent. If patients are contraindicated to antiplatelets they are likely to also be unsuitable for oral anticoagulation (the treatment likely to be provided if AF is detected).

Table 5. CRYSTAL-AF baseline characteristics

Baseline patient characteristics	**ICM - continuous monitoring (n = 221)**	**Conventional follow-up (n = 220)**	**p value**
Mean age, (with SD/SE if given), years (range)	61.6 (11.4)	61.4 (11.3)	0.84
Sex (M/F), n (%)	142 (64.3) male 79 (35.7) female	138 (62.7) male 82 (37.3) female	0.77
Ethnicity, n (%)			0.60
Asian	3 (1.4)	2 (0.9)	
Black	7 (3.2)	10 (4.5)	
Hispanic or Latino	2 (0.9)	2 (0.9)	
White	194 (87.8)	191 (86.8)	
Other	0	3 (1.4)	
Not available	15 (6.8)	12 (5.5)	
Geographic region, N (%)			0.32
North America	83 (37.6)	72 (32.7)	
Europe	138 (62.4)	148 (67.3)	
Patent foramen ovale, N (%)	52 (23.5)	46 (20.9)	0.57
Index event, N (%)			0.87
Stroke	200 (90.5)	201 (91.4)	
TIA	21 (9.5)	19 (8.6)	

Prior stroke/TIA, N (%) Stroke TIA	 37 (16.7) 22 (10.0)	 28 (12.7) 27 (12.3)	 0.28 0.45
Score on modified Rankin scale, N (%) 0 to 2 >2 (0 to 6, lower=better)	 184 (83.3) 36 (16.3)	 186 (84.5) 34 (15.5)	0.85
Mean (SD) NIH Stroke Scale (0 to 42, lower=better)	1.6 (2.7)	1.9 (3.8)	0.37
Hypertension, N (%)	144 (65.2)	127 (57.7)	0.12
Diabetes, N (%)	34 (15.4)	38 (17.3)	0.61
$CHADS_2$ score, N (%) 2 3 4 5 6	 69 (31.2) 92 (41.6) 50 (22.6) 9 (4.1) 1 (0.5)	 81 (36.8) 91 (41.4) 34 (15.5) 14 (6.4) 0	0.17
Hypercholesterolemia, N (%)	125 (56.6)	128 (58.2)	0.77
Current smoker, N (%)	43 (19.5)	44 (20.0)	0.91
Coronary artery disease, N (%)	16 (7.2)	9 (4.1)	0.22
Use of antiplatelet agent, N (%)	212 (95.9)	212 (96.4)	1.00
Abbreviations: ICM, implantable cardiac monitor; M/F, male or female; N, number of patients; NIH, National Institutes of Health; SD, standard deviation; SE, standard error; TIA, transient ischemic attack			

3.2.1.1 CRYSTAL-AF: Quality Assessment

As discussed in Section 2.4, it was decided to conduct the quality assessment for CRYSTAL-AF using the Cochrane risk of bias 2.0 tool and the only outcomes assessed were AF detection at 6, 12 and >12-months. The results of the risk of bias assessment are presented in Appendix 9.6 and summarised in Table 6.

The overall risk of bias rating for all three timepoints of AF detection was that there were "some concerns". For the 6 and 12-month follow-up results this was mostly related to the open-label study design and patients not receiving the randomised intervention as per the study protocol (12 [5.4%] patients assigned to ICM received conventional follow-up and 6 [2.7%] patients in conventional follow-up arm received the ICM), and in the ICM arm, device implantation was delayed in 24 (11.5%) of the

patients who actually received the ICM (median delay, 6 days; interquartile range, 1 to 32). Results were analysed for intention-to-treat (ITT) population and so, by including patients who did not receive an ICM, received one late, or crossed over to standard care, the estimated benefit of receiving an ICM may be conservative. In addition to these issues around the open-label nature of the study and intervention not being received as per the study protocol, the low number of patients achieving follow-up beyond 12 months is likely to make the 24- and 36-month results less reliable than those at 6 and 12 months, although the direction of this bias is unpredictable.

Table 6. Summary of CRYSTAL-AF risk of bias assessment

Risk of bias domain	**6-months**	**12-months**	**>12-months**
1. Risk of bias arising from the randomisation process	Low	Low	Low
2. Risk of bias due to deviations from the intended interventions (*effect of assignment to intervention)*	Some concerns: Lack of blinding unlikely to affect relative AF detection rates between groups. Only small numbers of patients received the alternative interventions (12 [5.4%] patients assigned to ICM and 6 [2.7%] patients in standard care arm). Results analysed for ITT population (Sanna 2014)[35] so, by including patients who did not receive an ICM, received one late, or crossed over to standard care, the estimated benefit of receiving an ICM may be conservative. Delays in ICM insertion were mostly short and unlikely to impact this outcome.		
3. Missing outcome data	Low	Low	Some concerns: The reasons for loss to follow-up beyond 6 months are not reported and a large number of patients are censored in the 24-month and 36-month analyses (Only 88 patients completed 24 months follow-up in ICM arm and 89 in standard care arm, and this dropped to only 24 patients in each study arm by 36 months follow-up).
4. Risk of bias in measurement of the outcome	Low	Low	Low
5. Risk of bias in selection of the reported result	Low	Low	Low
Overall risk of bias	Some concerns	Some concerns	Some concerns
Optional: What is the predicted direction of bias due to selection of the reported result?	Including patients who did not receive an ICM, received one late, or crossed over to standard care in the ITT analysis may give a conservative estimate of the true benefit of ICM, although these issues may reflect clinical practice. Incomplete follow-up at later that 24 months+ is likely to make these results less reliable than those at 6 and 12 months, although the direction of this bias is unpredictable.		
Abbreviations: AF, atrial fibrillation; ICM, implantable cardiac monitor; ITT, intention-to-treat.			

3.2.2 CRYSTAL-AF: Diagnostic Test Accuracy results

3.2.2.1 Device sensitivity and specificity

There were no data on the sensitivity or specificity of the Reveal XT reported in the identified CRYSTAL-AF publications. However, one study (Choe 2015)[14] conducted simulations using the CRYSTAL-AF data to establish the relative sensitivity of the Reveal XT compared to various simulated external monitoring strategies including one-off 24-hour Holter monitoring and 30 days continuous Holter monitoring assuming that the Reveal XT had a sensitivity of 100%. This study along with its results is discussed further alongside the observational studies in Section 3.3.3 as it is not an RCT.

3.2.2.2 Diagnostic yield: AF detection rate

AF detection rate at 6-months was the primary outcome of CRYSTAL-AF. The definition of AF in CRYSTAL-AF was an episode of irregular heart rhythm, without detectable P waves, lasting more than 30 seconds. However, AF episodes are detected by the ICM using an automatic algorithm that is based on R-wave interval variability detected within 2-minute analysis windows.[6, 36] It is therefore possible that some AF episodes between 30 seconds and 2 minutes in duration may have been missed in the ICM arm because of the 2-minute analysis window of the ICM.[36, 38] As such, there was a potential discrepancy in the duration of episodes of AF between the ICM and conventional follow-up arms in CRYSTAL-AF that potentially bias the results in favour of conventional follow-up. In addition, as discussed in Section 3.2.1.1, the open-label nature of CRYSTAL-AF may have resulted in bias in the conventional follow-up arm as the outcome assessor was aware of the intervention assignment and was able to influence the ECG or other assessment of AF. The ICM arm was unlikely to be affected by bias relating to the outcome assessor as all episodes of AF that qualified for analysis were adjudicated by an independent committee. These factors should therefore be taken into consideration when interpreting the results for AF detection along with the risk of bias assessment findings. However, it is unclear what the resulting direction of the potential biases would be on the results. For the 6-month and 12-month results it is most likely that the bias would favour AF detection with conventional follow-up, although beyond 12 months it is much less certain what direction the bias would be due to the large number of people censored in the analyses.

The results for AF detection demonstrated a trend in favour of the ICM across all timepoints (Table 7), although the only statistical between group comparisons reported were hazard ratios for the time to AF detection, which are discussed in Section 3.2.3.1.1. At 6-months there were 19 patients diagnosed with AF in the ICM arm compared to only 3 patients in the conventional follow-up (Table 7). The number of patients with AF diagnosed had risen to 42 patients in the ICM arm at 36 months compared to only 5 in the conventional follow-up arm and this is despite incomplete and low numbers of patients followed-up at 36-months. Also, there was only 1 patient diagnosed with AF beyond 12 months follow-up in the conventional follow-up arm, whereas is the ICM arm a further 13 patients were diagnosed

with AF (9 patients between 12 and 24 months, and 4 patients between 24 and 36 months [Table 7]). These results would suggest that long-term monitoring with an ICM, such as the Reveal XT, is beneficial in detecting more cases of AF and thus enables the treatment of AF to help reduce the risk of a further stroke or TIA.

Table 7. CRYSTAL-AF AF detection rate results

Diagnostic yield		Months	ICM		Conventional follow-up		Notes
			n (% ITT)	N	n (% ITT)	N	
AF detection		1	8 (3.6%)	221	1 (0.5%)	220	
		6	19 (8.6%)	221 (208 with ICM)	3 (1.4%)	220	Control group AF from 88 ECGs (65 patients), 20 24-hour Holters (17 patients), and event recording in 1 patient
		6-12	10 (4.5%)	221 (189 with ICM and no AF before 6m)	1 (0.5%)	220	Control group AF from 34 ECGs (33 patients) and 12 Holters (10 patients).
		12	29 (13.1%)	221 (208 with ICM)	4 (1.8%)	220	Control group AF from 122 ECGs, 32 Holters and 1 event recorder
		12-24	9 (4.1%)	221 (208 with ICM)	1 (0.5%)	220	Control group AF from 62 ECGs and 14 Holters
		24	38 (17.2%)	221	5 (2.3%)	220	
		24-36	4 (1.8%)	221 (208 with ICM)	0	220	Control group AF from 19 ECGs and 6 Holters
		36	42 (19%)	221	5 (2.3%)	220	Control group AF from 256 AF monitoring tests
Asymptomatic AF detection (of all detected AF)		6	14	19	1	3	
		12	23	29	2	4	
		36	34	42	2	5	
AF detection by index event	Stroke TIA	6	17 (8.3%) 3 (15%)	200 21	3 (1.6%) 0	201 19	Index event numbers from baseline table. P-value for interaction, 0.99.
	Stroke TIA	12	23(11.6%) 4 (20.0%)	200 21	4 (2.2%) 0	201 19	
	Stroke TIA	36	(31.2%) NR	200 21	(3.3%) 0.0%	201 19	

Abbreviations: AF, atrial fibrillation; ECG, electrocardiogram; ICM, implantable cardiac monitor; ITT, intention-to-treat; n, number of events; N, number of patients; TIA, transient ischemic attack.

AF detection with the ICM compared to conventional follow-up was reported to be consistent across all the prespecified subgroups in CRYSTAL-AF (age, sex, race or ethnic group, index event, presence or absence of PFO, and $CHADS_2$ score), with no significant interactions. In addition, it was reported that the subgroup analysis results at 12 months were consistent with those at 6 months. The EAG notes that the subgroup results by index event (i.e. stroke or TIA) suggest higher incidence of AF in the ICM arm of the TIA subgroup compared to the stroke subgroup, although it is also noted that the number of patients in the TIA subgroup was very small (21 patients in the ICM arm). The trend favouring ICM over conventional follow-up seen in the primary study results was consistent in both the TIA and stroke subgroups.

3.2.2.3 Diagnostic yield: Detection of other cardiac pathologies

There were no results reported for the detection of other cardiac pathologies in CRYSTAL-AF.

3.2.3 CRYSTAL-AF: Clinical outcome results

3.2.3.1 Atrial fibrillation

3.2.3.1.1 Time to diagnosis

There were only 5 cases of AF detected in the conventional follow-up arm of CRYSTAL-AF during the 36 months follow-up and so it is difficult to draw any conclusions from the median time to AF detection data. As the number of patients detected with AF increased with longer follow-up, the median time to AF detection also increased. However, there was also a significant increase in the median time to AF detection with the ICM compared to with conventional follow-up across all three timepoints irrespective of whether the analysis was adjusted for baseline characteristics (Table 8). The rationale for this may be that there was a higher proportion of symptomatic AF detected in the conventional follow-up arm compared to in the ICM arm beyond 6 months. The timing of study follow-up visits may also have caused interval censoring in the conventional follow-up arm (and so influenced the estimated median time to AF detection), whereas in the ICM arm study follow-up is less influential as the device is constantly monitoring for episodes of AF.

Table 8. CRYSTAL-AF time to AF detection results

Time to event	Months	ICM		Conventional follow-up		HR; 95% CI (p value)
		Median (IQR)	N	Median (IQR)	N	
Time to AF detection, unadjusted	6	41 days (4 to 84)	19 detected	32 days (2 to 73)	3 detected	6.4; 1.9 to 21.7 (<0.001)
	12	84 days (18 to 265)	29 detected	53 days (17 to 212)	4 detected	7.3; 2.6 to 20.8 (<0.001)
	36	8.4 months (NR)	42 detected	2.4 months (NR)	5 detected	8.8; 3.5 to 22.2 (<0.001)
Time to AF detection, adjusted for PFO, hypertension and coronary artery disease	6	-	-	-	-	5.1; 1.7 to 15.3 (0.009)
Time to AF detection, censoring data at the time of crossover	6	-	-	-	-	6.1; 1.8 to 20.8 (0.009)

Abbreviations: AF, atrial fibrillation; CI, confidence interval; HR, hazard ratio; ICM, implantable cardiac monitor; IQR, interquartile range; N, number of patients; NR, not reported; PFO, patent foramen ovale.

3.2.3.1.2 Hospitalisations

There were no results reported for AF related hospitalisations in CRYSTAL-AF.

3.2.3.1.3 Outpatient monitoring

There were no results reported for outpatient monitoring in CRYSTAL-AF.

3.2.3.2 Anticoagulant use

3.2.3.2.1 Uptake of anticoagulants

The data reporting of the use of OAC in CRYSTAL-AF suggest that some patients not diagnosed with AF were commenced on OAC and a small proportion of patients diagnosed with AF did not receive OAC (

Table 9). The rationale for patients having an ICM for AF detection following a CS and being diagnosed with AF but not started on OAC is unclear. However, the results suggest that the majority of patients diagnosed with AF in the ICM arm were commenced on OAC (>90% of patients). Results were not reported for OAC uptake after AF detection in the conventional follow-up study arm.

Table 9. Initiation of oral anticoagulants in CRYSTAL-AF

Outcome	Time	ICM		Conventional follow-up		HR; 95% CI (p value)
		n	N	n	N	
Use of oral anticoagulants	6 m	22 (10.1%)	221	10 (4.6%)	220	(0.0375)
	12 m	14.7% 29	197 (from CT.gov)	6.0% 11	185 (from CT.gov)	NR
	24 m	26.1%	88	5.6%	89	(0.0002)
	36 m	38.5%	26	8.3%	24	(0.0195)
Use of oral anticoagulants in patients diagnosed with AF	6 m	18 (94.7%)	19	NR	NR	NR
	12 m	28 (96.6%)	29	NR	NR	NR
	24 m	36 (92.3%)	39	NR	NR	NR
	36 m	38 (90.5%)	42	NR	NR	NR

Abbreviations: AF, atrial fibrillation; CI, confidence interval; HR, hazard ratio; ICM, implantable cardiac monitor; m, months; n, number of events; N, number of patients; NR, not reported.

3.2.3.2.2 Time to initiation of anticoagulants

There were no results reported for the time to initiation of anticoagulants in CRYSTAL-AF.

3.2.3.3 Incidences of device failure and removal

There was no data reported to suggest any incidences of device failure in CRYSTAL-AF, although premature removal of the device due to infection or pocket erosion was reported in 5 out of the 208 (2.4%) patients in the ICM study arm who received the Reveal XT device by 36 months (

Table 10). There were also data reported on the number of patients who still had their ICM device *in situ* at the 6 and 12-month follow-ups and although the numbers of ICMs that had been removed was low it was unclear why the devices were removed if it was not related to infection or pocket erosion. The EAG also note that the number of ICMs removed was much lower than the number of patients with AF detected at 6 or 12 months, suggesting many patients kept the ICM *in situ* after AF was diagnosed.

Table 10. ICM device removal in CRYSTAL-AF

Outcome	Months	ICM	
		n (%)	N
ICM removal due to infection or pocket erosion	36	5 (2.4)	208
ICM no longer *in situ*	6	4 (1.9)	208
	12	7 (3.4)	208
Abbreviations: ICM, implantable cardiac monitor; n, number of events; N, number of patients.			

3.2.3.4 Ease of use of devices for clinicians

There were no results reported for the ease of use of devices for clinicians in CRYSTAL-AF.

3.2.3.5 Mortality

There were no results reported for mortality in CRYSTAL-AF.

3.2.3.6 Further strokes or TIAs

Outcome data on recurrent stroke or TIAs during CRYSTAL-AF study follow-up were presented for the composite of recurrent stroke or TIA and demonstrated a non-significant trend in favour of fewer recurrent events in the ICM arm compared to with conventional follow-up ($p>0.05$; Table 11). It should also be noted that in the ICM arm there were fewer recurrent strokes or TIAs compared to the number of patients with AF detected at each of the timepoints, whereas in the conventional follow-up arm there were higher numbers of recurrent stroke and TIA events compared to the number of patients diagnosed with AF at each timepoint. However, outcome data were not reported by intervention and diagnosis of AF and so it is unclear whether the recurrent stroke or TIA events occurred in patients diagnosed with AF or in the undiagnosed subgroup.

Table 11. Composite outcome of further ischaemic stroke or TIA in CRYSTAL-AF

Time	ICM (N = 221)		Conventional follow-up (N = 220)		HR; 95% CI (p value)
	n	%	n	%	
6 m	11	4.98	18	8.18	NR
12 m	15	6.79	19	8.64	0.63; 0.22 to 1.80 (0.39)
36 m	20	9.05	24	10.91	0.77; 0.30 to 1.97 (0.59)
Abbreviations: CI, confidence interval; HR, hazard ratio; n, number of events; N, number of patients; NR, not reported; TIA, transient ischemic attack.					

3.2.3.7 Other thromboembolisms

There were no results reported for other non-stroke or TIA related thromboembolisms in CRYSTAL-AF.

3.2.3.8 Heart failure

There were no results reported for the diagnosis of heart failure in CRYSTAL-AF.

3.2.3.9 Adverse events

3.2.3.9.1 Device related adverse events

All adverse event (AE) data identified from CRYSTAL-AF were extracted and are presented in Table 12. The data suggest that the incidence of device related AEs such as pain and infection was relatively low with the ICM, although AEs did lead to device removal in 2.4% of patients (5 patients; Table 12). In addition, it was reported that over 25% of patients in both the ICM and conventional follow-up study arms suffered from a serious adverse event (SAE), although it is unclear what the SAEs were. The proportion of SAEs was slightly higher in the ICM arm compared to in the conventional follow-up arm (30.8% vs 27.9%, respectively) and there was also a much higher proportion of non-serious AEs in the ICM arm compared to the conventional follow-up study arm (18.6% vs 4.1%, respectively). There were no details reported on what the non-serious AEs were for either study arm and so it is unclear why there was such a large difference in AEs between the study arms.

Table 12. Adverse events reported in CRYSTAL-AF

Adverse events	Months	ICM		Conventional follow-up	
		N	N	n	N
ICM removal due to infection or pocket erosion	36	5 (2.4%)	208	NA	NA
AE: infection	Unclear	3 (1.4%)	208	NA	NA
AE: pain	Unclear	3 (1.4%)	208	NA	NA
AE: irritation or inflammation	Unclear	4 (1.9%)	208	NA	NA
CV or stroke/TIA-related hospital admissions	12	23 (10.5%)	221	16 (7.2%)	220
Patients with SAE	Unclear [a]	68 (30.8%)	221	58 (27.9%)	220
Total patients with non-serious AE	Unclear [a]	41 (18.6%)	221	9 (4.1%)	220

[a] Average FU was 19.7 +/- 9.7 m (range: 0 - 42.7).
Abbreviations: AE, adverse event; CV, cardiovascular; ICM, implantable cardiac monitor; n, number of events; N, number of patients; NA, not applicable; SAE, serious adverse events; TIA, transient ischemic attack.

3.2.3.9.2 Anticoagulant related adverse events

There were no results reported for anticoagulant-related AEs in CRYSTAL-AF.

3.2.4 CRYSTAL-AF: Patient-reported outcome results

3.2.4.1 Health-related quality of life

The EuroQol 5-Dimensions (EQ-5D) tool was used to collect health-related quality of life (HRQoL) data during CRYSTAL-AF and the results are summarised in Table 13 and Table 14. [redacted]

Table 13. Summary of EQ-5D domain HRQL responses from CRYSTAL-AF

[redacted]	[redacted]	[redacted]		[redacted]	
		[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
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	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]					

Table 14. EQ-5D VAS (0 to 100 scale) results from CRYSTAL-AF

[redacted]	[redacted]			[redacted]			
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]							

3.2.4.2 Acceptability of the devices to patients

There were no results reported beyond the HRQoL data reported in Section 3.2.4.1 for the acceptability of the devices to patients in CRYSTAL-AF.

3.3 Observational studies

As outlined in Section 3.1, the eligibility criteria of the systematic literature search were broadened to identify observational studies of ICM use in CS populations. The EAG's searches were cross checked with study lists provided by the company, which identified 26 relevant observational studies. The studies are primarily single-arm prospective observational studies and therefore subject to internal biases associated with this study design, but the EAG considered them useful to supplement the evidence from CRYSTAL-AF[35] by providing data for an additional outcome from the NICE scope and providing a larger data set to reflect the generalisability of the results from the RCT. The EAG did not consider data synthesis appropriate due to the clinical heterogeneity between studies across a range of variables that are likely to affect AF detection and clinical outcomes. Key sources of heterogeneity between studies include patient characteristics, rigor of stroke assessment, stroke risk score, definition and adjudication of AF, and length of follow-up (see Table 15 and Table 16).

The EAG emphasises that CRYSTAL-AF[35] is the only study that met the original eligibility criteria and, representing the most robust evidence for ICM in the population of interest, is the primary source of clinical data to answer the NICE final scope.[2] Formal quality assessment was not possible due to the single-arm designs, but the EAG considers the 26 studies discussed hereafter to be at high risk of bias. The observational evidence base is presented to illustrate the existing evidence outside of RCTs and to provide clinical data on the Reveal LINQ in the absence of data from RCTs.

3.3.1 Observational studies: study details

Study design and brief population characteristics of the 26 non-RCTs are presented in Table 15. Details of time to ICM insertion, AF threshold (e.g. 30 seconds), method and frequency of data transmission, and how episodes were adjudicated are presented with AF detection rates for each study in Section 3.3.2.2. AF detection rate was the main outcome in all studies, and other outcomes of relevance to the

NICE scope[2] were time to AF detection, uptake of anticoagulants, device failure, subsequent stroke, and AEs.

Nine studies tested the Reveal LINQ device,[14, 15, 39-46] six included a mix of Reveal LINQ and XT,[47-52] and ten studies tested only the XT device.[14, 53-61] One study included a mix of Reveal XT and BIOTRONIK BioMonitor (an earlier model of the BioMonitor 2-AF), although only 13% were inserted with a BioMonitor (n = 16),[62] and no studies reported using the Abbott Confirm RX. None of the identified studies provide comparative data between groups of patients receiving an ICM versus those who were monitored with alternative strategies. Three studies conducted within-patient comparisons of ICM versus other monitoring strategies,[14, 15, 60] two of which by using ICM detection data to simulate outcomes for intermittent monitoring (discussed later with diagnostic accuracy results in Section 3.3.2.1).[14, 15]

All studies included CS populations, although the terms and definitions used varied (e.g. embolic stroke of unknown origin [ESUS], cryptogenic ischemic stroke [CIS]), as did the range of exploratory tests performed before patients were considered to have CS (Table 15). Mean or median age was between 60 and 70 in most studies (range 51.5 to 72), percentage male ranged from 45 to 92% (median 55%), and median $CHADS_2VASC$ was between 3 and 5, indicating moderate to high risk of AF-related stroke (Table 15). Two studies exclusively recruited patients with TIA or minor stroke.[50, 53]

Most studies recruited patients at a single centre and sample sizes ranged from 14[57] to 1,247[15] (median 80; mean 131). The most common countries in which studies were conducted are the USA (n = 10) and Germany (n = 8), and only one was conducted in the UK.[54] Devices were implanted from 2011 in line with the emergence of each model. Seventeen studies were prospective single-arm observational studies that followed patients who met predefined inclusion criteria and were implanted with an ICM after CS during a set timeframe.[41, 43, 45-51, 53, 55-59, 61, 62] Five studies collected data retrospectively from CS patients who had received an ICM[39, 40, 42, 44, 52] and one study did not report a clear methodology.[54] The EAG reiterates the inherent biases within the observational evidence due to the single-arm designs and the clinical heterogeneity identified, and encourages caution in drawing conclusions from naïve comparisons between studies.

Table 15. Study and population characteristics of included observational studies

Study ID	Device	Country (sites)	N	Design	Enrolment	Eligibility and diagnostic work-up	Baseline characteristics
Asaithambi 2018[39]	Reveal LINQ	USA (1)	234	Retrospective single arm	Apr 2014–Oct 2017 (implanted)	CS (TOAST), no other details	Median age 72 (IQR 61–78); 55% male; median CHADS2VASC 5 (IQR 4–6)
Chalfoun 2016[40]	Reveal LINQ	USA (NR)	192	Retrospective single arm,	May 2014–Oct 2015 (implanted)	CS and no prior AF after 48 hrs of inpatient telemetry 48-hr inpatient telemetry	NR
Ferrara 2017[41]	Reveal LINQ	USA (NR)	68	Prospective single arm	NR	CS, no other details	Mean age 71; 63% male; mean CHADS2VASC 4.1 (SD 2)
Heckle 2018[42]	Reveal LINQ	USA (2)	133	Retrospective single arm	Sep 2014–Nov 2017 (implanted)	CS, no other details	Mean age 65.2; 73.7% white
Kotlarz-bottcher 2018[43]	Reveal LINQ	Germany (1)	100	Prospective single arm	Implanted in 2016	'ESUS criteria', no other details	None reported
Li 2018[44]	Reveal LINQ	USA	19[ii]	Retrospective single arm	Apr 2014–Apr 2017 (implanted)	CIS or TIA not attributed to large-vessel atherosclerosis, apparent cardio-embolism source or small-vessel disease. Extensive cardiac, vascular, hematologic, and serologic evaluation, life expectancy >18m	Median (assumed) age 67; 92% male (not CS subgroup)
Seow 2018[46]	Reveal LINQ	Singapore (1)	71	Prospective single arm	Aug 2014–Feb 2017 (referred)	CS or TIA after MRI or CT, TEE, duplex carotid artery ultrasound, transcranial Doppler, 24hr+ inpatient continuous ECG, 24-hour Holter, eligible for OAC, no prior AF	Mean age 61.9; 77.5% male; 0% white; mean CHADS2VASC 4.2 (SD 1.3), median 4 (range 2–7)
Ziegler 2017[15]	Reveal LINQ	International (NR)	1247	ICM registry vs. simulated intermittent monitoring	Feb 2014–Jul 2014 (implanted)	CS designated by implanting physicians	Mean age 65.3; 53% male
Pallesen 2017[45]	Reveal LINQ (NeuroLINQ)	Germany (NR)	75	Prospective single arm	Jan 2014–Jun 2015 (implanted)	ESUS, 95% of patients complied with CRYSTAL-AF eligibility criteria	Median age 61; 64% male
Carrazco 2018[48]	Reveal LINQ (90%) XT (10%)	USA (1)	100	Prospective and retrospective single arm	Sep 2013–Sep 2015 (admitted)	CIS, eligible for implant after brain MRI/CT, MR/CT angiography, TTE or TEE, 24-hr+ cardiac telemetry, ECG, blood work. Excluded patients with severe disabling stroke.	Mean age 65.8; 48.5% male; 57% white; mean NIHSS 5.6 (SD 6.2) with AF, 5.3 (5.8) without AF

Abichandani 2016[47]	Reveal LINQ (60%) and XT (40%)	USA (1)	74	Prospective single arm	Oct 2009–Sept 2015	CS, no other details	Mean age 66; 49% male
Poli 2016[51]	Reveal LINQ (51.4%) or XT (48.6%)	Germany (1)	75[iii]	Prospective single arm	NR	CIS (89%) or TIA (TOAST), ≥1 AF risk factor (CHADS2VASC 4+, atrial runs, left atrium size >45 mm, LAA flow ≤0.2m/s or spontaneous echo contrast), CT or MRI (with angiography), neurosonology, TEE, 72hr+ ECG, ≥1 24 h Holter ECG, thrombophilia screening if <55 years.	Mean age 66.4; 47% male; median CHADS2VASC 5 (IQR 4–6)
Joseph 2018[49]	Reveal LINQ or XT	USA (NR)	64	Prospective single arm	Ongoing registry enrolment	CS with embolic- appearing infarct, 48-hr+ inpatient telemetry, brain MRI +/- angiography, no prior AF, TEE	Mean age 66.9; 58.4% male; median NIHSS 5.2
Salahuddin 2015[52]	Reveal LINQ or XT	USA (1)	31	Retrospective single arm	May 2012–Sep 2014 (implanted)	CS (96.8%) or TIA (3.2%) diagnosed by board certified vascular neurologists	Mean age 66.1; 45.2% male; 38.7% prior stroke (other than index event); 16.1% PFO
Pedersen 2018[50]	Reveal XT (72.4%) or LINQ (27.6%)	Denmark (1)	105	Prospective single arm	Nov 2013–Oct 2015 (diagnosed)	TIA (neurologic deficit episode, presumed ischemia, symptoms remission within 24hrs regardless brain infarction), standard ECG, 72-hour Holter, 12-lead ECG, carotid ultrasound, brain CT or MRIs, 18–81 years, eligible for OAC.	Median age 65.4; 46% male; median CHADS2VASC 4 (range 2–7)
Choe 2015[14]	Reveal XT	CRYSTAL-AF population: International (55)	168	Simulated intermittent monitoring [i] using CRYSTAL-AF ICM arm	Jun 2009–Apr 2012	CS as defined for CRYSTAL-AF	Mean age 61.3; 68% male; mean CHADS2VASC 2.9 (SD 0.8)
Christensen 2014[53] (SURPRISE)	Reveal XT	Denmark (1)	85	Prospective single arm	NR	CS after 12-24-hr telemetric monitoring and standard work-up, CT- or MRI-verified acute ischaemic lesion, mRankin score ≤2, no prior AF	Mean age 56.7 (pooled); 55.1% male; median CHADS2VASC 4 for those with AF, 3 without
Cotter 2013[54]	Reveal XT	UK (1)	51	Unclear	Aug 2010–Oct 2011 (implanted)	CIS (TOAST), ASCO-defined brain infarct, no prior AF, no high risk cardiac embolic source, structural cardiac imaging, standard EKG, 24-hr+ Holter. Excluded TIA and prior AF.	Mean age 51.5; 54.9% male; median CHADS2VASC 3 (IQR 2–4); 22/30 known PFO
Etgen 2013[55]	Reveal XT	Germany (1)	22	Prospective single arm	Admitted in 2011	CS (TOAST) after MRI, 12-lead ECG, 24–72-hour continuous ECG, ≥1 additional 24-hour Holter-ECG, TTE, TEE, CT/MRI angiography, <55 years prothrombotic screening, eligible for OAC. Exclusion as for CRYSTAL-AF.	Mean age 61.6 (pooled); 50% male;

Holtzman 2013[56]	Reveal XT	USA (NR)	22	Prospective single arm	NR	CS with embolic appearing infarct, TEE, no AF on cardiac telemetry, MRI or CT angiogram, carotid Doppler < 50% ipsilateral stenosis	None reported
Merce 2013[57]	Reveal XT	Spain (1)	14	Prospective single arm	Aug 2009–Feb 2011 (referred)	CS, daily ECG, laboratory tests, brain CT, Holter, TEE and TTE, Doppler, brain MRA, no prior AF, >45 years, mRankin 0-1, embolic infarct, MRA daily ECG, 24h Holter, TTE and TEE, eligible for OAC.	Mean age 65.4; 71.4% male
Muller 2017[58]	Reveal XT	Germany (4)	90	Prospective single arm	Mar 2013–Apr 2015 (recruited)	Acute CS (TOAST), ≥18 years, 12-lead ECG, 72-h ECG, additional 24-h ECG and TEE. Brain and vascular imaging (MRI scan with DWI and CTA), eligible for OAC. No prior AF or pacemaker.	Mean age 57.7; 52% male; mean CHADS2VASC 3.4 (SD 1.7)
Reinke 2018[59]	Reveal XT	Germany (1)	105	Prospective single arm	Mar 2013–Dec 2014 (admitted)	CS (TOAST) or TIA (18.1%) after accurate workup: MRI or cardiovascular CT, standard 12-lead ECG upon admission, 24-h Holter ECG, ultrasound of the brain supplying arteries and TEE	Mean age 64.4; 56.2% male; median CHADS2VASC 4 (IQR 3–6); median NIHSS 2 (IQR 1–5)
Ritter 2013[60]	Reveal XT	Germany (1)	60	Within-patient comparison of 7-day ECG vs ICM	Nov 2010–May 2012	CS (TOAST), embolic patterns on brain MRI or CT; Duplex ultrasound, CTA or MRA, routine ECG, 72-hour continuous ECG, 24-h Holter ECG, TEE with PFO testing. Excluded lacunar strokes, prior AF.	Median age 63; 56.7% male; median CHADS2VASC 4 (IQR 3–5)
Rojo-Martinez 2013[61]	Reveal XT	Spain (1)	86	Prospective single arm	NR	CS patients with high suspicion of embolic cerebral ischemia. Full diagnostic workup including brain MRI with diffusion and FLAIR during admission	Mean age 67; 47.7% male
Israel 2017[62]	Reveal XT (87%) or BioMonitor (13%)	Germany (1)	123	Prospective single arm	Jun 2013–Jan 2015 (admitted)	Acute ESUS, embolic pattern on cranial CT or MRI, serial 12-lead ECGs, 24-hr Holter, 72-hr telemetry, TTE, TEE, cervical duplex, transcranial Doppler, blood tests. Excluded, known AF, stroke mimics, TIA, lacunar strokes.	Mean age 65; 60.2% male; mean CHADS2VASC 4.5 (SD 1.3)

Abbreviations: CIS, cryptogenic ischemic stroke; CS, cryptogenic stroke; CT, computed tomography; CTA, CT angiography; DWA, diffusion weighted image; ECG, electrocardiogram; ESUS, embolic stroke of unknown source; ICM, implantable cardiac monitor; LAA, left atrial appendage; mRankin modified Rankin scale; MRA, magnetic resonance angiography; MRI, magnetic resonance imaging; NIHSS, National Institutes of Health Stroke Scale; NR, not reported; OAC, oral anticoagulants; PFO, patent foramen ovale; TIA, transient ischemic attack; TOAST, Trial of Org 10172 in Acute Stroke Treatment; TEE, transoesophageal echocardiogram; TTE, transthoracic echocardiogram; UK, United Kingdom; USA, United States of America.

i. Repeated iterations (10,000) of ICM-recorded AF events to estimate the proportion of patients with AF detected by the ICM who would also have been identified as having AF by intermittent monitoring.

ii. Cryptogenic stroke subgroup. Total population n = 95.

iii. 1 patient did not receive implant

3.3.2 Observational studies: Diagnostic Test Accuracy results

3.3.2.1 Device sensitivity and specificity

None of the observational studies provided comparative DTA between a group of patients who were monitored with an ICM compared with a group who received standard monitoring. However, two studies used AF detection data for a group of patients with CS who were monitored for AF with an ICM to estimate the sensitivity of intermittent monitoring strategies if the ICM is assumed to have a sensitivity of 100%. One study[14] used data from 168 patients who received the Reveal XT in CRYSTAL-AF (those with adequate follow-up from the 221 randomised to the ICM group), and another used data from a large registry of patients with the Reveal LINQ device[15] (n=1,247). Choe 2015 used a 30-second episode threshold and Ziegler 2017 used a 2-minute threshold, but both studies used the same technique of modelling episodes of AF detected by the ICM; repeated iterations (10,000) were run to estimate the number of patients whose AF would not have been detected should alternative intermittent monitoring strategies have been used.

Based on the assumption that the ICMs had 100% sensitivity for AF in CS, Table 16 shows the estimated sensitivity of other monitoring strategies from the model simulations. Ziegler 2017 found sensitivities of between 2.9% from a single 24-hour Holter monitor to 29.9% from quarterly 7-day Holter monitoring and results were similar in Choe 2015 based on the CRYSTAL-AF cohort. As such, even the best performing intermittent monitoring strategy detected less than a third of AF detected by the ICM.

Three other studies reported false positive rates as the proportion of episodes detected by ICM algorithm that were not subsequently verified as AF by a clinician. Li 2018 reported a 79.7% false positive rate from the Reveal LINQ, Merce 2013 reported a rate of 71% for the Reveal XT and Israel 2017 reported that over 90% of detected episodes were not confirmed by manual review (Reveal XT and BioMonitor). In their response to queries about individual studies identified by the EAG, Medtronic emphasised that false positive rates vary considerably depending on the model of device, sensitivity configuration and episode detection threshold.

Table 16. Diagnostic accuracy in the observational studies

Study ID	Device	Follow-up (months) [i]	Diagnostic accuracy
Ziegler 2017[15]	Reveal LINQ	19 (ongoing)	Assuming 100% sensitivity of Reveal LINQ in a registry cohort, modelled sensitivities of other strategies: 2.9% 24-h Holter 5.0% 48-h Holter 9.0% quarterly 24-h Holter 11.0% 7-day Holter 14.0% quarterly 48-h Holter 20.0% monthly 24-h Holter 22.0% 21-day recorder 25.0% 30-day Holter 29.9% quarterly 7-day Holter Estimated negative predictive values ranged from 86.3% to 89.7%
Li 2018[44]	Reveal LINQ	13.4 (median)	79.7% (98/123) of algorithm-detected AF episodes were not confirmed in the clinician review (i.e. false positives); 20.3% (25/123) were true positives
Choe 2015[14]	Reveal XT (CRYSTAL-AF)	11.3 (minimum)	Assuming 100% sensitivity of Reveal LINQ in CRYSTAL-AF, modelled sensitivities of other strategies: [i] 1.3% 24-h Holter 3.0% 48-h Holter 3.1% quarterly 24-h Holter 6.0% quarterly 48-h Holter 8.0% 7-day Holter 11.0% monthly 24-h Holter 14.0% 21-day recorder 20.8% quarterly 7-day Holter 22.8% 30-day Holter Estimated negative predictive values ranged from 82.3% to 85.6%.
Merce 2013[57]	Reveal XT	11.5 (median)	The devices in 10 patients (71%) recorded 24 episodes of AF that were not confirmed after manual review.
Israel 2017[62]	Reveal XT (87%) or BioMonitor (13%)	12.7	> 90% of algorithm-detected AF episodes were not confirmed in the clinician review (i.e. false positives)

Abbreviations: CS, cryptogenic stroke; ECG, electrocardiogram; h, hour; iAF, intermittent atrial fibrillation; ICM, implantable cardiac monitor; NR, not reported; OAC, oral anticoagulants; TTE, transthoracic echocardiogram.
Follow-up reported as mean unless otherwise specified.
i. Sensitivities estimated from graph in Choe 2015.

3.3.2.2 Diagnostic yield: AF detection rate

All 26 included observational studies reported AF detection rates during follow-up, although information about time from stroke to insertion, AF threshold, data transmission, and adjudication were inconsistently reported (Table 17). Nine studies used an AF episode threshold of 2 minutes,[15, 44, 46, 48, 50, 51, 53, 54, 62] four studies used a 30-second threshold in line with CRYSTAL-AF (including Choe 2015 which is based on the CRYSTAL-AF ICM population),[14, 58-60] two studies used shorter thresholds of 10–15 seconds,[49, 52] and 9 studies did not state a threshold.[39-43, 45, 47, 56, 61] Where reported, studies generally stated that standard AF detection settings were used and recordings were automatically transmitted daily. Sixteen studies described episode verification and adjudication,[14, 15, 39, 41, 42, 44, 46, 48, 50, 51, 53, 54, 58-60, 62] although to varying levels (e.g. by a study clinician or by two independent cardiologists). Patient activated recording was outlined in seven studies of Reveal LINQ and XT.[14, 15, 44, 46, 51, 59, 62]

AF detection rates at the main follow-up (ranging from 6 to 24 months) were highly variable, ranging from 6.7% (Pedersen 2018, Reveal LINQ and XT, 12-month follow-up) to 40.9% (Holtzman 2013, Reveal XT, unknown follow-up). The EAG reiterates that data synthesis was considered inappropriate due to the clinical heterogeneity between studies across a range of variables that are likely to affect AF detection and clinical outcomes, including but not limited to device model and detection settings, patient characteristics, rigor of stroke assessment, stroke risk score, definition and adjudication of AF, and length of follow-up (Table 15 and Table 16).

Seven studies[15, 39, 40, 46, 58, 60, 62] reported AF detection after different lengths of follow-up which gives an indication of the rate of AF detection over time. In general, the studies indicate that a minority of patients are diagnosed within the first month (mostly in the region of 10% detected by a year), around 70–80% by 6 months, and a small number beyond a year of monitoring. Clinical experts advised the EAG that in patients detected with AF after more than two years of cardiac monitoring the AF may not be related to the index event although its management is likely to still be the same and the patient would be considered for long-term treatment with an OAC. In the large registry population reported by Ziegler 2018, around 20% of those with AF detected by two years were picked up in the first month, 60% by 6 months, and 80% by the end of the first year.[15] In Seow 2018, 80% of patients with AF detected by 12 months had been diagnosed by 6 months,[46] and around 70% of detected AF by 13 months in Ritter 2013 had been picked up at 3 months.[60] Very few patients reported in Asaithambi 2018 were detected with AF in the first month and around 70% of those detected by 18 months had been diagnosed by 6 months,[39] and the AF detection rate in the first month of Chalfoun 2016 had roughly doubled by six months.[40] AF detection in the first month was much higher in Muller 2017, with just under half of detected AF (by 11 months) picked up in the first month.[58] Around half of those detected by 13 months in Israel 2017 had been detected at 3 months, and nearly all by 9 months.[62]

Where described, all or most AF detected was asymptomatic and so would not likely have been picked up without continuous ICM monitoring.[46, 51, 57] All patients detected with AF in Poli 2016 (by 6 months), Merce 2013 and Seow 2018 (at 6 and 12 months) were asymptomatic. Two additional patients detected between 6 and 12 months in Poli 2016 experienced symptoms of AF.

Table 17. Intervention characteristics and AF detection in observational studies

Study ID	Device	Time from index event to implant	AF threshold, data transmission, and adjudication	Follow-up (months) [i]	AF detection rate
Asaithambi 2018[39]	Reveal LINQ	Median 4 days (IQR 2–9)	Threshold, programming and data transmission not reported. AF episodes adjudicated by group of cardiac electrophysiologists.	1	9%
				6	20.1%
				Median 18	29.1%
Chalfoun 2016[40]	Reveal LINQ	At discharge vs 30 days later	NR	0.5	7.3%
				0.5 to 1	2.1%
				1 to 6	7.8%
				6	17.2%
Ferrara 2017[41]	Reveal LINQ	NR	Threshold not reported, AF detection settings, daily automatic data transmission, episodes adjudicated.	11	14.7%
Heckle 2018[42]	Reveal LINQ	NR	Threshold and programming not reported. Episodes interrogated remotely and at clinic visits.	10	27.1%
Kotlarz-bottcher 2018[43]	Reveal LINQ	NR	NR	12	17.0%
Li 2018[44]	Reveal LINQ	NR	AF ≥ 2 minutes; AF high sensitivity settings, episodes stored and transmitted daily to CareLink. Home monitoring device for patient triggered events. Reviewed by physicians and adjudicated independently if disagreement. Seen in clinic after 2–4 weeks; routine follow-ups at physician discretion.	14	31.6%
Seow 2018[46]	Reveal LINQ	66 days (median)	AF ≥ 2 minutes, auto-detected, patient-activated recordings and daily ECG transmitted via Care-Link and adjudicated by cardiac electrophysiologists. Patients with AF counselled for OAC. No scheduled clinic visits until the battery expired.	6	12.7%
				12	15.5%
Ziegler 2017[15]	Reveal LINQ	NR	Patient registry data used to simulate comparison with intermittent monitoring strategies (Table 16). ≥ 2-minute threshold; daily auto-transmission or patient-initiated via CareLink. Adjudicated by a single, blinded reviewer.	1	4.1%
				6 to 12	3.6%
				12 to 24	3.6%
				24 [i]	19.1%
Pallesen 2017[45]	Reveal LINQ [ii]	Within 1 month	NR	12	19.2%
Carrazco 2018[48]	Reveal LINQ (90%) or XT (10%)	Mean 4.2 days (+/- 2.6) from admission	≥ 2 minutes, and shorter flutter. AF adjudicated by study cardiac electrophysiologist	Minimum 8	25.0% (31% incl. flutter)

Abichandani 2016[47]	Reveal LINQ (60%) and XT (40%)	NR	NR	12	20.3%
Poli 2016[51]	Reveal LINQ (51.4%) or XT (48.6%)	NR	≥ 2 minutes; XT patients instructed to do daily readings and present to clinic if alarm activated. All patients included in CareLink Network with automatic daily transmission, phoned if detected. Episodes reviewed by cardiologists blinded to AF risk factors. Clinic visit after 1m and every 3m thereafter.	6	28.0%
				12	33.3%
Joseph 2018[49]	Reveal LINQ or XT	NR	≥ 10 seconds. No other details	7	17.2%
Salahuddin 2015[52]	Reveal LINQ or XT	NR	≥ 15 seconds. Significant PAF was defined as an episode of irregular heart rhythm, without detectable P waves.	NR	32.3%
Pedersen 2018[50]	Reveal XT (72.4%) LINQ (27.6%)	113 days (median; range 30–294)	≥ 2 minutes; AF = irregularly irregular heart rhythm without p-waves. Monitored via CareLink. XT transmitted at 1, 3, 6, 9 and 12 months; LINQ daily transmissions. Other arrhythmias stored. Adjudicated by two experienced senior electrophysiologists.	12	6.7%
Choe 2015[14]	Reveal XT	NR	Subset of CRYSTAL-AF used to simulate comparison with intermittent monitoring strategies (Table 16). AF ≥ 30 seconds, standard programming, automatic detection and recording of AF, remote data transmission via CareLink. AF episodes adjudicated by independent committee.	Minimum 11	17.9%
Christensen 2014[53] (SURPRISE)	Reveal XT	Median 69, mean 107 days (usually within 1 week of work-up)	≥ 2 minutes; AF = irregular R-R intervals and no visible p-waves; minimum bi-weekly patient data transmission. Programmed to detect and store one-lead ECG of all arrhythmia episodes. Adjudicated by two independent cardiologists.	19	16.1% (20.7% including those not by ICM)
Cotter 2013[54]	Reveal XT	174 (mean), 148 (median)	≥ 2 minutes or by patient activation; 0.05 mV threshold, standard detection limits; AF = irregularly irregular R-R interval and no distinct P waves. Independent verification by a second cardiologist. FU recommended at 1-month intervals by hospital or CareLink. Daily CareLink assessment recommended.	8 [iii]	25.5%
Etgen 2013[55]	Reveal XT	9 days (mean)	≥ 6 minutes; AF detection algorithm. No other details.	12	27.3%
Holtzman 2013[56]	Reveal XT	NR	No details	NR	40.9%
Merce 2013[57]	Reveal XT	≤ 1 month	Follow-up at 1 month and every 3 months thereafter, or additional if symptoms or recorder's alarm was activated.	Median 6	35.7%
Muller 2017[58]	Reveal XT	NR	≥ 30 seconds 0.05 mV sensitivity. Adjudicated by a cardiologist blinded to TTE results.	1	8.9%
				11	17.8%

Reinke 2018[59]	Reveal XT	≤ 4 weeks	≥ 30 seconds; standard AF algorithm and hand-held Patient Assistant. Monitored for 20 months and analysed by experienced cardiologists.	20	18.1%
Ritter 2013[60]	Reveal XT	13 days (median; IQR 10–65)	≥ 30 seconds; daily patient transmission of 7 minute ECG reviewed independently by 2 cardiologists. All patients received platelet aggregation inhibitors at study start and were seen in clinic every 3 months. Immediately phoned if AF detected; OAC [illegible] if confirmed	0.25	1.7%
				3	11.7%
				Median 13	16.7%
Rojo-Martinez 2013[61]	Reveal XT		No details	10	30.2%
Israel 2017[62]	Reveal XT (87%) or BioMonitor (13%)	20 days; mostly before discharge	≥ 2 minutes; automatic AF detection algorithms and ECG storage. Manually analysed and adjudicated. Daily transmission by patient via CareLink® or HomeMonitoring®). In-hospital follow-up at 1 month and every 6 months thereafter.	3	12.2%
				9	22.8%
				13	23.6%

Abbreviations: CS, cryptogenic stroke; ECG, electrocardiogram; iAF, intermittent atrial fibrillation; ICM, implantable cardiac monitor; NR, not reported; OAC, oral anticoagulants; TTE, transthoracic echocardiogram.
Follow-up reported as mean unless otherwise specified; times were converted to months for [illegible] and rounded to the nearest month unless <1 month.
i. 14.6% had multiple episodes detected and 4.5% had a single episode detected after 2-years follow-up
ii. Described as NeuroLINQ in the abstract and assumed Reveal LINQ
iii. For those in whom AF was not detected. Not reported for full population but minimum was 50 days

3.3.2.3 Diagnostic yield: Detection of other cardiac pathologies

The primary aim of the observational studies was to detect AF in patients with CS, but five studies also reported incidental detection of other arrhythmias by the ICM. Three studies of the Reveal LINQ (or primarily LINQ in a mix of LINQ and XT) suggest the proportion of patients detected with other arrhythmias is in the region of 10%, consisting mainly of bigeminy, pause and bradycardia. Two primarily Reveal XT studies that reported the breakdown of arrhythmias gave rate of 1% (atrial flutter, cardiac arrest, sick sinus node, bigeminy, ventricular tachycardia) to 7–8% (atrioventricular block and ventricular extra systole). No information was presented about whether and how the detected arrhythmias were treated, and whether outcomes were improved for patients by having the arrhythmias identified.

Table 18. Incidental detection of other arrhythmias in the observational studies

Study ID	Device	Follow-up (months)	Other arrhythmias
Asaithambi 2018[39]	Reveal LINQ	17.6 (median)	12% any arrhythmia (28/234)
Li 2018[44]	Reveal LINQ	13.4 (median)	True positive episodes detected by ICM: 177/202 bradycardia (87.6%) 212/531 pause (39.9%) 85/107 tachycardia (79.49.49.4du)
Carrazco 2018[48]	Reveal LINQ (90%) or XT (10%)	8 (minimum)	7% bigeminy 5% sinus bradycardia 5% sinus pauses
Pedersen 2018[50]	Reveal XT (72.4%) or LINQ (27.6%)	12.5	1% cardiac arrest 3.8% complete atrioventricular block 1.9% non-sustained ventricular tachycardia 1.0% sick sinus node 3.8% supra ventricular tachycardia
Christensen 2014[53] (SURPRISE)	Reveal XT	18.7	1.1% atrial flutter (1/87) 6.9% atrioventricular block (6/87) 1.1% bigeminy (1/87) 2.3% ectopic beats (2/87) 3.4% sinus arrhythmia (3/87) 2.3% supra ventricular tachycardia (2/87) 8.0% ventricular extra systole (7/87) 1.1% ventricular tachycardia (1/87)

Abbreviations: CS, cryptogenic stroke; ECG, electrocardiogram; iAF, intermittent atrial fibrillation; ICM, implantable cardiac monitor; NR, not reported; OAC, oral anticoagulants; TTE, transthoracic echocardiogram.
Follow-up reported as mean unless otherwise specified.

3.3.3 Observational studies: Clinical outcome results

3.3.3.1 Time to AF diagnosis

Eighteen observational studies reported time from device insertion to AF detection: 5 with the Reveal LINQ, seven with Reveal LINQ or XT, five with the Reveal XT, and one with Reveal XT or BioMonitor (Table 19). Overall average follow-up ranged from 7 to 20 months, and median time to first AF detection was highly variable, ranging from 21 to 217 days. Where reported, interquartile ranges (IQRs) also indicate a high degree of variability within studies.

Table 19. Time to AF detection in the observational studies

Study ID	Device	Follow-up (months)	Days to AF detection	
			Median	Interquartile range (IQR)
Asaithambi 2018[39]	Reveal LINQ	17.6 (median)	94.5	16 to 239
Heckle 2018[42]	Reveal LINQ	10.2	42	NR
Seow 2018[46]	Reveal LINQ	NR	50	NR
Pallesen 2017[45]	Reveal LINQ [i]	12	57	NR
Ziegler 2017[15]	Reveal LINQ	24	112	35 to 293
Carrazco 2018[48]	Reveal LINQ (90%) or XT (10%)	8 (minimum)	34 (mean 108)	0 to 514 (range)
Abichandani 2016[47]	Reveal LINQ (60%) or XT (40%)	12	243.3	NR
Poli 2016[51]	Reveal LINQ (51.4%) or XT (48.6%)	12	105 (mean)	0 to 361 (range)
Joseph 2018[49]	Reveal LINQ or XT	7.3	35	NR
Salahuddin 2015[52]	Reveal LINQ or XT	10.4	52 (mean 57.1)	21 to 57
Pedersen 2018[50]	Reveal XT (72.4%) or LINQ (27.6%)	12.5	21	5 to 146 (range)
Reinke 2018[59]	Reveal XT or LINQ	20	217	72.5 to 338
Cotter 2013[54]	Reveal XT	7.5 [ii]	48	34 to 118 (range 0 to 154)
Etgen 2013[55]	Reveal XT	12	152.8 (mean)	61.6 to 244.1 (95% CI)
Merce 2013[57]	Reveal XT	11.5 (median)	176.4	NR
Muller 2017[58]	Reveal XT	10.9	30 (mean 40.7)	SD 42.2
Ritter 2013[60]	Reveal XT	12.5	64	1 to 556 (range)
Israel 2017[62]	Reveal XT (87%) or BioMonitor (13%)	12.7	109.5	SD 103.4

Abbreviations: CI, confidence interval; CS, cryptogenic stroke; ECG, electrocardiogram; iAF, intermittent atrial fibrillation; ICM, implantable cardiac monitor; NR, not reported; OAC, oral anticoagulants; TTE, transthoracic echocardiogram.
Follow-up reported as mean unless otherwise specified.
i. Described as NeuroLINQ in the abstract and assumed Reveal LINQ.
ii. For those in whom AF was not detected. Not reported for full population, but minimum was 50 days.

3.3.3.2 Anticoagulant use

In seven studies of Reveal LINQ and/or XT, uptake of OAC in patients detected with AF was consistently high (Table 20). Most of the studies had small populations, but the evidence suggests uptake of anticoagulation is in the region of 90 to 100% once AF is detected. Christensen 2014[53] (SURPRISE) reported the overall uptake of OAC regardless of whether AF was detected and did not report whether the 19 patients starting OAC included all 14 patients with AF.

Table 20. Uptake of anticoagulation following diagnosis of atrial fibrillation

Study ID	Device	Follow-up (months)	Anticoagulant use, of those with detected AF
Asaithambi 2018[39]	Reveal LINQ	17.6 (median)	91.2% (62/68)
Li 2018[44]	Reveal LINQ	13.4 (median)	83.3% (5/6)
Seow 2018[46]	Reveal LINQ	NR	90.9% (10/11)
Carrazco 2018[48]	Reveal LINQ (90%) or XT	8 (minimum)	96.8% (30/31)
Christensen 2014[53] (SURPRISE)	Reveal XT	18.7	14 patients diagnosed with AF, 19 in total ICM cohort started OAC
Etgen 2013[55]	Reveal XT	12	100% (6/6)
Merce 2013[57]	Reveal XT	11.5 (median)	100% (5/5)

Abbreviations: CS, cryptogenic stroke; ECG, electrocardiogram; iAF, intermittent atrial fibrillation; ICM, implantable cardiac monitor; NR, not reported; OAC, oral anticoagulants; TTE, transthoracic echocardiogram.
Follow-up reported as mean unless otherwise specified.

3.3.3.3 Incidences of device failure and removal

Three studies of Reveal LINQ and/or XT[39, 53, 60] reported number of device removals during follow-up. Ritter 2013[60] (Reveal XT) offered removal to patients once AF was detected, but it was not clear how many of the 18/60 (30%) removals were for this reason or other reasons such as tolerability or battery life. Christensen 2014[53] (Reveal XT) reported that the device was prematurely explanted in 5 of 87 (5.7%) patients (3 due to skin reactions and 2 due to discomfort) and that the median time to removal was 45 days; a further 3 patients (3.4%) chose to have the device removed after more than one year of monitoring without AF being detected. Asaithambi 2018[39] reported that, of the 234 patients implanted with Reveal LINQ, 5.1% were removed from patients who died or required palliative care, 2.6% were removed electively, 1.3% were lost to follow-up, and 0.9% migrated or fell out.

3.3.3.4 Further strokes or TIAs

Six studies reporting recurrent stroke indicate that a minority of patients have recurrence in the first year after device implantation, although the data were variable (0–14.6%). The data for recurrent stroke or TIA in patients with AF suggest higher rates compared to in those without AF detected, but it is unclear how many of these strokes and TIA's in the AF patients occurred prior to the detection of AF.

Table 21. Recurrent stroke/TIA in the observational studies

Study ID	Device	Follow-up (months)	Recurrent stroke/TIA	Notes
Poli 2016[51]	Reveal LINQ (51.4%) or XT (48.6%)	12	1.4% recurrent stroke (1/74)	No AF detected in the patient with recurrent stroke, and the stroke occurred 14 months after index event
Pedersen 2018[50]	Reveal XT (72.4%) LINQ (27.6%)	12.5	2.9% recurrent stroke (3/105) 6.7% recurrent TIA (7/105)	In patients with new-onset AF only one patient experienced a new TIA and none had a stroke. The difference in TIA recurrence in patients with and without AF was not statistically significant (log-rank test, P = 0.98)
Christensen 2014[53] (SURPRISE)	Reveal XT	18.7	4.6% recurrent stroke confirmed by imaging (4/87) 10.3% had clinical diagnosis of TIA with no imaging to confirm (9/87) (a further 10 patients were admitted for suspected new cerebrovascular event but had no final diagnosis of stroke or TIA recorded)	Ischaemic event rate, defined as either stroke or TIA (independent of imaging confirmation), was higher in the AF group (6 [33.3%]) than in the non-AF group (7 [10.1%]), P = 0.024.
Etgen 2013[55]	Reveal XT	12	0% recurrent stroke (0/22)	
Ritter 2013[60]	Reveal XT	12.5	0% recurrent stroke (0/60)	
Israel 2017[62]	Reveal XT (87%) or BioMonitor (13%)	12.7	14.6% recurrent stroke (18/123)	5 (17.9%) recurrent strokes in those with AF detected (n=28), 4 of which occurred before AF detection 13 (13.7%) recurrent strokes in people without AF detected (n=95)

Abbreviations: CS, cryptogenic stroke; ECG, electrocardiogram; iAF, intermittent atrial fibrillation; ICM, implantable cardiac monitor; NR, not reported; OAC, oral anticoagulants; TTE, transthoracic echocardiogram.
Follow-up reported as mean unless otherwise specified.

3.3.3.5 Adverse events

In addition to the device removal data summarised above, some of which related to tolerability, five studies reported AEs. Three studies of Reveal XT,[57, 59, 60] one of Reveal LINQ and XT,[51] and one of Reveal XT and BioMonitor[62] all reported that no complications of the procedure or insertion site were noted during follow-up.

3.4 Evidence on ICMs in non-CS populations

All the studies discussed below (Section 3.4) are a different population to that specified in the NICE final scope as they are not in patients with a prior CS (or do not report subgroup data for the included CS patients and >50% of the study population are not CS patients). As discussed in Section 3.1, the performance (e.g. PPV and NPV) of AF detection in ICM devices, is dependent on the patient

population, incidence rate of AF, the duration of monitoring and the type of AF.[1] As such, the data reported here in Section 3.4 are not necessarily representative of the respective ICM device performance in CS patients. In addition, none of the results are directly comparable between the devices. However, the decision was made to consider these data from non-CS populations as no data have been identified for the Confirm RX or BioMonitor 2-AF in the CS population and only limited outcome data were identified in the CS population for the Reveal LINQ. It should be noted that the studies discussed below were obtained directly from company recommendations and a full systematic literature search was not conducted to validate their inclusion due to time constraints and concerns regarding the applicability of their results to the CS population.[1] The data presented in the following subsections of Section 3.4 may be subject to study selection bias as well as clinical heterogeneity due to the variation in the patient populations of each of the studies.

The eligibility criteria applied when selecting studies to report from non-CS populations were as follows:

- Sources searched: references supplied in the individual company submissions;
- Study type: RCT or observational studies with or without a comparator arm;
- Population: No restrictions applied;
- Intervention: Any one of the following ICMs: SJM Confirm DM2102, Confirm RX DM3500, BioMonitor 2-AF, Reveal XT or Reveal LINQ;
- Comparator: No restrictions applied. DTA data required Holter monitoring (any duration) as the reference standard;
- Outcomes: All outcomes listed in the protocol and as listed in Section 2.1.

The results of the searches are presented in the subsections below for each of the three ICM companies.

3.4.1 Abbott

The information provided in the company submission by Abbott regarding the Confirm RX was that the only relevant study was the Detect AF study (Nölker 2016).[63] The EAG notes that the patients in Detect AF were not restricted to CS patients and therefore the EAG did not consider this study to meet the review inclusion criteria. In addition, the ICM device used in Detect AF was the Confirm ICM, Model DM2102, whereas supporting documents for the company submission included a user guide for the Confirm RX Model DM3500. The company clarified that Confirm DM2102 was an older and larger model of the Confirm RX, which is the model specified in the NICE final scope[2]. The EAG is unsure

how the firmware in the models differs but in the absence of any suitable clinical data for the Confirm RX DM3500, the data for the Confirm DM2102 are summarised below.

In addition, the company reported that Healey 2017[64] may provide some useful clinical data for the assessment of the Confirm RX. The EAG notes that this is an observational cohort study that uses the Confirm DM2100, the predecessor to the DM2102. The study population in Healey 2017[64] comprised of patients at risk of AF who were aged ≥65 years and attending outpatient cardiology and neurology clinics. Healey 2017[64] does not specifically report whether it includes any CS or cTIA patients although 48.0% had a history of stroke, TIA or systemic embolism. The EAG considers the data from Detect AF[63] to be more appropriate given they are based on a more recent model of the Confirm ICM and so the results from Healey 2017[64] are not discussed further.

Detect AF[63] was a prospective observational study to assess the diagnostic accuracy of the Confirm ICM in detecting AF compared to Holter monitoring. The intervention comprised of 4-days simultaneous monitoring for AF using the Confirm ICM and a Holter monitor and was required to take place at least 2 weeks after ICM implantation. A total of 90 patients were enrolled from 12 centres in Germany and the Netherlands between September 2012 and December 2013; although only 79 patients were deemed eligible for inclusion in the analyses. Reasons for exclusion from the analysis included clock synchronisation issues due to batteries running low in the Holter or patient ICM external symptom activator (total of 5 patients) and insufficient duration of analysable Holter recordings (4 patients). Patients were required to have either been diagnosed with paroxysmal AF or to have a clinical suspicion of paroxysmal AF. In total 8 of the enrolled patients had a history of prior stroke or TIA although it is unclear whether any of these were CS or cTIA patients.

The ICM monitored for AF episodes lasting at least 2 minutes and the Holter monitor data were analysed by a blinded, independent core laboratory. Patient and episode sensitivity, specificity (SP), PPV, and NPV were calculated.

At least one AF episode was detected in 16 of the 79 patients analysed, and all 16 patients had episodes of AF recorded by both the ICM and the Holter monitor. There were no incidences where the Holter monitor detected additional episodes of AF compared to the ICM. However, 9 patients had at least one 2-minute AF detection by the ICM, without any corresponding AF episode detected on the Holter recording. However, most of these false positives were due to irregular sinus rhythms and not noise (44/58 episodes, number of patients not reported and clinical consequence of detecting these not reported). In a per patient analysis, the sensitivity was 100% (95% CI: 79.4% to 100%), PPV was 64.0% (95% CI: 42.5% to 82.0%), SP was 85.7% (95% CI: 74.6%, 93.3%), and NPV was 100% (95% CI: 93.4% to 100%) for the Confirm ICM using Holter monitoring (minimum of 45 hours analysable data)

as the reference standard. The results of the per patient analysis, therefore, suggest that the Confirm DM2102 ICM can detect AF with a high sensitivity and a reasonably high specificity.

DETECT AF also reported no AEs during the follow-up time for any of the 90 enrolled patients who received the ICM device.

3.4.2 BIOTRONIK

BIOTRONIK provided 12 publications in support of their company submission with clinical data that they deemed to be of relevance to the assessment of BioMonitor 2-AF in patients with CS. However, [redacted] were deemed to meet the inclusion criteria for a discussion of non-CS or mixed population data. The key characteristics of the five included studies are summarised in Table 22 and their results are discussed below. The EAG notes that only [redacted] and that the primary indication for the ICM is CS [redacted] of the study participants for each of the included studies. As discussed earlier (Section 3.1 and 3.4), AF detection in ICM devices is dependent on the patient population, incidence rate of AF, the duration of monitoring and the type of AF and so these results may not be a true reflection of the ICM performance in CS patients.[1] It is also unclear in [redacted] what proportion of the study participants received the BioMonitor 2-AF model of the BioMonitor 2 as specified in the NICE final scope and it should be noted that [redacted]

[redacted]

[redacted]

Table 22. Summary of included BioMonitor 2 studies

Study ID	Study Name	% BioMonitor 2-AF model	Country (sites)	Enrolment	N	N of CS patients	Last planned follow-up
Ooi 2017[68]	BioMonitor 2 pilot study	NR	Australia (5 sites)	Patients with an accepted indication for long-term cardiac monitoring. The most common indications for ICM were primary indications were syncope (42%) and symptomatic or asymptomatic AF or flutter at baseline (42%).	31	1 (3.2%)	1-month
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Reinsch 2018[72]	N/A	36%	Germany (1 site)	Consecutive patients with an indication for long-term cardiac monitoring. Most common indication was unexplained syncope (80%)	30	1 (3%)	3-months

Abbreviations: AF, atrial fibrillation; CS, cryptogenic stroke; ICM, implantable cardiac monitor; ID, identification; N, Number; N/A, not-applicable; NR, not reported.

Clinician time taken to insert the BioMonitor 2 was reported in four studies[65, 68, 69 66, 68] Reinsch 2018[72] reported that all devices were successfully implanted in a cath lab with a median time from skin cut to last suture of 8 minutes (IQR: 7–10) and Ooi 2017[68] reported that all implantations were successfully performed in cath labs on the first attempt with a median time from incision to last suture of 9 minutes

(IQR: 5–14). [redacted]

Four studies[65, 68, 69 66, 72] reported data on AEs, with one study[65] also reporting subgroup data for CS patients. Ooi 2017[68] reported that there was one pocket infection observed and successfully treated with oral antibiotics. Reinsch 2018[72] reported that no devices had migrated by the 3-month follow-up but two patients experienced AEs: one patient (3%) who was immunosuppressed developed a device related pocket infection requiring ILR explantation and oral antibiotic treatment; the second patient (3%) complained of slight discomfort in the area of the flexible ICM antenna. [redacted]

One study[72] also provided data on additional patient-related outcomes of interest to the NICE final scope. Reinsch 2018[72] reported that at least one therapeutic intervention was performed in 23% of patients following the recording of arrhythmias during follow-up and this included initiation of oral anticoagulation in one patient (3%). Reinsch 2018[72] also reported results from patient satisfaction

surveys at 1 day and 3-months. The results were generally good, with only 7% reporting moderate to severe pain and 20% reporting mild pain within 24 hours post intervention at the implantation site. Sustained paresthesia was moderate in 7% and mild in 17% of patients and moderate impairment in daily life was by 1 (3%) patient. The cosmetic result was mostly reported to be very satisfying (63%) or satisfying (30%).

In summary, the studies of the BioMonitor 2 suggest that it is clinically effective in detecting AF and is associated with low levels of AEs and reasonably good levels of patient satisfaction. However, it should be noted that these results are not exclusively for the BioMonitor 2-AF or a CS population and therefore should be interpreted with caution.

3.4.3 Medtronic

The documents supplied by Medtronic were reviewed for data and all relevant studies relating to the CS population have been included and discussed in Sections 3.1 to 3.3, however, due to time constraints and the large volume of citations of potential relevance for data in a non-CS or mixed population provided by the company the EAG took the pragmatic decision to limit the inclusion of non-CS studies to those studies directly referred to and reporting clinical outcome data that were reported in the request for information document received on 28 July 2017. There were five studies[1, 37, 73-75] identified from the company submission in non-CS or mixed populations with four studies[1, 37, 74, 75] reporting data on the DTA of the Reveal ICMs and two studies[73,75] providing AE data for the Reveal LINQ. These five studies are discussed briefly below along with their relevant results. As discussed earlier (Section 3.1 and 3.4), it is important to remember when interpreting these results that the performance (e.g. PPV and NPV) of AF detection in ICM devices, is dependent on the patient population, incidence rate of AF, the duration of monitoring and the type of AF and so these results may not be a true reflection of the ICM performance in CS patients.[1]

The "Reveal XT Performance Trial" (XPECT; Hindricks 2010)[37] was a single arm prospective observational study of 247 patients to assess the performance of the Reveal XT in detecting AF (of at least 2 minutes). Patients were enrolled between September 2007 and July 2008, from 24 medical centres mainly in Europe and Canada. Eligible patients were those who:

1. Were scheduled for pulmonary vein (PV) ablation or surgical rhythm control intervention; or
2. Had documented frequent AF or frequent symptoms attributable to AF; or
3. Had undergone PV ablation within the last 6 months and still had symptoms attributable to AF.

The study protocol required the enrolled patients to be implanted with the Reveal XT and 4 to 6 weeks after the ICM implantation they were to receive 46 hours of Holter monitoring (with a minimum of 18

hours Holter recording required for inclusion in the analyses). There was a total of 206 patients with analysable Holter recordings, of which 76 (37%) had at least one episode of AF although only 73 (96.1% of the Holter detected AF patients) of these patients were also identified as having AF by the ICM. The XPECT study results demonstrate that the dedicated AF detection algorithm in the Reveal XT identified the presence or absence of AF with an accuracy of 98.5% compared to the Holter monitor (Table 23). In addition, statistical analysis demonstrated that the AF burden measured with the ICM was well correlated with the reference value derived from the Holter monitor (Pearson coefficient=0.97).

Puerefellner 2014[74] used the XPECT trial data set and applied a change to the ICM AF detection algorithm so that it also incorporated data on P-waves when classifying patients with AF (this algorithm change was applied in the Reveal LINQ). The revised data set was compared to the original Holter monitor data and the results are presented in Table 23.

The Reveal LINQ Usability Study (Sanders 2016)[75] was a non-randomised, single-arm prospective multi-centre observational study to assess the diagnostic accuracy of the new Reveal LINQ ICM for AF detection using 24 hours of Holter monitoring as the reference standard. The Holter monitoring was scheduled to occur at the 1-month follow-up visit, 1-month following ICM insertion and AF was defined as a minimum of 2 minutes. The patients enrolled in the Reveal LINQ Usability study comprised of 30 patients with any indication for an ICM and 121 patients with a documented history of AF (including patients awaiting AF ablation). The reference standard and patient population are, therefore, different in this study to in the XPECT study. The results of the Reveal LINQ Usability study are summarised in Table 23. There were 138 patients with Holter monitor recordings suitable for inclusion in the analyses and the ICM correctly identified 37 of the 38 patients with Holter-detected AF (diagnostic sensitivity of 97.4). The results of the new AF detection algorithm in the Reveal LINQ ICM demonstrate an improvement in terms of AF detection compared to the Reveal XT.

Puerefellner 2018[1] was similar to Puerefellner 2014 in that it was applying a further P-wave related algorithm enhancement for the Reveal ICMs AF detecting capability to existing datasets to see what impact it had on the diagnostic accuracy of the ICMs. Puerefellner 2018 used both the XPECT and Reveal LINQ Usability study datasets. The first 56 patients in the XPECT study with suitable data were used as the development dataset for testing the algorithm enhancement and then data from 176 patients were used as the validation dataset. In addition, the algorithm enhancement (adaptive P-sense [TruRhythm]) was applied to the Reveal LINQ. The per-patient results were only reported in the paper for the LINQ Usability study dataset (Table 23) although the EAG notes that there is no explanation provided for the discrepancy in the number of patients with AF diagnosed on Holter monitor in the TruRhythm analysis reported in Puerefellner 2018 compared to in the Sanders 2016 publication for LINQ Usability study (37 vs 38 patients, respectively). Nonetheless, assuming the results of Puerefellner 2018 are accurate, they suggest that the new adaptive P-sense (TruRhythm) enhancement

results in an improvement in sensitivity, specificity and accuracy in the Reveal LINQ in detecting AF. Medtronic reported in their company submission that Reveal LINQ with TruRhythm detection was rolled out in 2017.

Table 23. Diagnostic text accuracy data for the Reveal XT and Reveal LINQ in non-CS populations (patient-based analysis)

Outcome	Hindricks 2010[37] (XPECT study)	Puerefellner 2014[74] (XPECT dataset)	Sanders 2016[75] (LINQ usability study)	Puerefellner 2018[1] (LINQ usability dataset)
ICM	Reveal XT	Reveal XT with P-sense enhancement	Reveal LINQ	Reveal LINQ with adaptive P-sense (TruRhythm)
Sensitivity	96.1%	96.1%	97.4%	100%
Specificity	85.4%	90.0%	97.0%	99.0%[b,c]
PPV	79.3%	84.9% [a]	92.5%	97.4%[b,d]
NPV	97.4%	97.5%[a]	99.0%	100%[d]
Accuracy	89.3%	92.2%[a]	97.1%	99.3%[e]

[a] Calculated by EAG using data reported in Puerefellner 2014
[b] Calculated to 1 decimal place by EAG using data reported in Puerefellner 2018
[c] Reported in company submission as 98.1%
[d] Reported in company submission as 92.5%
[e] Not reported in company submission

The results of the DTA studies in the non-CS population suggest that the enhancements over time to the AF diagnosis algorithm in the Reveal XT and Reveal LINQ ICMs has improved the DTA of the ICMs (sensitivity and specificity; Table 23). However, it should be noted that these data are not in the CS population and the data in the XPECT and Reveal LINQ Usability studies used to make some of these comparisons are heterogeneous due to differences in the way in which the reference standard was applied (Holter monitoring 48 hours vs 24 hours, respectively) and differences in the patient populations (e.g. reasons for ICM insertion). Nonetheless these data suggest that the Reveal LINQ is likely to be as effective if not better at detecting AF as the Reveal XT (as the Reveal LINQ has fewer false positives and fewer false negatives) and therefore the AF detection rate from CRYSTAL-AF is potentially a conservative estimate for the Reveal LINQ given that it was the Reveal XT that was used in CRYSTAL-AF.

Mittal 2015[73] reported AE data for two observational studies of the Reveal LINQ; one was the LINQ Usability study already discussed above[75] and the second was the Reveal LINQ registry. The registry is a post-market surveillance study of patients with a Reveal LINQ ICM for any indication (proportion with CS indication not reported) and the AE data discussed in Mittal 2015 for this study were limited to 122 patients from seven centres who were enrolled pre-device insertion. The combined cohort of 273 patients from the two studies had an infection rate of 1.5% (n=4), an AE rate of 4.0% (n=11), and SAE rate of 1.1% (n=3). The company highlighted that the definition of an AE varies across studies and the EAG notes that the analysis in Mittal 2015 does not take into account the differences between the two

study populations and thus the analysis is subject to clinical heterogeneity. The results do however suggest that the Reveal LINQ is associated with a low rate of AEs and SAEs.

3.5 Summary of clinical effectiveness results

3.5.1 Quantity and quality of evidence

- The clinical evidence searches sought to identify RCTs and comparative observational studies that compared any of the three devices (Confirm RX, Abbott; BioMonitor 2-AF, BIOTRONIK; and Reveal LINQ, Medtronic) with at least 24 hours of Holter monitoring to detect AF in people with CS. Electronic database searches were run on 13 September 2018 and results were assessed together with reference lists of systematic reviews and evidence submitted by the companies.

- A single RCT assessing an earlier Medtronic Reveal model (XT rather than LINQ) met the original eligibility criteria (CRYSTAL-AF)[35], so the criteria were widened to find evidence for the BioMonitor 2-AF, Confirm RX and Reveal LINQ. First, non-comparative observational studies were sought within the correct CS population, and then evidence was considered from studies of mixed populations submitted by each company. Only CRYSTAL-AF[35] falls within the eligibility criteria outlined in the original published protocol for this diagnostics assessment, so the additional evidence should be interpreted with caution. 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 32 32 32 32 32 32 3232

- CRYSTAL-AF[35] (n = 441) represents the most robust clinical evidence to inform the decision problem, despite assessing the Reveal XT. The study was open-label and compared the ICM with conventional follow-up in a population with CS or TIA and no history of AF after extensive diagnostic workup. The study was conducted in North America and Europe and the population was considered generally applicable to patients who would be eligible for an ICM in UK clinical practice.

- Twenty-six single-arm observational studies were identified after widening the eligibility criteria to include non-comparative studies. The studies were conducted in North America and Western Europe (one in the UK) and all assessed the Reveal XT and Reveal LINQ in populations with CS or TIA; none provided evidence to assess the efficacy of BioMonitor 2-AF (other than a mixed device study that did not provide separate results) or Confirm RX for patients with CS. The observational studies represent a wide sample of patients who have received an ICM in practice (N = 3,414) and provide evidence for the Reveal LINQ and for additional outcomes that were not available from CRYSTAL-AF.

- In total 1 study for Confirm RX (older model the Confirm DM2102), 5 studies of the BioMonitor 2-AF (all BioMonitor 2 but only one of which we can be certain was of the '-AF' model) and 5 studies of the Reveal LINQ (3 studies Reveal LINQ and 3 studies Reveal XT [note: one study included both devices]) in mixed populations were included based on the recommendations of the companies. All of these mixed population studies are either single-arm observational studies or they provide DTA data for the ICM using Holter monitoring as the reference standard.

- All the observational studies were single-arm and therefore high risk of bias. Three conducted within-patient comparisons of ICM versus other monitoring strategies.[14, 15, 60] Key sources of heterogeneity between the observational studies include patient demographics (mean or median age 52 to 72 years), rigor of stroke assessment, stroke risk score (CHA_2DS_2VASC score 3 to 5), definition and adjudication of AF, and length of follow-up – all are likely to affect AF detection and other clinical outcomes.

- Eight ongoing studies of potential relevance were identified although only five (3 RCTs and 2 observational studies) reported details of their current status and the ICM being studied and none relate to the BioMonitor 2-AF. The three ongoing RCT's all involve the Reveal LINQ with only one RCT solely in a CS population: a Canadian randomised trial comparing the clinical and cost-effectiveness of the Reveal LINQ ICM with external loop recording in 300 CS patients which is estimated to complete in December 2019 (PERDIEM; NCT02428140). There was only one ongoing study identified relating to the Confirm RX: the SMART registry, a post-approval study planning to recruit at least 2000 patients with Confirm RX (NCT03505801) across multiple indications, but with a planned subgroup analysis for CS; completion is expected during 2019.

3.5.2 Overview of effectiveness results

- AF detection rate was the primary outcome in CRYSTAL-AF (at 6 months), and all 26 observational studies. Other outcomes reported by CRYSTAL-AF and the observational studies were AF at longer follow-ups (up to 36 months), time to AF detection, uptake of anticoagulants, device removals, subsequent stroke and AEs. Quality of life data are only available from CRYSTAL-AF, and diagnostic accuracy and detection of other arrhythmias were only available from the observational or mixed population studies.

- *Diagnostic accuracy (CRYSTAL-AF and observational studies)*: CRYSTAL-AF was designed to measure diagnostic yield rather than accuracy, and none of the observational studies provided comparative DTA between an ICM and standard monitoring. Two studies modelled patient AF

detection data from CRYSTAL-AF (Choe 2015[14]) and a large patient registry (Ziegler 2017[15]) with repeated iterations (10,000) to estimate the number of patients whose AF would not have been detected should an intermittent monitoring strategy have been used (based on assumption that the ICM has 100% sensitivity). The studies found that the best performing intermittent monitoring strategy detected less than a third of AF detected by the ICM (ranging from around 3% for a single 24-hour Holter monitor to 30% with a quarterly 7-day Holter monitor). Studies reporting false positive rates as the proportion of episodes detected by ICM algorithm that were not subsequently verified by a clinician were highly dependent on model and sensitivity configuration.

- *Diagnostic accuracy (mixed population studies)*: The results of the mixed population DTA studies suggest that the enhancements over time to the AF diagnosis algorithm in the Reveal XT and Reveal LINQ ICMs has improved the DTA (sensitivity and specificity) of the ICMs. A naïve comparison of the sensitivity and specificity data from non-CS or mixed populations in the studies flagged of relevance by the respective companies of the Confirm DM2102 (older model of Confirm RX) and Reveal LINQ suggests they both have 100% sensitivity for AF detection although specificity varies (85.7% and 99.0%, respectively); the BioMonitor 2 [redacted]

  However, it should be noted that this analysis is subject to clinical heterogeneity in terms of the patient populations, interventions and study designs. In addition, as discussed earlier, the device related performance of ICMs is dependent on the patient population and the incidence rate of AF. These data are thus not necessarily reflective of the respective ICMs performance in CS patients and also, they do not necessarily reflect the performance of the current device model firmware, for example, the Confirm RX data are based on an earlier model.

- *Diagnostic yield*: AF detection in CRYSTAL-AF was higher with the Reveal XT than conventional follow-up at all timepoints. At the primary 6-month analysis, AF had been detected in 19 (8.6%) patients with an ICM and 3 (1.4%) patients in the conventional follow-up group. By 36 months, the number of patients detected were 42 (19%) with ICM and 5 (2.3%) with conventional follow-up, demonstrating the continued and increasing benefit of ICM monitoring. AF detection rates reported at the primary follow-up (6 to 24 months) across the 26 observational studies were highly variable, ranging from 6.7%[50] (Reveal LINQ and XT at 12-months) to 40.9%[56] (Reveal XT, unknown follow-up). These data demonstrate that even within a CS population AF detection rates are highly variable, and it is impossible to make any meaningful comparison between the observational studies and CRYSTAL-AF. Observational studies reporting AF detection at different lengths of follow-up indicate that a minority of patients are diagnosed within the first month (mostly in the region of 10% of those detected by

a year), around 70–80% by 6 months, and a small number beyond a year of monitoring.[15, 39, 46, 60, 62] In comparison, the 36-month data from the ICM arm of CRYSTAL-AF show higher proportions of AF diagnosed at 1-month (19.0%) and beyond 12-months (31.0%) and a lower proportion at 6-months (45.2%) compared to the observational studies. The EAG reiterates that synthesis of the observational studies was considered inappropriate due clinical heterogeneity (see limitations in the following Section 3.5.3). Where described, all or most AF detected was asymptomatic and so would not likely have been picked up without continuous ICM monitoring.

- *Time to diagnosis of AF*: Time to AF detection was significantly shorter for patients with the Reveal XT in CRYSTAL-AF compared with conventional follow-up at 6 months (HR 6.4, 95% CI: 1.9 to 21.7, p<0.001), 12 months (HR 7.3 95% CI: 2.6 to 20.8, p<0.001) and 36 months (HR 8.8, 95% CI: 3.5 to 22.2, p<0.001). The benefit of the ICM increased with length of follow-up because very few patients in the conventional follow-up arm were diagnosed, whereas detection continued steadily in the group with an ICM. Eighteen observational studies (five Reveal LINQ, seven Reveal LINQ or XT, five with Reveal XT, and one Reveal XT or BioMonitor), at average follow-up between 7 and 20 months, showed highly variable median time to first AF detection, ranging from 21 to 217 days. These results are however, broadly consistent with the results from CRYSTAL-AF, where median time to AF diagnosis was 41 days (Interquartile range [IQR]: 14 to 84) at 6-months, 84 days (IQR: 18 to 355) at 12-months and 8.4 months (IQR not reported) at 36 months follow-up.

- *Detection of other arrhythmias*: Three of the observational studies, primarily of the Reveal LINQ, suggest the proportion of patients in which the ICM detected other arrhythmias is in the region of 10%, consisting mainly of bigeminy, pause and bradycardia. No information was presented about whether and how the detected arrhythmias were treated to prevent related complications, and other arrhythmias were not available from CRYSTAL-AF.

- *Uptake of anticoagulation*: In CRYSTAL-AF, more than 90% of patients diagnosed with AF in the ICM arm started an oral anticoagulant. Data were only available for the conventional follow-up group irrespective of AF diagnosis, indicating 8.3% were on an anticoagulant by 36 months (24 patients, whereas 5 had been diagnosed with AF by that timepoint). In seven observational studies of Reveal LINQ and/or XT, uptake of anticoagulants in patients detected with AF was in the region of 90 to 100%. Time to anticoagulation and AEs related to anticoagulant use were not reported in any of the identified evidence.

- *Device failures (battery, transmission, removal)*: After 36 months, 5 devices had been removed due to infection or pocket erosion in CRYSTAL-AF (2.4%). Within the observational evidence,

three studies of Reveal LINQ and/or XT[39, 53, 60] reported removals but it was often not clear whether they were for tolerability, battery life, or after AF detection. Two observational studies reported a small number of premature device removals for reasons such as skin reactions, migration or discomfort (0.9% to 5.7%) in line with CRYSTAL-AF (2.4%). At 12 months follow-up, 3.4% of ICMs had been removed in CRYSTAL-AF, in contrast in Ritter 2013[60] (Reveal XT), where removal after AF detection was offered in addition to removal for other reasons, 30% of patients had their ICM device removed during the study (median follow-up time in the study for all patients was 13 months).

- *Subsequent stroke and TIA*: In CRYSTAL-AF, recurrent stroke or TIA rates were 5.0% in the ICM arm versus 8.2% in the conventional follow-up arm at 6 months (p>0.05). At 12 and 36 months, rates were 6.8% vs 8.6% and 9.0% vs 10.9%; none suggest statistically significant stroke prevention benefits of the Reveal XT vs conventional monitoring. Six of the observational studies, primarily assessing the Reveal XT, also observed relatively low stroke recurrence rates in the first year after device implantation (most were less than 7% in line with CRYSTAL-AF; range 0 to 14.6%). It was unclear how many recurrent strokes occurred in patients diagnosed with AF, and no studies reported other thromboembolisms or related morbidities.

- *Adverse events*: Device-related AEs such as pain and infection were low in CRYSTAL-AF, the single-arm observational studies and the mixed population studies. In CRYSTAL-AF, the rate of SAEs was similar between groups (around 25–30%) but more patients in the ICM group had non-serious AEs compared with conventional follow-up (18.6% vs 4.1%, respectively). No procedure- or insertion site complications were reported in the Reveal LINQ and XT observational studies, and none of the studies reported AEs relating to anticoagulation.

- *Health-related quality of life*: EQ-5D data collected throughout CRYSTAL-AF were [redacted]

- *Ease of use for clinicians and acceptability to patients*: CRYSTAL-AF did not collect any ease of use or acceptability data, and information from the observational studies was anecdotal. However, company submissions and the EAG's clinical experts reported that the newer models of the ICM's (e.g. Reveal LINQ and Confirm RX) were easier to insert and were suitable for insertion by trained nurses and cardiac physiologists which could help to free up clinician time.

3.5.3 Limitations of the evidence

- Despite extensive evidence searches, the clinical evidence for this DAR is based primarily on a single RCT for the older Medtronic Reveal XT device. Clinical expert opinion and evidence from a mixed population suggest that the Reveal LINQ has better sensitivity and specificity than the XT and leads to fewer complications due to its size, but there are no head to head clinical trials to confirm these findings in a CS population.[28]

- Despite widening the eligibility criteria to include low quality non-comparative observational studies, no data were found for the BioMonitor 2-AF or Confirm RX devices; evidence for these devices is limited to mixed population diagnostic accuracy and single-arm observational studies submitted by the companies.

- No evidence was found for any device for several outcomes (mortality, hospital and outpatient care for AF, related morbidities, AEs related to anticoagulation) and information about the ease of using each device for clinicians and their acceptability to patients was anecdotal or limited to data supplied in observational studies flagged by the companies.

- The EAG's clinical experts considered CRYSTAL-AF generally reflective of UK clinical practice, although all UK patients receive a transthoracic echo (TTE) and some patients who were excluded from the trial might be considered for ICM (i.e. those with a history of MI). Patients in CRYSTAL-AF were slightly younger than would be expected and all patients would be expected to be on an antiplatelet agent in UK clinical practice.

- Most patients in CRYSTAL-AF had received a median 23 hours of Holter monitoring (71.2%), but the remainder received a median or 68 hours of inpatient telemetry monitoring (29.7%), which is not in line with the scope of this DAR which required a minimum of 24 hours outpatient monitoring. Other issues noted with CRYSTAL-AF, such as baseline differences (e.g. in the proportion of patients with patent foramen ovale and history of prior stroke), crossover between groups, insertion delays (11.5%) and withdrawals are unlikely to have an important impact on the results of CRYSTAL-AF.

- AF detection rate varies considerably between and within the types of evidence considered by the EAG, (CRYSTAL-AF RCT, uncontrolled observational studies, mixed population studies) The EAG recommends caution in drawing conclusions from naïve comparisons between the additional studies due to the number of uncontrolled variables and inherent biases of their single-arm design. Sources of heterogeneity that likely contribute to the differences in AF detection include the episode threshold used (varying from 10 seconds to 2 minutes), population characteristics (such as stroke risk score), time from stroke to ICM insertion, length of follow

up, and method of AF adjudication. CRYSTAL-AF is the most robust evidence on which to base conclusions of ICM efficacy.

- There is evidence from the observational studies that the ICMs also detected some non-AF cardiac arrhythmias although no data on this additional potential benefit of ICMs was available from CRYSTAL-AF or in comparison to external ECG monitoring. It is also unclear whether detecting these additional arrhythmias led to any change in the management of the patients in which they were identified.

- The open-label design of CRYSTAL-AF introduces potential bias because the outcome assessor was aware of the intervention assignment and was able to influence the ECG or other assessment of AF. The ICM arm was unlikely to be affected by bias relating to the outcome assessor as all episodes of AF that qualified for analysis were adjudicated by an independent committee.

- The results of the mixed population DTA studies suggest that the Reveal LINQ is likely to be as effective if not better at detecting AF as the Reveal XT (as the Reveal LINQ has fewer false positives and false negatives) and therefore the AF detection rate data from CRYSTAL-AF is potentially a conservative estimate for the Reveal LINQ given that it was the Reveal XT that was used in CRYSTAL-AF.

4 METHODS FOR ASSESSING COST-EFFECTIVENESS

The Evidence Assessment Group's (EAG's) economic evaluation assessed the cost-effectiveness of implantable cardiac monitors (ICMs) compared with no further monitoring, to detect atrial fibrillation (AF) in people who have had a cryptogenic stroke (CS), including transient ischaemic attacks (TIAs), and have received at least 24 hours of non-invasive external cardiac monitoring. A systematic literature review (SLR) of existing economic evaluations was undertaken to inform the conceptualisation and development of a *de novo* economic model.

4.1 Systematic literature review for cost-effectiveness studies

4.1.1 Methods

A systematic review of the literature was undertaken in September 2018 to identify published economic evaluations of ICMs to detect AF in people with CS. The sources identified in those searches were also used to identify resource use and cost data that could be utilised in the economic model. In addition, one further systematic review was conducted, in September 2018, aiming to identify studies providing utility (generic, preference-based) data on the health-related quality of life (HRQoL) of people with AF and stroke, that could be used for the estimation of quality-adjusted life years (QALYs) in the economic model.

The following databases were searched for relevant studies:

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

Further to the database searches, experts in the field were contacted with a request for details of relevant published and unpublished studies of which they may have knowledge; reference lists of key identified studies were also reviewed for any potentially relevant studies.

The search strategy for existing economic evaluations and studies reporting resource or cost use data combined terms capturing the interventions of interest (ICM, i.e. Reveal LINQ™ [Medtronic, Minneapolis, USA], BioMonitor 2-AF™ [BIOTRONIK, Berlin, Germany] and Confirm RX™ [Abbott, Illinois, USA]) and the target population (patients with CS) with economic or healthcare resource use terms, applied to all electronic databases. The search strategy for HRQoL data was not restricted by intervention, and combined terms capturing the target population with HRQoL terms.

The search for resource use and cost data was limited to the UK/ National Health Service (NHS) setting, as the aim of this search was to identify data directly relevant to the NHS context that could inform the economic model; however, no country restrictions were applied to searches for existing economic evaluations.

Due to the high volume of hits in the searches for HRQoL evidence, searches were restricted by date, starting from 1997; the year 1997 was selected as this was the year the utility index for the EuroQol-5-Dimensions (EQ-5D) was published. Studies were then restricted to those collecting data in the Organisation for Economic Co-operation and Development (OECD) countries, as HRQoL data collected in low income countries was unlikely to be generalisable to the UK.

Initially, the EAG considered studies reporting utility data elicited using a generic, preference-based measure (EQ-5D, Health Utilities Index [HUI], Short-Form Health Survey [SF-36], Short-Form Six-Dimension [SF-6D]) or self-reported validated, choice-based technique for valuation (i.e. time-trade-off [TTO] or standard gamble [SG]). However, given the availability of relevant EQ-5D data in this population (made apparent to the EAG during the first-sift) and the National Institute for Health and Care Excellence's (NICE's) preference for EQ-5D data, the EAG decided to restrict studies to primary sources of EQ-5D data.

Limits were applied to all searches to remove animal studies, letters, editorials, comments or case studies. Only conference abstracts published within the last two years were considered for inclusion; it was assumed that any high-quality studies reported in abstract form before that date would have been published in a peer-reviewed journal. Full details of the search strategies are presented in Appendix 7, Section 9.1.

The titles and abstracts of papers identified through the searches were independently assessed for inclusion by two health economists using pre-defined eligibility criteria. Due to the high volume of studies retrieved by the HRQoL search, one health economist reviewed all identified citations and a

second health economist reviewed 20% of citations, to confirm that the same studies were included for second pass.

The inclusion and exclusion criteria for each of the three systematic reviews described above are outlined in Table 24. The methodological quality of the full economic evaluations identified in the review was assessed using the Drummond checklist.

Table 24. Inclusion and exclusion criteria for the systematic reviews of economic and health-related quality of life evidence

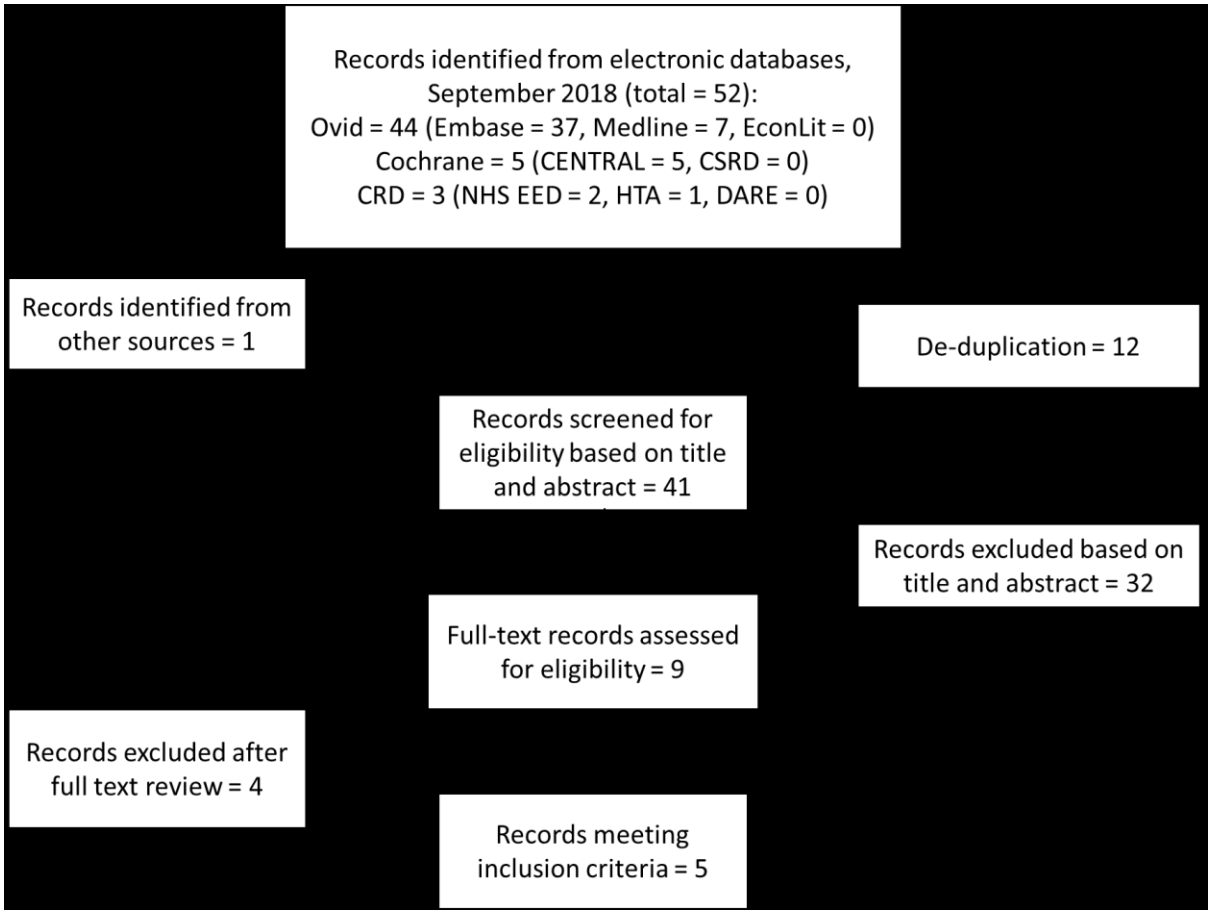
Inclusion criteria – economic
• intervention or comparators according to the scope of the assessment (ICMs); • study population according to the scope of the assessment (people with AF, a cryptogenic embolic stroke or cryptogenic TIA); • full economic evaluations (cost-utility, cost-effectiveness, cost-benefit or cost-consequence analyses) that assess both costs and outcomes associated with the interventions of interest; • economic evaluations that utilise clinical effectiveness data from randomised or non-randomised clinical trials, prospective cohort studies or systematic reviews and meta-analyses of clinical studies; economic analyses that utilise clinical data from studies with a mirror-image or other retrospective design will not be considered.
Inclusion criteria – resource use and costs
• study population according to the scope of the assessment (people with AF, a cryptogenic embolic stroke or cryptogenic TIA); • UK resource use or costing studies; • any setting (to be as inclusive as possible).
Inclusion criteria – HRQoL
• studies reporting EQ-5D utility data referring to specific health states associated with the care pathway (to investigate patients with cryptogenic stroke or TIA for underlying AF); • primary sources of utility data; • studies undertaken in the 36 OECD countries.
Exclusion criteria
• abstracts with insufficient methodological details; • conference papers published 2 years before the search was performed (September 2018).
Abbreviations: AF, atrial fibrillation; SG, standard gamble; OECD, Organisation for Economic Co-operation and Development; ICM, implantable cardiac monitors; TIA, transient ischaemic attack; TTO, time trade-off

4.1.2 Results

4.1.2.1 Economic evaluations

The SLR identified a total of 41 papers after de-duplication and based on title and abstract, a total of nine papers (including one unpublished report supplied by Biotronik) were identified as potentially relevant and were obtained for full text review based on the criteria listed in Table 24. Of the nine papers identified for full text review, five papers were included for data extraction (Appendix 9, Section 9.3).[76-80] Reasons for exclusion of the ordered papers are provided in Appendix 8, Section 9.2)

Figure 2. PRISMA diagram of economic evaluation systematic literature review.



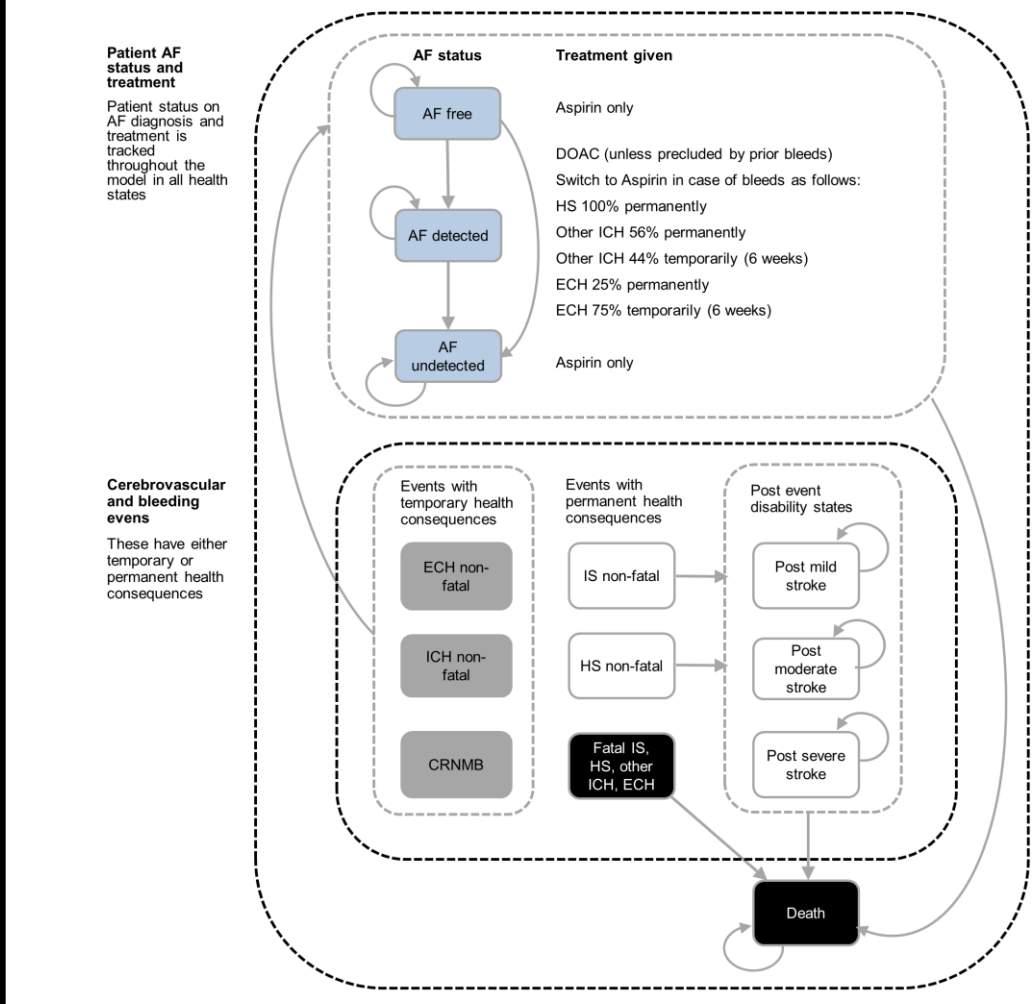
All economic evaluations meeting the inclusion criteria in the SLR were based on a Markov model structure with model cycles ranging from 1 to 3 months.[76-80] Two studies assessed the cost-effectiveness of Medtronic's Reveal XT® device with standard of care (SoC) monitoring.[76, 77] One study was based on Biotronik's BioMonitor 2-AF® device compared with SoC.[78] [redacted] Two studies did not indicate which model or brand of ICM was being assessed in the economic evaluations.[79, 80]

Of the five studies, only one was based on the UK (NHS) payer perspective and as such will be the focus of a more in-depth analysis of model structure and parameter estimation.[77] In addition to the search, the manufacturer of BioMonitor 2®, made an unpublished report and economic model available to the EAG, which assessed the cost-effectiveness of BioMonitor 2-AF® in patients with CS. [redacted]

The study by Diamantopoulos *et al*. 2016 is a cost-utility analysis assessing the use of an ICM (Reveal XT®) to detect AF in patients who have had a stroke or TIA that is considered cryptogenic after an initial 24-hour period of non-invasive external Holter monitoring. The comparator in the study was no further monitoring after the initial 24-hour period. The perspective of the analysis was the UK, and the time horizon of the model was lifetime.

The model was developed using a Markov structure with three main health states for AF status: AF-free, AF-detected, and AF-undetected. Figure 3 presents the model schematic.

Figure 3. Model schematic of CRYSTAL-AF cost-effectiveness analysis[77]



ibrillation; CRNMB, clinically relevant non-major bleed; ECH, extracranial haemorrhage; HS, haemorrhagic stroke; ICH, intracranial haemorrhage; IS, stroke; MB, major bleed; MI, myocardial infarction; DOAC, Directly acting oral anticoagulants; SE, systemic embolism; TIA, transient ischemic attack

Patients start in the AF-free state, from which they can move to AF-undetected or AF-detected at any given model cycle. From the AF-undetected state, patients can either remain or move to the AF-detected state, and patients remain in the AF-detected state unless the patient experiences a subsequent cerebrovascular event or bleeding event as follows.

The consequences of these subsequent events were modelled in two separate categories for either temporary or permanent effects. Events with temporary consequences were non-fatal extracranial haemorrhage (ECH) or intracranial haemorrhage (ICH), or a clinically relevant non-major bleed (CRNMB). Events with permanent consequences were non-fatal ischaemic stroke (IS), non-fatal haemorrhagic stroke (HS), or fatal ECH, ICH, IS or HS events. Deaths of any cause could also occur from any heath state in the model.

Following a temporary event, patients return to their previous AF status health state and can continue to move between these health states as described previously. For patients who moved to a post-stroke health state following a permanent event, patients were assumed to remain there and face no further risk of stroke or bleeding events, with the only possible remaining transition being to the death state.

Treatment in the AF-free and AF-undetected states was assumed to be aspirin. In the AF-detected state, treatment was assumed to change to a directly acting oral anticoagulant (DOAC) until a bleeding event (HS, other ICH or ECH) occurs, at which point patients were assumed to revert to aspirin.

The risk of subsequent ischaemic stroke was determined by AF status, virtual $CHADS_2$ score, age and treatment received. Evidence was synthesised from six studies, which included systematic reviews, randomised controlled trials and registry data. The severity of ischaemic stroke was considered to measure the expected impact on quality-of-life and resource use. The distribution of severity (mild, moderate, sever and fatal) was taken from two published cost-effectiveness analyses, comparing anticoagulant treatments for stroke prevention in patients with AF. The distribution of severity was assumed to be independent of treatment so the average across all treatments was used.

Bleeding consequences were also included in the model and the risks were assumed to be treatment and age related. Data for these risks were derived from five studies including a systematic review plus various trials comparing anticoagulants for patients with AF. The same cost-effectiveness analyses used to inform the distribution of ischaemic stroke severity were used to inform the distribution of type and severity of bleeding events, which were also assumed to be independent of treatment.

Age-dependent mortality was applied in the model and based on interim UK life-tables. It was adjusted, where applicable, to exclude deaths caused by cerebrovascular events as these were modelled separately. Following a non-fatal stroke, the mortality risk was increased depending on the severity of stroke and the treatment received for it.

Health-related quality-of-life (HRQoL) data for patients experiencing stroke events were collected in the Oxford Vascular Study (OX-VASC)[81]. Disutilities associated with bleeding events were also included and informed by two published models.[82-84] Utilities were adjusted to account for age and sex using previously published methods.

The price year of the model was 2013. Costs for the insertion of the ICM (£1,836) were included in the economic analysis, as well as per-cycle costs to account for follow-up visits and monitoring as well as drug treatments. The resource use required was determined by an unpublished *post-hoc* analysis of the CRYSTAL-AF study data. The lifetime of the ICM was assumed to be three years at which point the device was removed. The cost of removal (£491) was also included. These costs were sourced form NHS reference costs 2012-13. Costs associated with events such as stroke were included, as well as estimated long-term costs associated with living in a post-stroke health state.

Results of the deterministic base case analysis showed that ICM was £2,587 more expensive than SoC and provided a benefit of 0.151 QALYs, resulting in an incremental cost-effectiveness ratio (ICER) of £17,175 per QALY gained. A probabilistic sensitivity analysis (PSA) was performed, which reduced the incremental cost to £2,574 and increased the QALY gain to 0.161, therefore, reducing the ICER.

The EAG considers that the results produced by the model are potentially unreliable as there is significant uncertainty around the estimation of the clinical parameters in the model, particularly around the estimation of treatment effects by indirect comparison, AF incidence and detection rates used in the company's analysis. The authors conducted an indirect comparison to estimate hazard ratios (HRs) for ischaemic stroke, bleeding events, ICHs and ECHs and mortality, that are conditional on treatment received. The EAG attempted to validate the hazard ratios (HRs) used in the model but could not verify the source data used by the authors: details of how the indirect comparison was conducted, as well as how the publications informing the analysis were identified were not sufficiently described. Furthermore, the EAG considers that estimation of some of the HRs could be flawed; e.g. the authors estimate a HR to adjust mortality in the model, but the source data used is based on standardised mortality ratios.

Lastly, patients who are not detected as having AF are assumed to be given aspirin as their treatment option. However, the EAG's clinical experts stated that patients would be given clopidogrel (75mg) as their anti-platelet treatment.

However, the EAG considers that the initial health states of the Diamantopoulos *et al.* model to determine AF status is useful to inform a short-term model, where the time horizon is linked to the battery life of an ICM device. From the short-term model, patients with AF (whether detected or undetected) will then feed into a long-term (lifetime) model, assessing the costs and benefits of anticoagulation therapy.

Models assessing the long-term impact of anticoagulation therapy for patients with AF

In addition to the systematic literature review, the EAG were notified by NICE of an ongoing diagnostic assessment review (DAR) for lead-I electrocardiogram (ECG) devices for detecting AF using single-

time point testing in primary care (DAP39).[85] The population considered in DAP39 is adults presenting to primary care with signs and symptoms of AF who have an irregular pulse. Lead-I ECG devices are handheld instruments that can be used in primary care to detect AF at a single-time point in people who present with relevant signs and symptoms (i.e. palpitations, dizziness, shortness of breath and tiredness).[85] If a lead-I device detects AF, the patient initiates anticoagulation and rate control therapy (unless contraindicated) and a 12 lead ECG is conducted to provide more diagnostic information and inform treatment. The EAG assumed anticoagulation therapy would be with apixaban, which is a simplifying assumption.

The comparator in this study was no further immediate testing after manual pulse palpation (MPP), with patients referred for a 12-lead ECG if the GP was suspicious of AF after MPP (standard care pathway). In the standard care pathway, no AF treatment is initiated if the general practitioner (GP) is suspicious of AF until after the results from the 12-lead ECG are available, confirming diagnosis.

While the technology and population under assessment are not relevant to the decision problem of the current report, the EAG was interested in the approach taken to estimate long-term costs and benefits of anticoagulation therapy once patients have been identified as having AF using lead-I devices. For DAP39, once patients had a diagnosis of AF confirmed they enter a post-diagnostic Markov model with either no history of cardiovascular events (CVE), one or two CVEs. In each cycle, patients can remain in their current health state, have a CVE and move to a worse health state or die. Patients with two CVEs can only remain in their current health state until death.

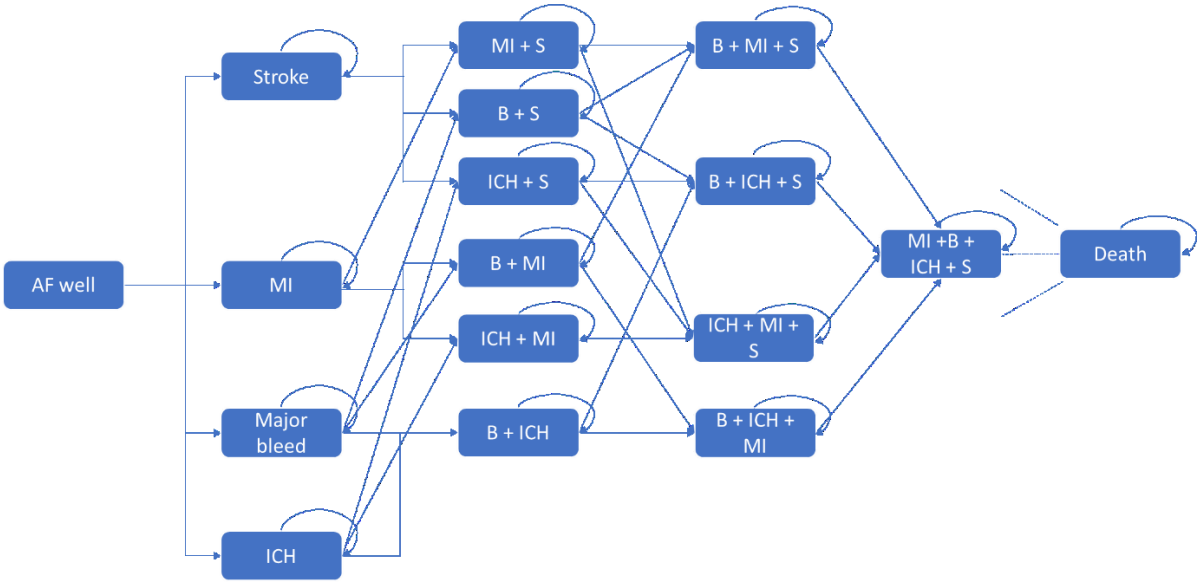
The model parameters used to estimate the transition probabilities for the post-diagnostic Markov model were derived mainly from a cost-effectiveness study by Sterne *et al*. 2017,[86] which assessed the long-term costs and benefits of anticoagulation therapy for prevention of stroke in patients with AF (hereafter referred to as the DOAC model). The EAG reviewed the publication for the DOAC model and deemed it relevant for the current decision problem, and as such contacted the authors to obtain a copy of the model for assessment. After reviewing the DOAC model and discussing it with the model developer, the EAG was made aware of an adapted version of the DOAC model, which was used for another publication,[87] that would be appropriate to review and potentially use for development of the ICM model.

The adapted DOAC model was developed to assess the cost-effectiveness of screening strategies for AF.[87] The model structure employed by the authors was a hybrid model, with a short-term decision tree which used sensitivity and specificity estimates of different screening strategies to detect AF (confirmed by a 12-lead ECG) and initiate anticoagulation therapy and a long term adapted version of the DOAC Markov model. In the analysis, it was assumed that 75% of patients not contraindicated to anticoagulation therapy and that are prescribed anticoagulants use DOACs, with the remaining 25%

prescribed warfarin. Patients who are diagnosed with AF, but who are contraindicated to anticoagulation therapy, not prescribed or choose not to take oral anticoagulants, would receive aspirin.

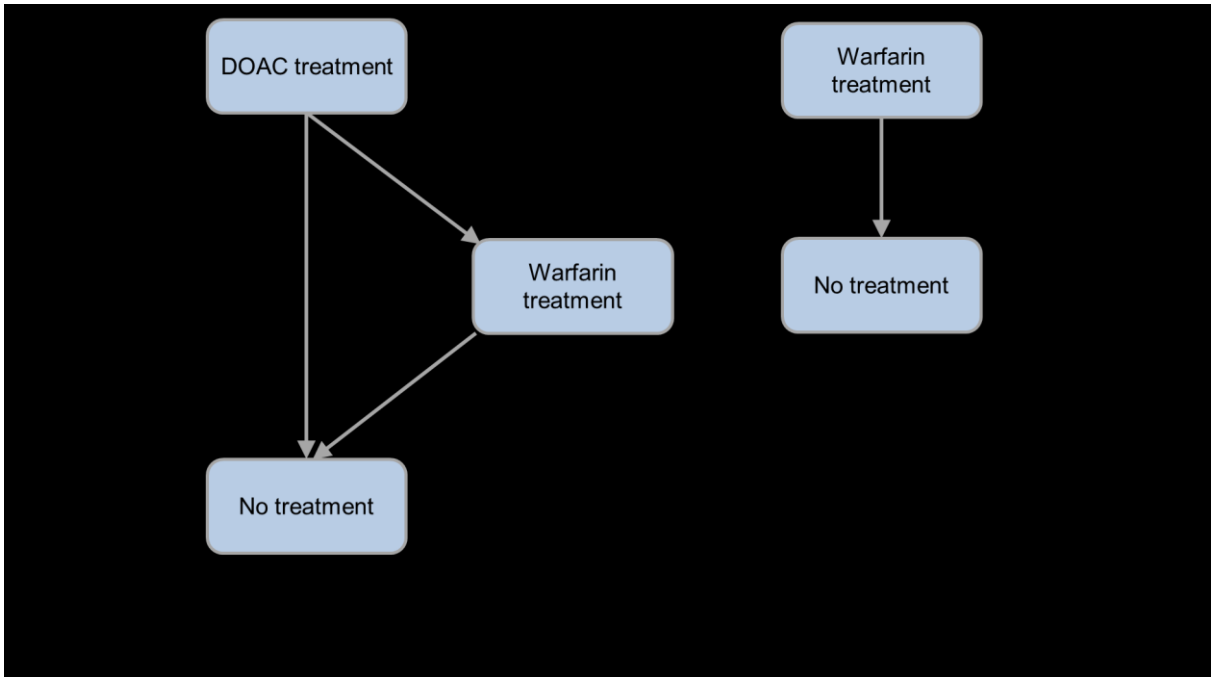
The results of the screening decision tree model feed directly into the adapted DOAC model (Figure 4). The discrete-time Markov multistate model implemented a cycle length of 3 months and employed a lifetime horizon with a cut-off at 100 years. Patients who are prescribed an OAC enter the model either on first-line apixaban or warfarin (INR range 2-3), with the remainder on aspirin. The authors assumed the use of apixaban as it was determined to be the most cost-effective DOAC in the anticoagulation therapy cost-effectiveness analysis, but state the results are similar when considering other available DOACs.

Figure 4. Prevention of stroke in atrial fibrillation model structure (Sterne *et al*. 2017)[86]



Depending on the occurrence of ischaemic stroke or serious adverse events (such as ICH), treatment switching can occur (see Figure 5). For patients on first-line apixaban, second-line treatment may be either warfarin or no treatment. No treatment is the only third-line treatment available. For those who fail on warfarin, no further treatment would be given.[86]

Figure 5. Treatment strategies and switching/ discontinuation rules for the prevention of stroke in atrial fibrillation model (Sterne *et al*. 2017)[86]



The same model structure is used for each treatment option (Figure 4), but is adjusted for the different costs, utilities and transition probabilities relevant to treatment. Patients start the model in the AF well health state (no event). From any health state in the Markov model, patients can have an ischaemic stroke, myocardial infarction, clinically relevant (extracranial) bleeding (CRB), ICH, systemic embolism, TIA or die. The authors of the DOAC model assumed systemic embolism and TIA have only short-term impacts on future risks, costs and utilities, but ischaemic stroke, ICH, CRB and myocardial infarction (MI) have long term impacts which will change future risks, costs and utilities. For example, a patient who experiences an MI and ICH will have different risks, costs and utilities compared to a patient who only experiences an MI or ICH. In addition, the model does not distinguish between minor and major ischaemic strokes due to limited published evidence on the relative rates of these events from the randomised controlled trials (RCTs).

As with all Markov models, patient history through the model is not recorded, therefore future health state transitions depend only on the current health state the patient occupies. An assumption is made in the model that transition probabilities do not change with time, but that as the cohort ages, mortality risk increases in line with general population life tables.

The authors of the screening model adapted the long-term DOAC model by including hazard ratios for events (stroke, systemic embolism, TIA) affected by AF type (paroxysmal relative to permanent or persistent). Furthermore, the DOAC model depends on age, sex, previous history of ischaemic stroke or TIA and previous history of MI.

Treatment effects implemented in the model were based on a competing risks network meta-analysis (NMA) to jointly estimate log hazard ratios of each treatment relative to warfarin for the different possible health states in the model.

The costs included in the analysis comprised of pharmacotherapy costs and costs of acute and chronic AF and anticoagulant-related events. Sources of cost data included the British National Formulary (BNF) for drug costs (March 2015 update), NHS reference costs and other published sources. Where necessary, cost data were inflated to 2015 prices using the Office for National Statistics (ONS) Consumer Price Inflation Index for Medical Services (DKC3)[88].

Quality adjusted life years (QALYs) were estimated by applying health state utility values to the proportion of patients occupying each health state per model cycle. Utilities were identified from a previous NICE technology appraisal submission on rivaroxaban (TA256)[89], which included a systematic literature search for evidence on EQ-5D utility index scores in health states related to AF. For acute health states (such as CRB, systemic embolism, TIA, ICH, acute ischaemic stroke and acute MI), disutilities were applied for one model cycle. For patients who have multiple chronic health conditions, utilities for the health states were assumed to be multiplicative. All utilities were adjusted for age.

Total costs and QALYs were estimated for each first-line anticoagulation therapy were generated as well incremental results compared with warfarin. The authors did not calculate ICERs, but instead calculated the incremental net benefit (INB) of each DOAC compared with warfarin, when a QALY is valued at either £20,000 or £30,000. Compared with warfarin, all DOACs had a positive incremental net benefit, with Apixaban (5 mg, twice daily) estimated to have the highest expected INB (£7533), followed by dabigatran (150 mg twice daily; £6365), rivaroxaban (20 mg once daily; £5279) and edoxaban (60 mg once daily; £5212). The 95% confidence interval around INB for apixaban was positive, suggesting that apixaban is cost-effective compared with warfarin.

The EAG considers that the adapted DOAC model is suitable to inform the long-term costs and benefits of anticoagulation treatment versus antiplatelet treatment in the CS population, who have suspected AF and therefore will be incorporated into the model structure assessing ICMs in this population. Please see Section 4.2.3 for more detail on the integration of the DOAC model to the EAG's excel model.

4.1.2.2 Health related quality of life evidence

The systematic literature search identified a total of 7,641 papers after de-duplication. Based on a review of titles and abstracts, a total of 112 papers were identified as potentially relevant and were obtained for full text review based on the criteria listed in Table 24. An additional two papers were identified from the reference lists of identified papers. Of the 114 papers identified for full text review, 25 papers were

included for data extraction (Appendix 9, Section 9.3). Reasons for exclusion of the 89 papers are provided in Appendix 8, Section 9.2. The results of the process to identify HRQoL evidence is summarised in Figure 6

Figure 6. PRISMA diagram of the HRQoL systematic literature review

Data from patients with cerebral infarction, ischaemic stroke, haemorrhagic stroke (intracranial, intracerebral, or subarachnoid) or TIA were collected by 21 studies,[81, 84, 90-108] while data on patients specifically with AF (with or without stroke) were collected in six studies.[90, 91, 99, 109-111] Four of the included studies also provided data for patients with MI[84, 91, 99, 109] and two assessed the impact of additional bleeding events.[99, 111] The studies differed in how stroke was defined, with some having much broader definitions than others, which hindered comparisons by type of stroke.

All studies reported EQ-5D-3L data and two[96, 97] also collected EQ-5D-5L data. EQ-5D responses were converted into utilities using UK population tariffs developed by Dolan 1997 in nine studies.[81, 84, 95, 100-102, 105, 106, 109] Two of those studies were undertaken in the UK.[81, 110] The remaining studies were undertaken in Spain, Germany, USA, Korea, Sweden, Poland, Finland, Norway, Canada, The Netherlands, or in multiple countries.

The EAG considers that the most relevant utilities for the model are those from the OX-VASC study[81], which were also utilised in the CRYSTAL-AF economic evaluation[77], and Berg *et al.* 2010.[109]

The OX-VASC study consisted of stroke and TIA patients from a UK population-based study (Oxford Vascular Study) whose quality of life was assessed using the EQ-5D-3L questionnaire at regular follow-ups of 1, 6, 12, 24 and 60 months after their stroke or TIA event. The baseline population consisted of 748 patients with stroke and 440 TIA patients. EQ-5D-3L responses were available for 759 patients at 1 month, 723 patients at 12 months and 479 at 60 months. EQ-5D-3L responses were converted into utilities using UK population tariffs.[81] Mean age of the population was 75 years and 44% were female. Utilities were estimated for different events including, TIA, all stroke, ischaemic stroke, ICH and subarachnoid haemorrhage, as well as different severities of stroke.

The study by Berg *et al*. 2010 assessed HRQoL for patients with AF, based on data from the Euro heart survey.[109] Mean age of the population was 66 year and 41.9% were female. HRQoL was measured at baseline and at 1-year follow-up using the EQ-5D-3L questionnaire. At baseline, 5,050 EQ-5D-3L responses were recorded, with 3,045 responses recorded at 1-year follow-up. EQ-5D-3L responses were then converted into utilities using UK population tariffs. Baseline utility for patients with AF were estimated, as well as utility decrements for adverse events during follow-up, including: MI; stroke; congestive heart failure; and other major adverse events.

Section 4.2.5 describes the utility values for events that have been included in the economic model.

4.2 Development of a health economic model

4.2.1 Population

The population considered in the model are patients who have had a CS, including TIAs, for whom there is a suspicion of paroxysmal AF, and who have received at least 24 hours of outpatient external ambulatory ECG monitoring that has not detected AF. The diagnostic data included in the model is based on the results of the systematic literature review that identified the CRYSTAL-AF RCT[35] assessing the Reveal XT implantable cardiac monitor compared with standard monitoring in the patient population of interest. The mean age (61 years) and gender split (~65% male) of patients in the model is based on data from CRYSTAL-AF. The EAG's clinical experts considered that, in general, the population in CRYSTAL-AF is reflective of UK patients, though some inconsistencies were noted but were not deemed significant. Please refer to Section 3.2 for further detail.

4.2.2 Intervention and comparator

As per the NICE final scope, the interventions included in the model are as follows:

- BioMonitor 2-AF;
- Confirm RX;

- Reveal LINQ.

The comparator for the analysis listed in the NICE final scope was no further monitoring after at least 24 hours of outpatient external ambulatory ECG monitoring that has not detected AF. Data for the comparator arm is taken from CRYSTAL-AF, where patients in the control arm underwent assessment at scheduled visits (every 3 months) and unscheduled visits, if patients were experiencing symptoms of AF.[77] To match the monitoring period of the ICM devices (three years), the SoC monitoring period was also three years. Tests for the control arm included ECGs and Holter monitoring (24 hours, 48 hours and 7 days). Table 25 presents the tests performed per person per year in the control arm of CRYSTAL-AF.

Table 25. Tests performed per person per year in comparator arm of CRYSTAL-AF[77]

Period	No test	ECG	Holter 24 hours	Holter 48 hours	Holter 7 days
0-12 months	0.31	0.55	0.06	0.02	0.06
12-24 months	0.51	0.40	0.04	0.01	0.05
24-36 months	0.58	0.31	0.02	0.00	0.08
Abbreviations: ECG, electrocardiogram					

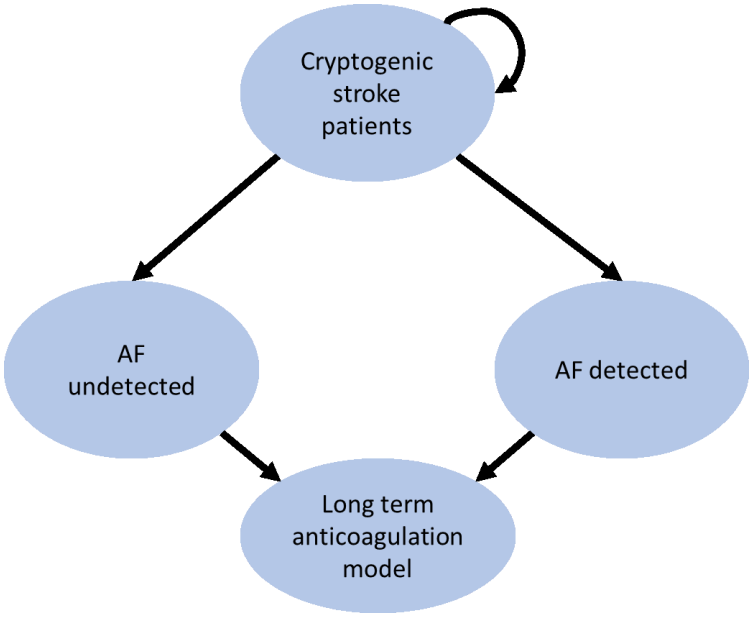
4.2.3 Model structure

The EAG developed a two-stage economic model, to assess the cost-effectiveness of using ICMs to detect AF in patients with CS. The comparator in the analysis was 24 hours of external ambulatory ECG monitoring.

The development of the model was informed by published models identified in the SLR. The first stage of the model (short-term model) outlines the initial patient-flow over a three-year period (battery life of Reveal XT). The second stage of the model (long-term DOAC model) estimates the lifetime risks, costs and benefits for patients on either long-term anticoagulation or antiplatelet therapy. Figure 7 presents the schematic for the short-term model and Figure 8 presents the long-term DOAC model. Each stage of the model is described in more detail below.

All patients enter the model as CS patients who have received at least 24 hours of outpatient external ambulatory ECG monitoring that has not detected AF. The initial cohort is a mixture of patients with and without pre-existing paroxysmal AF who are given antiplatelet therapy for stroke prevention. Over the time horizon of the short-term model (three years), patients who have an episode of AF may be detected and thus will move to the AF-detected health state, where they enter the anticoagulation arm of the long-term DOAC model. However, episodes of AF may not be detected and thus patients will then move to the AF-undetected health state where they enter the antiplatelet arm of the long-term DOAC model).

Figure 7. Short-term patient flow model



The proportion of patients who are identified as having AF in each of the 12, three-month cycles is informed by data from the CRYSTAL-AF trial. It is assumed that patients in the SoC arm are detected either during follow-up appointments or due to developing symptoms of AF. Explicit transitions from AF-undetected to AF-detected are not modelled, as the data from CRSYTAL AF presents cumulative detection rates. However, as a simplifying assumption, patients receiving SoC and have undetected AF by the end of the short-term model (3 years) will remain undetected and on antiplatelet treatment for the remainder of the modelled time horizon.

Sensitivity data for the Reveal LINQ device, in a broader AF population, indicate a sensitivity of 100%, enabling the calculation of the AF-undetected health state occupancy for the SoC arm of the model (please see Section 3.4.3 for more detail).[1] Furthermore, based on the sensitivity and data on AF detection rates for the ICM arm, patients from the initial cohort who do not have AF are excluded from the long-term analysis of outcomes as the proportion is assumed to be the same in each arm of the model (i.e. no false positives) and thus incremental costs and quality adjusted life years are zero. However, it should be noted that all patients in the ICM cohort incur the cost of the device, implantation, removal of device and follow-up. All SoC patients incur the cost of monitoring. Patients who do not have AF detected are assumed to incur the cost of follow up appointments with a consultant cardiologist at 1, 3, 6 and 12 months as per the advice of the EAG's clinical experts.

The second stage long-term model uses the adapted version of the DOAC model, previously described in Section 4.1.2.1. The DOAC model is a probabilistic model that outputs total costs and QALYs for DOAC treatments (apixaban, rivaroxaban, edoxaban and dabigatran etexilate), warfarin and antiplatelet treatment. The EAG adapted the model code to allow the output to be given as per-cycle costs and

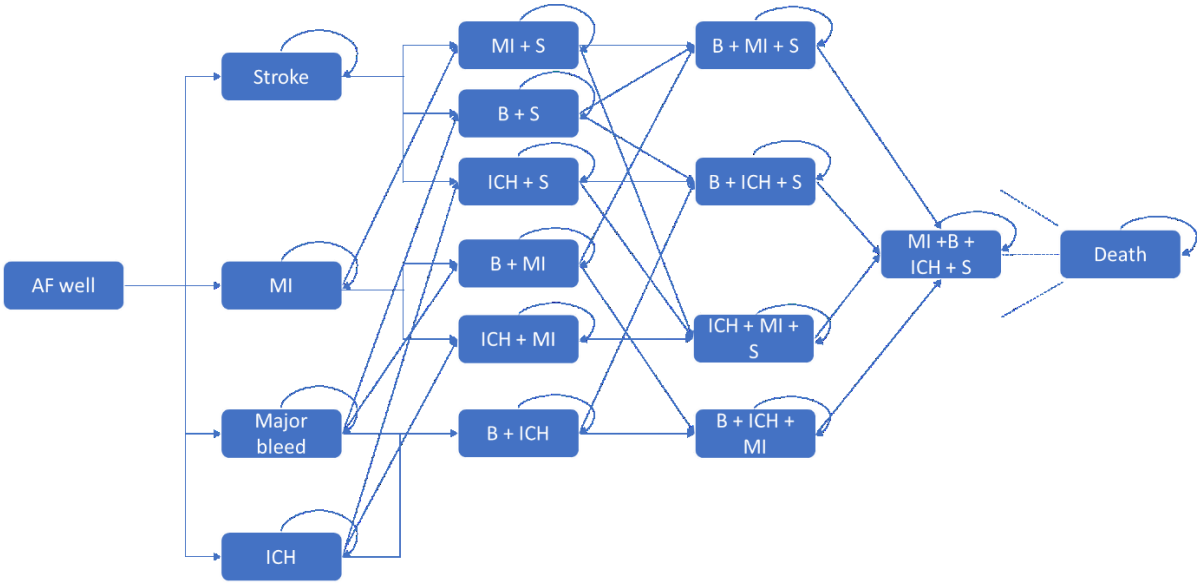
QALYs over a lifetime time horizon. This enabled the application of costs and QALYs to each cycle in the ICM Excel model from the point at which patients are either AF-detected and start anticoagulation treatment or AF-undetected and continue with antiplatelet treatment.

Data inputs were updated to reflect the CRYSTAL-AF population, e.g. the starting age was set at 62 and the ratio of males to females was set at 65:35 to weight the general mortality death rates. The model was adapted to include all DOACs plus warfarin. Costs in the DOAC model were updated or inflated to 2018 prices, where appropriate to reflect current values, as described in Section 4.2.6. Based on the HRQoL SLR, utility inputs were also updated as described in Section 4.2.5. Life tables were also updated to the most recent year available (2015 –2017).[112]

Mean costs and benefits per cycle (based on 10,000 samples run in the long-term model) related to AF patients treated with either anticoagulation or antiplatelet medication and are estimated for each individual DOAC treatment in the model. Figure 8 presents the model schematic for the adapted DOAC model. The same structure is used for each treatment included in the model (i.e. DOACs for patients with detected AF and antiplatelet treatments for patients with undetected AF) and is adjusted for treatment specific transition probabilities, costs and utilities. It should be noted that for the current model, the adapted DOAC model population was pre-specified for previous history of ischaemic stroke and paroxysmal AF (e.g. the risks of events in the model were adjusted to reflect a secondary stroke population with paroxysmal AF).

The mean, per-cycle, costs and benefits of anticoagulation treatment are then applied to the proportion of patients in each cycle of the AF-detected health state and the mean, per-cycle, costs and benefits of antiplatelet therapy are applied to the proportion of patients in each cycle of the AF-undetected health state.

Figure 8. Long term DOAC model (Sterne *et al.* 2017[86])



The economic assessment is taken from the perspective of the NHS and Personal Social Services and both costs and benefits are discounted at 3.5% per annum.

4.2.4 Clinical input parameters

Diagnostic efficacy of ICMs

The clinical effectiveness SLR only identified diagnostic yield data for the Reveal XT device from the CRYSTAL-AF RCT. AF detection rates for the comparator arm of the model are also derived from CRYSTAL AF. In CRYSTAL-AF, an episode of AF was defined as irregular heart rhythm lasting more than 30 seconds.[35] Table 26 presents the cumulative AF detection rate per model cycle (3 months) for both Reveal XT and SoC monitoring implemented in the short-term Excel model. As no data were identified for BioMonitor 2-AF and Confirm RX, the EAG sought advice from clinical experts as to whether there would be any differences in the detection rates between the devices. The EAG's clinical experts acknowledged that the main source of efficacy for ICMs is the CRYSTAL-AF trial, but that there would not be any substantial differences in detection rates for the devices. As such, the EAG has assumed equal efficacy for all devices.

Table 26. Cumulative AF detection rates from CRYSTAL-AF

Month	Cycle	Reveal XT	Standard of Care
0	0	0%	0%
3	1	8%	1%
6	2	9%	1%
9	3	10%	1%
12	4	12%	2%

15	5	16%	2%
18	6	18%	2%
21	7	19%	3%
24	8	21%	3%
27	9	24%	3%
30	10	26%	3%
33	11	30%	3%
36	12	30%	3%

Table 27 presents the battery length of each device used in the short-term Excel model. The Confirm RX has the shortest battery life of 2 years and the EAG's clinical experts advised that it is unlikely a device will be replaced once the battery has expired. As such, those detected with the Reveal LINQ or BioMonitor 2-AF between 24 and 36 months would not be detected with the Confirm RX. Thus, the EAG adjusted the detection rates of the Confirm RX, to reflect the number of AF cases that would be missed due to the relatively shorter battery life of the device.

Furthermore, the battery length of BioMonitor 2-AF is 4 years. However, data for AF detection is only available for 3 years. As such, in the absence of additional data, the EAG have capped the BioMonitor 2-AF detection rates to 3 years. It is difficult to predict what impact this assumption has for the cost-effectiveness of BioMonitor 2-AF, as the additional year of monitoring with the device could mean that there is potential (if limited) for additional cases of AF to be picked up compared to the SoC arm.

Table 27. Device battery length

Device	Battery length
Reveal LINQ	3 years
BioMonitor 2-AF	4 years
Confirm RX	2 years

Diagnostic accuracy data for the Reveal LINQ device indicates a sensitivity and specificity of 100% and 98.1% respectively.[1] However, the sensitivity and specificity values for the Reveal LINQ are based on an update to the Reveal XT algorithm which incorporates p-waves and is applied to the dataset of the XPECT trial, which assessed the performance of the Reveal XT device in a population with known AF.[1] While the sensitivity estimated in a population with known AF may not be a reliable measure for a population with paroxysmal AF, the EAG's clinical experts advised that the ICM's will likely pick up all cases of paroxysmal AF. As such, an assumption has been made in the model that the detection rate of the device estimates the true prevalence of AF in the CS population. Please see Section 3.4.3 for further detail.

Therefore, the detection rate in each cycle of the ICM arm provides an estimate of the proportion of patients in the cohort who have AF at any given cycle. The proportion of AF-undetected per cycle in

the SoC arm can then be calculated as the difference between the detection rate of the ICM and the SoC arm per cycle.

It should be noted that based on the CRYSTAL-AF data, the proportion of patients at the end of the 3-year follow-up period who have AF is estimated to be 30%. Theoretically, the subset of CS patients who have AF is known at the start of the model and therefore all patients could enter the model in the AF-undetected state and over time this would reduce as patients are detected in each arm. However, the EAG chose to start all patients in the model without AF status known and use the per cycle incidence of AF, based on the detection rate and sensitivity of the ICM to calculate the number of patients with undetected AF (calculated as per cycle incidence of AF minus the per cycle AF-detection rate). If the overall AF prevalence is used, then the calculation of AF undetected patients in the ICM arm infers that there is a large proportion of AF patients which the ICM devices miss, which contradicts the 100% sensitivity. In fact, because of the nature of paroxysmal AF, it may not be true that all patients have AF at the start of the model, particularly those that are detected by ICM late in the model time horizon as they may have developed AF as they age in the model. However, using either method to define the starting population of the model, based on the detection rates of CRYSTAL-AF has no impact on the results.

Long-term clinical outcomes

Long-term outcomes for patients with AF (whether detected or undetected) are modelled using the adapted DOAC model.[86, 87] Outcomes assessed in the model include ischaemic stroke, MI, TIA, systemic embolism, clinically relevant (extracranial) bleed, ICH and death (all causes). The long-term model is structured so that as well as experiencing single events, patients can have multiple events (up to a maximum of 3).

As discussed in Section 4.2.3, each treatment considered in the model (OACs and antiplatelets) has the same long-term model structure, but adjusted for treatment-specific risks, costs and benefits. The authors of the model estimated treatment effects by performing a competing risks network meta-analysis, based on the clinical effectiveness SLR conducted for the study, to estimate HRs for the different events considered.[86]

The clinical effectiveness SLR conducted by Sterne *et al* identified twenty-three completed RCTs for inclusion in the review.[86] Seventeen types of events were included in the NMA to account for correlation and competing risks. However, as mentioned previously, the events of interest for the economic model are ischaemic stroke, MI, TIA, systemic embolism, clinically relevant (extracranial) bleed, ICH and death (all causes). Three types of outcome data were incorporated into the model to estimate the HRs

and included: number of first events; number of individuals experiencing at least one event of a given type; and total number of events.

Baseline treatment in the adapted DOAC model is warfarin (INR 2-3) and as such the authors developed a competing risks model for warfarin separately to estimate the baseline hazard for the outcomes of interest in the model. Further detail on the methodology and estimates used in the long-term model can be found in the publication by Sterne *et al*., 2017[86]

The treatment effects for antiplatelet therapy used in the model have been estimated in the competing risks NMA using outcomes for aspirin treatment. The EAG consulted with clinical experts to confirm that patients would be given aspirin after stroke and if, in lieu of any diagnosis of AF, they would remain on lifetime treatment with aspirin. The clinical experts advised that in current clinical practice, treatment for CS patients is, in fact, with clopidogrel (75mg, once daily) and would be the long-term treatment if patients are not diagnosed with AF.

Consequently, the EAG performed targeted searches to identify evidence on the relative efficacy of clopidogrel and aspirin in AF patients at risk of ischaemic events, as this population reflects the cohort who occupy the AF-undetected health state and would therefore be receiving antiplatelet treatment. The EAG found that much of the literature assesses clopidogrel in combination with aspirin.[113, 114] The EAG identified a systematic review and network meta-analysis by Cameron *et al*. 2013, comparing antithrombotic agents for the prevention of stroke and major bleeding in patients with AF.[115] The review included aspirin and aspirin plus clopidogrel (dual antiplatelet therapy). Compared with standard dose vitamin K antagonist (e.g. warfarin), aspirin and dual antiplatelet therapy produced similar odds ratios (ORs) for an increase in risk of all cause stroke or systemic embolism (aspirin OR 1.87, 95% confidence interval [CI]: 1.26 to 2.8; dual antiplatelet therapy OR 1.93, 95% CI: 1.42 to 2.64). Similar results were seen for major bleeding (aspirin OR 1.05, 95% CI: 0.60 to 1.87; dual antiplatelet therapy OR 1.1, 95% CI: 0.83 to 1.47).

While the review did not assess clopidogrel on its own, the NMA demonstrated a non-significant increase in risk with dual antiplatelet therapy. Thus, in the economic analysis the EAG have used this evidence to base an assumption that in the long-term model, clopidogrel is as effective as aspirin for patients with undetected AF and therefore the effectiveness estimates used for antiplatelet therapy in the adapted DOAC model remain unchanged. The EAG acknowledges this is a simplifying, conservative assumption and a limitation of the analysis.

Mortality

Mortality risk implemented in the long-term DOAC model was estimated using the competing risks NMA, as described previously for the age and sex split obtained from CRYSTAL-AF. The mortality

risk is then adjusted for general population mortality, using life tables for England and Wales[112] for each age group beyond the baseline age and weighted by the proportion of males and females in CRYSTAL-AF.

Anticoagulation treatment

For patients diagnosed with AF, anticoagulation treatment with either a DOAC or warfarin would be prescribed. However, analysis of prescribing trends, based on data from the openprescribing.net database published by the University of Oxford,[116] has shown that prescriptions of warfarin have been declining, with prescriptions of DOACs overtaking warfarin in April 2018. It should be noted that the prescribing data is not broken down by indication, but an assumption can be made that DOACs are becoming the preferred treatment for patients requiring anticoagulation. Therefore, for the base case analysis, the EAG assumed that all patients with detected AF will start treatment on a DOAC (either apixaban, dabigatran etexilate, rivaroxaban and edoxaban).

The results from the DOAC model indicate that DOACs are more cost-effective than warfarin and apixaban is the most cost-effective DOAC treatment (See Section 4.1.2.1). However, prescribing data show that apixaban only accounts for 48% of all DOAC prescriptions, with the remainder distributed between rivaroxaban (44%), dabigatran etexilate (6%) and edoxaban (3%).[116] In the base-case analysis, the proportion of patients on each of the treatments is based on the proportion of prescriptions of each drug between September 2017 to September 2018 from the openprescribing.net database.[116] Table 28 presents the proportion of patients on each treatment implemented in the short-term Excel model.

Table 28. Propotion of patients on each type of DOAC 2017-2018 (openprescribing.net database)[116]

Drug	Proportion of patients
Apixaban	48.0%
Dabigatran etexilate	5.5%
Rivaroxaban	43.6%
Edoxaban	2.9%

In the short-term Excel model, the proportion of patients on each DOAC treatment is used to weight long-term costs and benefits. The EAG performed a scenario analysis including a proportion of patients on warfarin, as there may be clinicians who would prescribe this treatment to newly diagnosed AF patients. Please refer to Section 5.1.2 for further detail.

Treatment switching probabilities

In the long-term DOAC model, depending on the occurrence of ischaemic stroke or serious adverse events (SAEs, such as ICH), treatment switching can occur (see Figure 5). For patients on first-line

DOAC treatment, second-line treatment may be either warfarin or no treatment. For patients who fail on warfarin, no further treatment is given.[86] The probability of a patient switching treatment after experiencing an event was based on clinical expert opinion obtained by the authors of the DOAC model.

4.2.5 Utility values

As described in Section 4.1.2.2, the EAG conducted a HRQoL SLR to identify relevant utility values to be used, where possible, to update the DOAC model. Two papers were identified as providing relevant utility values for ischaemic stroke, ICH, MI and TIA events (both acute and chronic) that were used to update the long-term DOAC model.[81, 109] The papers estimate utilities using EQ-5D-3L data converted into UK population tariffs. The SLR did not identify any relevant studies which published utility values for clinically relevant bleeds (acute and chronic) and acute MI. As such the EAG used the values already populated in the DOAC model.[86]

Table 29 presents the utility values applied for acute events and Table 30 presents the values used for each health state of the model. The utility value used for the AF well health state is 0.78 based on data from Berg *et al.* 2010.[109] As per the assumption made in the DOAC model, the duration for an acute event is assumed to be 3 months (1 model cycle).

Table 29. Utility values for acute events

Utilities by event	Acute event	Duration of event	Reference or assumption
TIA utility decrement	-0.07	3 months	Luengo-Fernandez *et al.* 2013[81a] Control value for TIA from study was 0.85, which is higher that the baseline value of 0.78 used in this analysis. Furthermore, TIA utility from the study was estimated as 0.78. As such the EAG implemented a utility decrement in order to account for the impact of TIA
Ischaemic stroke	0.64	3 months	Luengo-Fernandez *et al.* 2013[81a]
ICH	0.56	3 months	Luengo-Fernandez *et al.* 2013[81a]
MI	0.68	3 months	Same as DOAC model[86]
Major bleed utility decrement	-0.03	3 months	Same as DOAC model[86]
Systemic embolism	0.78	3 months	Assumed to be equal to TIA (same as DOAC model[86])

Abbreviations: CRB, clinically relevant bleed; ICH, intracranial haemorrhage; MI, myocardial infarction; TIA, transient ischaemic attack.
Notes: a, 1-month value estimated in study was assumed to represent an acute event utility.

Table 30. Utility values for health states

Health state	Utility value	Reference
Ischaemic stroke	0.70	Luengo-Fernandez *et al.* 2013[81a]
ICH	0.67	Luengo-Fernandez *et al.* 2013[81a]
MI	0.72	Same as DOAC model[86]

Major bleed	0.70	Assumed to be equal to stroke (Same as DOAC model[86])
Abbreviations: AF, atrial fibrillation; ICH, intracranial haemorrhage; MI, myocardial infarction Notes: a.12-month value estimated in study was assumed to represent a chronic heath state utility.		

In the original DOAC model, utilities were adjusted for age and weighted by sex. Furthermore, as patients can experience more than one chronic health condition in the model, utilities for chronic health states are assumed to be multiplicative.[86]

4.2.6 Costs

The following costs are considered in the model:

- Device and standard monitoring costs;
- Cost of implantation and removal of devices;
- Follow-up costs;
- Pharmacotherapy costs;
- Acute and chronic care costs of AF and anticoagulant related events.

All costs considered in the model are valued in 2017 UK pound sterling (£). Where unit costs have been obtained from the published literature before 2017, costs were updated using the ONS Consumer Price Inflation Index for Medical Services (DKC3).[88]

Device costs

5.1.2.

Table 31 presents the costs of each device considered in the economic analysis and implemented in the short-term Excel model. The manufacturer of Reveal LINQ also provides an optional triage service, FOCUSON. The company provided two cost options for FOCUSON, the first option is £187 per patient per year and the second option is £374 per patient per device. Both options are explored in scenario analyses, presented in Section 5.1.2.

Table 31. Cost of devices (excluding VAT)

Device name	Unit cost	Source
Reveal LINQ	£1,800	Company submission to NICE
BioMonitor 2-AF	£1,030	Company submission to NICE
Confirm RX	£1,600	Company submission to NICE

The manufacturers of each of the devices have indicated that no additional training is required to perform the insertion procedure, as it is expected that staff will already have the necessary skills, competencies and experience in performing sterile device insertion procedures. However, the manufacturer of the Reveal LINQ device stated that training for staff is included in the cost of the Reveal LINQ ICM system. The manufacturer of BioMonitor 2-AF also stated that training is offered by the company but did not indicate whether the cost of this is covered by the device cost. As such, the EAG has assumed no additional costs of training for the base case analysis.

Furthermore, the costs of reviewing alerts generated by the ICM have not been included in the base case analysis as no data were available regarding the average number of alerts generated per day/ month that require review. However, based on discussions during the scoping phase of the topic, clinical experts advised that reviewing alerts are relatively quick and would form part of the clinician's normal workload, however it is dependent on volume.

Implantation and device removal costs

Table 32 presents the ICM implantation costs per patient implemented in the short-term Excel model. The costs of implantation for the base case analysis are based on resource use assumptions provided by the EAG's clinical experts for this report. The clinical experts also provided alternative resource use assumptions which are explored in a scenario analysis. The company for the Reveal LINQ device also provided a costing study comparing the costs of the Reveal XT implanted in a catheterisation lab setting versus the Reveal LINQ implanted in a sterile procedure room setting.[117] The resource use assumptions for this study were costed by the EAG and used in a scenario analysis. The cost for removal of an ICM device implemented in the Excel model is £238, taken from the NHS reference costs schedule 2017-18 (EY13Z – removal of electrocardiography loop recorder, outpatient setting, treatment function code 320).[118]

Table 32. Implantation costs

Resource	Role for procedure	Unit cost per hour	Time taken for procedure (minutes)	Cost per procedure	Source
Clinical expert assumptions (base case)					
Cardiologist	Implanter	£108	10	£18.00	PSSRU 2018[119]
Nurse (Band 5)	Assistant	£37	10	£6.17	PSSRU 2018[119]
Total				**£24.17**	
Clinical expert assumptions (scenario)					
Cardiac physiologist (Band 7)	Implanter	£57	10	£9.50	PSSRU 2018[119]
Nurse (Band 5)	Assistant	£37	10	£6.17	PSSRU 2018[119]
Total				**£15.67**	

Kanters et al., 2015 (scenario)[117]					
Cardiac physiologist (Band 7)	Implanter	£57	25.6	£24.32	PSSRU 2018[119]
Nurse (Band 5)	Assistant	£37	43.1	£26.58	PSSRU 2018[119]
Total				**£50. 90**	
Abbreviations: PSSRU, personal social services research unit.					

The most common adverse events associated with implantation of an ICM, based on data from CRYSTAL-AF, include infection (1.4%), pain (1.4%) and irritation or inflammation at the insertion site (1.9%).[35] However, there was not further detail on how severe the adverse events were in CRYSTAL-AF and as such the EAG has not included adverse event costs in the base-case analysis. However, it is anticipated that, given the relatively small proportions of patients experiencing each adverse event, it is not expected to have a substantial impact on the cost-effectiveness of the ICM devices.

Comparator arm costs

Costs of the comparator are based on the standard of care arm from the CRYSTAL-AF trial.[77] As previously presented in Table 25, Section 4.2.2, the standard of care arm comprises of various monitoring tests that are performed at 3 monthly intervals for the duration of the trial (3 years). The unit cost of monitoring is estimated to be £141, based on the NHS reference costs schedule 2017-18 (HRG code EY51Z – electrocardiogram monitoring or stress testing [outpatient procedures, service code 320]).[118] Table 33 presents the weighted cost of monitoring per cycle based on number of tests per patient recorded in CRYSTAL-AF (Table 25, Section 4.2.2).

Table 33. Weighted cost of monitoring (comparator costs)

Period	No test	ECG	Holter 24 hours	Holter 48 hours	Holter 7 days	Total	Per cycle cost
0-12 months	£0.00	£77.22	£8.86	£3.16	£8.23	£97.48	£24.37
12-24 months	£0.00	£55.94	£5.09	£1.02	£7.12	£69.17	£17.29
24-36 months	£0.00	£44.10	£2.94	£0.00	£11.76	£58.80	£14.70
Abbreviations: ECG, electrocardiogram							

In UK clinical practice, it is likely that monitoring tests will only be performed if a patient presents with symptoms. As such, the EAG explored a conservative scenario where the cost of monitoring for SoC is zero. Please see Section 5.1.2 for more detail.

Follow-up costs

In CRYSTAL-AF, follow-up visits were scheduled at 1, 6 and 12 months and then every 6 months until study closure, for both arms of the trial. However, the EAG's clinical experts advised that patients with

an ICM are only likely to have a follow-up visit one-month post-surgery and then after that will be remotely monitored, unless patients request a face to face appointment. The clinical experts' advice aligns with information provided in the company submissions. As such, due to the nature of virtual continuous follow-up with the ICM device, there is a reduction in the need for physical follow-up visits. However, once AF is detected, patients will need to be seen by a clinician to start anticoagulation treatment.

As such the EAG assumed for the base-case that all patients with an ICM will have one face to face follow-up appointment after one month and then a subsequent follow-up appointment when AF has been detected. For the SoC arm, follow-up is at 1, 3, 6 and 12 months, as per advice from the EAG's clinical experts and the cost of these follow-up appointments are applied to all patients who do not have detected AF. However, after 12 months, any newly AF-detected patients in the SoC arm will have the cost of a subsequent follow-up appointment applied to account for being identified. Table 34 presents the unit cost of follow-up appointments implemented in the short-term Excel model.

Table 34. Cost of follow-up appointments

Parameter	Unit cost	Source
Initial follow-up	£163.36	NHS reference costs 2017-2018) – WF01B (Treatment Function Code 32)
Subsequent follow-up	£121.05	NHS reference costs 2017-2018) – WF01A (Treatment Function Code 320)

Pharmacotherapy costs

As mentioned previously, DOACs considered in the model are apixaban, dabigatran etexilate, edoxaban and rivaroxaban. Based on clinical expert opinion, antiplatelet treatment in the model is clopidogrel. Warfarin (INR 2-3) was considered only in a scenario analysis. Drug costs used in the DOAC model are presented in Table 35. The costs of DOACs and clopidogrel used in the DOAC model were updated using prices obtained from the British National Formulary (BNF) September 2018 – March 2019 edition.[120] The original cost of warfarin used in the DOAC model was uplifted to 2017 prices for the current analysis.[86] All drugs considered in the model are taken orally, therefore it has been assumed there are no administration or monitoring costs.

Table 35. Drug costs

Drug	Dose	Pack size	Cost per pack	Cost per day	Cost per 3-month cycle
Apixaban	5mg, twice daily	56	£53.20	£1.90	£173.85
Dabigatran etexilate	110 – 150 mg twice daily (depending on age)	60	£51.00	£1.70	£155.55

Rivaroxaban	20mg, once daily	28	£50.40	£1.80	£167.40
Edoxaban	30-60 mg once daily (depending on weight)	28	£49.00	£1.75	£162.75
Clopidogrel	75mg, once daily	30	£1.52	£0.05	£4.71
Warfarin (INR 2-3)					£112.07[a]
Abbreviations: Mg, milligram a: Inflated to 2017 prices, using Office for National Statistics (ONS) Consumer Price Inflation Index for Medical Services (DKC3).[3] Original cost per cycle was £105.13[86]					

Acute and chronic care costs of AF and anticoagulant related events

In the long-term adapted DOAC model, acute management costs for ischaemic stroke, ICH, systemic embolism, TIA, MI, deep vein thrombosis (DVT), pulmonary embolism (PE) and CRB are considered.[86] The acute costs of ischaemic stroke and ICH in the DOAC model are derived from a UK-based population study, which estimated the acute and long-term costs of stroke in AF patients.[121] For the current analysis, costs were uplifted to 2017 prices using the ONS Consumer Price Inflation Index for Medical Services (DKC3).[3] All other event costs were derived from NHS reference costs and updated using the latest schedule (2017-18).[118] Acute event costs are presented in Table 36.

To ensure consistency, cost assumptions from the original model have been maintained. The authors of the original model assumed that the cost of MI obtained from NHS reference costs only accounts for direct hospitalisation and therefore doubled the total costs to account for follow-up costs. Furthermore, the cost of sudden fatal PE is assumed to be zero, and patients who have a non-fatal PE are assumed to accrue the full cost of PE.

Table 36. Acute event costs

Event	Mean event cost	Source and assumptions
Ischaemic stroke	£14,522 (SD = 21,070)	Luengo-Fernandez *et al.* 2013.[121] Based on data for All strokes, ischaemic stroke
ICH	£14,307 (SD = 17,256)	Luengo-Fernandez *et al.* 2013.[121] Based on data for All strokes, haemorrhagic stroke.
SE (non-fatal)	£1,666	NHS Reference costs.[118] Weighted average of cost codes YQ50A-F
TIA	£988	NHS Reference costs.[118] Weighted average of cost codes AA29C-F
CRB	£1,397	NHS Reference costs.[118] Weighted average cost of FD03A-H and VB07Z
MI	£5,804	NHS Reference costs.[118] Weighted average cost of EB10A-E for non-elective long and short stay. Sterne *et al.*, (2017) assumed costs doubled to included follow-up costs.[86]

Abbreviations: CRB, clinically relevant bleeding; DVT, deep vein thrombosis; ICH, intracranial haemorrhage; MI, myocardial infarction; PE, pulmonary embolism, SE, systemic embolism; TIA, transient ischaemic attack.

The costs of chronic ischaemic stroke and ICH management in the DOAC model are also derived from the study by Luengo-Fernandez *et al.*[121] The study estimated the annual cost of stroke, stratified by severity, in the post-acute phase (3 months post index event). The mean cost was calculated by weighting the cost of stroke by severity by the number of events, excluding deaths within 90 days, uplifted to 2017 prices (Table 37) for the current analysis. As per the original model, it is assumed that the cost for ICH is the same as stroke.

Table 37. Mean cost if chronic stroke management (based on study by Luengo-Fernandez *et al.* 2013)[121]

Stroke severity	Number of events (n = 136)	Mean annual cost (SD)
Non-disabling	6[illegible] ([illegible]%)	£2,13[illegible] (£[illegible])
Moderately disabling	58 ([illegible]%)	[illegible] (£7,[illegible])
Totally disabling	12 (9%)	£6,324 (£14,898)
Total weighted cost (uplifted to 2017 prices)		£4,514 (£8,585)
Abbreviations: SD, standard deviation.		

4.2.7 Summary of base case assumptions

Table 38 presents an overview of the parameter assumptions used in the base case model.

Table 38. Base case model assumptions

Parameter	Assumption or source	Justification
Mean age	62	Mean age reported in CRYSTAL-AF was 61.5 years. Age rounded up as a simplifying assumption.[35]
% female	36.5%	Proportion obtained from CRYSTAL-AF.[35]
Prevalence of AF	Based on the detection rate of Reveal XT in CRYSTAL-AF[35]	A 100% sensitivity was assumed for the ICM arm of the model, based on data for the Reveal LINQ.[1] Based on the sensitivity and the detection rates of the ICM in CRYSTAL-AF, it is assumed that the detection rate of the device picks up all AF events and as such, estimates the true prevalence of the disease in the population.
AF detection rates for Reveal LINQ	CRYSTAL-AF[35]	Efficacy data were only available for the Reveal XT ICM; therefore, it was assumed that the efficacy would be at least as good for the Reveal LINQ, which is a later version of the device. This is a conservative assumption.
AF detection rates for BioMonitor 2-AF and Confirm RX	Assumed the same effectiveness as Reveal LINQ.	No data were available for the devices and upon the advice of the EAG's clinical experts, it was assumed that all devices are likely to perform as well as each other.

		However, this is considered an optimistic assumption.
Percentage uptake of anticoagulation treatment for patients with AF detected.	100%	Simplifying assumption. Data from CRYSTAL-AF suggest that only a small proportion of patients diagnosed with AF did not receive anticoagulation. See Section 3.2.3.2 for more detail.[35]
Proportion of patients receiving anticoagulation who receive DOACs	100%	Prescribing trends that show prescriptions for DOACs overtook prescriptions for warfarin in 2018. Thus, the EAG interpreted the data to show that DOACs are becoming the treatment of choice for clinicians. As such the EAG assumed all newly diagnosed patients with AF will be prescribed a DOAC.
Distribution of DOACs	Openprescribing.net[116]	Data are available on the proportion of prescriptions for each DOAC, allowing the total costs and benefits of anticoagulation to be appropriately weighted.
Efficacy of clopidogrel	Assumed to be the same as aspirin, which is the modelled treatment in the DOAC model.	Simplifying assumption based on evidence from an NMA which demonstrated a non-significant increase in risk of dual antiplatelet (aspirin + clopidogrel) versus aspirin alone.[115]
Detection rates for BioMonitor 2-AF	Detection rates capped at 3 years even though battery life of device is 4 years.	AF-detection data are only available 3 years and as such it is unknown how many more cases of AF will be detected by an ICM in year 4. Therefore, the analysis for the BioMonitor 2-AF device is capped at 3 years.
Detection rates for Confirm RX	After 2 years, no further cases of AF are detected.	The battery life of the Confirm RX is 2 years and clinical experts have indicated that the device is unlikely to be replaced when the battery expires.
Detection rates post 3 years	Assumed no differential detection between ICMs and SoC post 3 years	When an ICM battery expires, it is no longer able to detect AF episodes and as such, detection rates would reflect that seen in SoC.
Implantation resource use	Assumed device would be implanted by a cardiologist, with a band 5 nurse assisting	Assumption based on advice provided by the EAG's clinical experts.
Time taken to implant an ICM device	10 minutes	Assumption based on advice provided by the EAG's clinical experts.
Costs of reviewing ICM alerts	Not included	Data on average volume of alerts were not available and therefore this cost was not included in the model. However, based on clinical expert opinion, reviewing alerts is relatively quick and form part of a clinician's daily workload. However, if the volume of alerts is high, then this could become burdensome. The direction of bias

		for this assumption is in favour of ICMs, but it is anticipated that this would not be a key driver of cost-effectiveness.
Administration and monitoring costs of oral medicines	Nil	All drugs considered in the model are taken orally, therefore it has been assumed there are no administration or monitoring costs.
Cost of MI	Double the total costs estimated from NHS Reference costs.[118]	In the original DOAC model it was assumed that the cost of MI obtained from NHS reference costs only accounts for direct hospitalisation and therefore the doubled the total costs to account for follow-up costs.[86]
Cost of sudden fatal PE	Nil	Original assumption from the DOAC model.[86]
Cost of ICH	Assumed to be the same as the cost of stroke.	Original assumption from the DOAC model.[86]
Follow-up costs – ICM	Assumed one follow-up appointment, one month after device implantation	Advice from EAG's clinical experts and company submissions to NICE.
Follow-up costs – SoC	Assumed follow-up appointments would occur at 1,3,6 and 12 months	Based on advice from EAG's clinical experts.
Duration of disutility for acute events	3 months (1 model cycle)	Original assumption from the DOAC model.[86]
Utility decrement for TIA	-0.07	Based on data from Luengo-Fernandez *et al.* 2013.[81] Control value for TIA from study was 0.85, which is higher that the baseline value of 0.78 used in this analysis. Furthermore, TIA utility from the study was estimated as 0.78. As such the EAG implemented a utility decrement in order to account for the impact of TIA.
Utility for systemic embolism	Assumed to be the same as TIA	Original assumption from the DOAC model.[86]
Detection of non-AF arrhythmias	Not included	Data on detection of non-AF arrhythmias were not available and therefore have not been included in the modelling. It is anticipated that the direction of bias for the cost-effectiveness analysis is in favour of SoC.
Abbreviations: AF, atrial fibrillation; DOAC, directly acting oral anticoagulant; EAG, evidence assessment group; ICH, intra-cranial haemorrhage; ICM, implantable cardiac monitor; MI, myocardial infarction; NMA, network meta-analysis; PE, pulmonary embolism; TIA, transient ischaemic attack; SoC, standard of care		

4.2.8 Uncertainty

Parametric uncertainty in the economic model is explored through deterministic and probabilistic sensitivity analysis, as well as running various scenarios around the base case results (Section 5.1.2). Probabilistic sensitivity analysis considers the uncertainty characterising the input parameter estimates by assigning probability distributions to them to reflect their imprecision. Probability distributions were determined by the available data or, where data were lacking, by plausible assumptions. Monte Carlo

simulation was then employed to reflect this uncertainty in the models' results: 10,000 iterations were performed, each drawing random values out of the distributions fitted onto the model input parameters. Results of the probabilistic analysis were averaged across the 10,000 iterations to provide a mean estimate of costs and QALYs for each intervention. Probabilistic sensitivity analysis results have been presented as cost-effectiveness acceptability curves (CEACs) where different willingness to pay thresholds for a QALY are used to show which strategy is likely to have the largest net benefit for that threshold.

4.2.9 Interpretation of results

The results of the cost effectiveness analysis are presented as ICERs. ICERs are can be interpreted as cost per QALY gained when comparing two interventions and are calculated as follows:

$$ICER = \frac{Cost\ of\ B - Cost\ of\ A}{QALY\ of\ B - QALY\ of\ A}$$

In order to compare several interventions against one another, incremental analyses are performed to calculate the ICERs. The incremental analyses involved ranking the interventions by cost, from least to most expensive. Any intervention that is more expensive and less effective then preceding strategy is classed as 'dominated' and is excluded from the analysis. ICERs are then calculated for each intervention compared with the next more expensive, non-dominated option. If an ICER for an intervention is higher than that of the next most effective strategy, it is ruled out by 'extended dominance'. ICERs are then recalculated excluding interventions that are 'dominated' or subject to 'extended dominance'. The remaining interventions then form an 'efficiency frontier' of interventions that are cost-effective and can be judged against the NICE cost-effectiveness threshold of £20,000 – £30,000 per QALY gained.[122]

5 COST-EFFECTIVENESS RESULTS

5.1.1 Base-case deterministic and probabilistic results

Table 39 presents the pairwise, deterministic base-case incremental cost-effectiveness ratios (ICERs) for Reveal LINQ, BioMonitor 2-AF and Confirm RX compared with standard of care (SoC) monitoring). The results show that ICMs could be considered cost-effective against the £20,000 – £30,000 ICER threshold used by the National Institute for Health and Care Excellence (NICE).[123] The results are also plotted on the cost-effectiveness plane in Figure 9.

Table 40 presents the fully incremental analysis of cost-effectiveness results and demonstrates that out of the ICMs under consideration, Reveal LINQ is dominated by BioMonitor 2-AF. However, BioMonitor 2-AF would not be considered cost-effective when compared with standard of care (SoC) monitoring.

It should be noted that the differences in QALYs for Confirm RX compared with the other two devices are driven by the assumption that after 2 years no further episodes of AF are detected for Confirm RX. as the battery would have expired and the device would not be replaced. In addition, detection rates for BioMonitor 2-AF were capped at 3 years, even though the battery life of the device is 4 years. The impact of this assumption is that the BioMonitor 2-AF may potentially pick up more episodes of AF. However, the results for BioMonitor 2-AF and Confirm RX should be viewed with caution, as no data were available for any version of these devices in the cryptogenic stroke (CS) population and as such they are based on a strong assumption of equivalence with Reveal LINQ, which are not proven.

Table 39. Base case incremental pairwise cost effectiveness results (discounted)

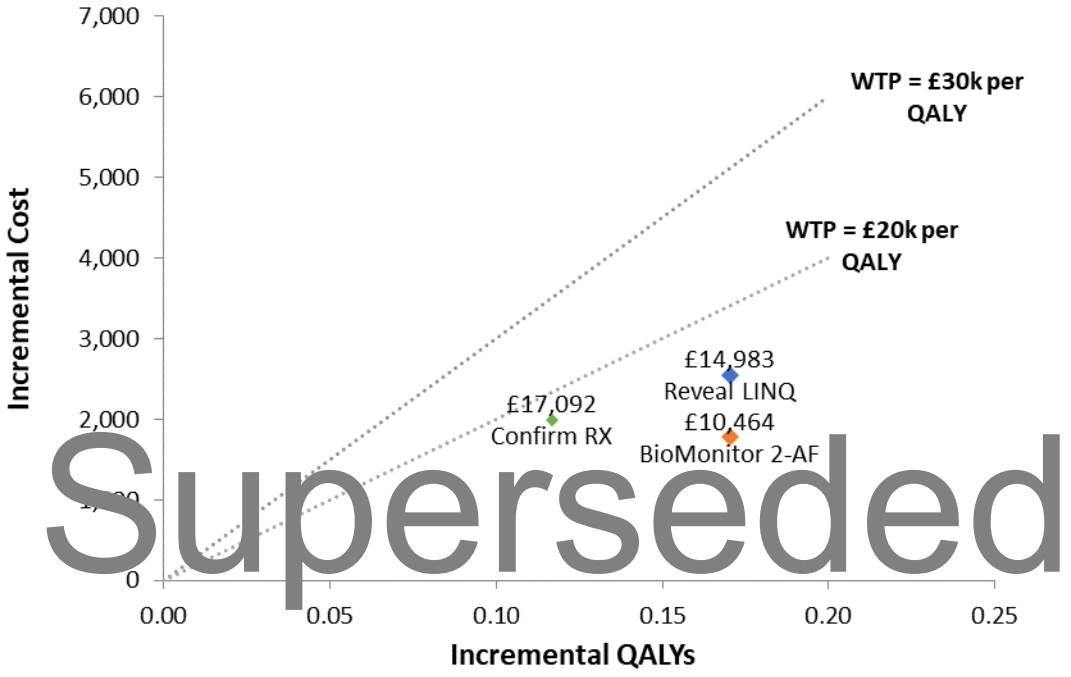
Intervention	Total Costs	Total QALYs	Incremental costs	Incremental QALYs	ICER
Standard of Care	£7,288	1.50	–	–	–
Reveal LINQ	£9,841	1.67	£2,553	0.17	£14,983
BioMonitor 2-AF	£9,071	1.67	£1,783	0.17	£10,464
Confirm RX	£9,287	1.62	£1,998	0.12	£17,092
Abbreviations: ICER, incremental cost effectiveness ratio; QALY, quality adjusted life year.					

Table 40. Base case incremental cost effectiveness results (discounted)

Intervention	Total Costs	Total QALYs	Incremental costs	Incremental QALYs	ICER
Standard of Care	£7,288	1.50	-	-	-
Confirm RX	£9,071	1.67	£1,783	0.17	£10,464
BioMonitor 2-AF	£9,287	1.62	£216	-0.05	Dominated
Reveal LINQ	£9,841	1.67	£770	0.00	Dominated
Abbreviations: ICER, incremental cost effectiveness ratio; QALY, quality adjusted life year.					

*compared to Standard of Care as Confirm RX is excluded because of extended dominance between BioMonitor 2-AF and Standard of Care.

Figure 9. Cost effectiveness plane showing the ICERs for each ICM versus SoC in relation to the £20k and £30k per QALY thresholds.



Abbreviations in figure: ICER, incremental cost effectiveness ratio; ICM, implantable cardiac monitor; QALY, quality-adjusted life-year; SoC, standard of care; WTP, willingness to pay.

5.1.2 Scenario analyses

The EAG conducted the following scenario analyses to assess the potential impact of the uncertainty around some of the assumptions made in the model.

Addition of optional FOCUSON triage costs

For the Reveal LINQ device only, the company provides a triage service, which can be provided in two ways. Option 1 provides the service at a cost of £187 per patient per year, whereas Option 2, provides the same service but at a one-off fee of £374 per patient per device. Each option is considered as a separate scenario.

Addition of optional BioMonitor 2-AF devices

The BioMonitor 2-AF has the option to include a remote assistant device and CardioMessenger transmitter, at a cost of £230 and £400, respectively. These costs are included as part of the intervention cost and considered as separate scenarios.

Different time horizons (1-year, 2-year)

This scenario assumes that the ICM devices only detect for a period of 1 year and 2 years, respectively. This means that any detections that were identified in the CRYSTAL-AF study beyond these time points were assumed to be missed by the devices; hence, reducing the benefits of the ICMs in comparison to SoC.

Constant detection rate

As an alternative to using the detection data directly from the CRYSTAL-AF trial, this scenario uses the 36-month detection proportion to calculate a constant monthly detection rate using the following formula:

$$r_m = \frac{-\log(1-p_{36})}{36};$$

where r_m is the monthly rate and p_{36} is the proportion who are detected at 36 months. The monthly proportions, p_m, are then calculated as:

$$p_m = e^{-r_m t};$$

where t is the time in months.

Using each DOAC separately to determine the long-term outcomes following AF detection

Instead of taking the weighted long-term DOAC outcomes based on the usage data, this applies the outcomes for each DOAC alone as separate scenarios.

Inclusion of warfarin as a treatment option for patients diagnosed with AF

Currently warfarin is still in use for the treatment of AF, although based on clinical expert opinion, the current primary treatments for newly diagnosed AF patients are DOACs. However, given that data suggest around 50% of anticoagulation usage comprises of warfarin, the EAG conducted a scenario to test the impact on this usage.[116] This scenario applies the same approach to weight the costs and QALYs for DOAC treatment from the R model, but now also includes warfarin as an option in this weighting. Therefore, this applies 50% of the warfarin outcomes and reduces the weighted DOAC outcomes used in the base case by 50%.

No removal of devices

The base case analysis assumes that the all devices are removed at the end of their battery life. This scenario assumes that the device will not need to be removed at all, as clinical expert advice suggests that they are safe to remain in place indefinitely.

Implanter and implanter assistant assumptions

Two separate scenarios were conducted, which assume that the implantation is performed by a Cardiac Physiologist (Band 7) and assisted by a Cardiac Physiologist (Band 5), respectively.

Implantation assumptions based on Kanters et al. 2015

This scenario assumes that Cardiac Physiologist (Band 7) performs the implantation, assisted by a Nurse (Band 5). The assumed time required for the Cardiac Physiologist (Band 7) is assumed to be 25.6 minutes, and for the Nurse (Band 5), is assumed to be 43.1 minutes based on data from Kanters *et al.* 2015[117].

No monitoring for SoC

This scenario removes all monitoring costs from the SoC group and assumes that no incidences of AF are detected, i.e. assuming a greater benefit for the ICM groups but also an increased total cost relative to the SoC group.

Table 41. Scenario anlyses for each ICM versus SoC (Discounted ICERs)

Scenario	ICERs versus SoC		
	Reveal LINQ	BioMonitor-2	Confirm RX
Base case	*£14,983*	*£10,464*	*£17,092*
Addition of FOCUSON triage costs (Option 1)	£19,156	NA	NA
Addition of FOCUSON triage costs (Option 2)	£42,101	NA	NA
Addition of FOCUSON follow-up costs	£18,419	NA	NA
Addition BioMonitor 2-AF remote assistant device	NA	£11,814	NA
Addition BioMonitor 2-AF CardioMessenger	NA	£12,811	NA
Time horizon for ICM monitoring (1 year)	£29,321	£16,883	£26,090
Time horizon for ICM monitoring (2 year)	£18,803	£12,217	NA
Constant detection rates (exponential)	£14,917	£10,386	£16,951
Long-term DOAC outcomes based on apixaban	£16,274	£11,648	£18,542
Long-term DOAC outcomes based on dabigatran	£14,042	£9,407	£16,065
Long-term DOAC outcomes based on edoxaban	£9,425	£6,459	£10,637
Long-term DOAC outcomes based on rivaroxaban	£14,272	£9,722	£16,323
Inclusion of warfarin as a treatment option for patients diagnosed with AF	£16,452	£11,990	£18,424
No explantation of devices	£13,721	£9,202	£15,189
Implantation by Cardiac Physiologist (Band 7)	£14,933	£10,414	£17,020

Implantation assisted by Cardiac Physiologist (Band 5)	£14,982	£10,463	£17,091
Implantation assumptions based on Kanters *et al.* 2015[117]	£15,140	£10,620	£17,321
No SoC monitoring or AF detections	£16,062	£12,003	£18,294
Abbreviations: ICER, incremental cost effectiveness ratio; ICM, implantable cardiac monitor; QALY, quality adjusted life year; SoC, standard of care.			

Figure 10. Tornado plot for scenarios with greatest impact (Reveal LINQ versus SoC)

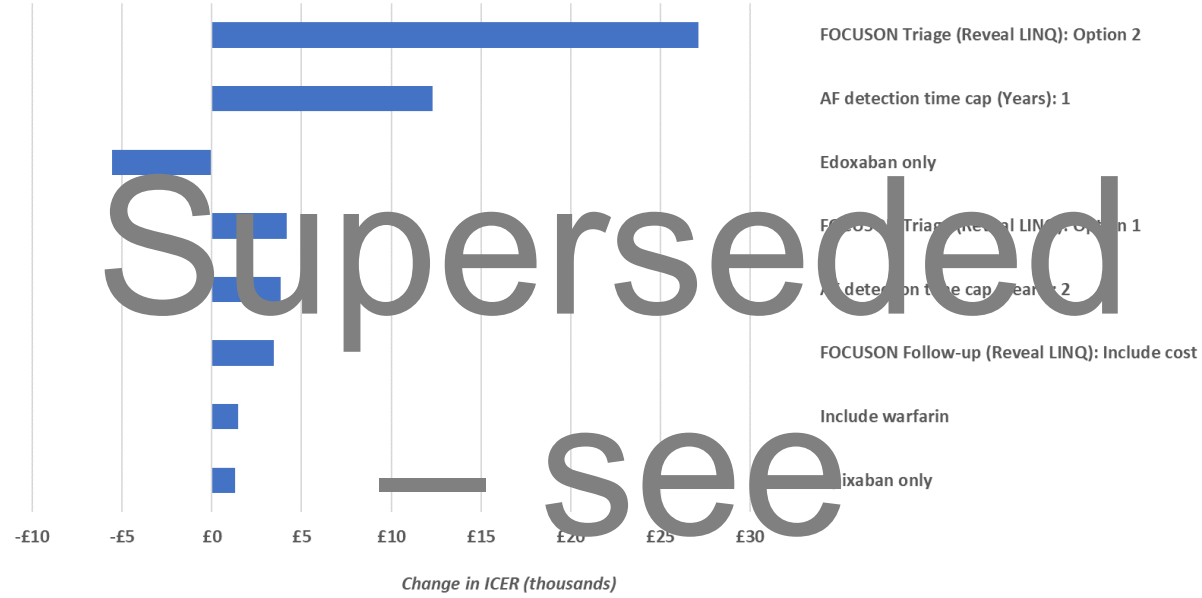


Figure 11. Tornado plot for scenarios with greatest impact (BioMonitor 2 AF versus SoC)

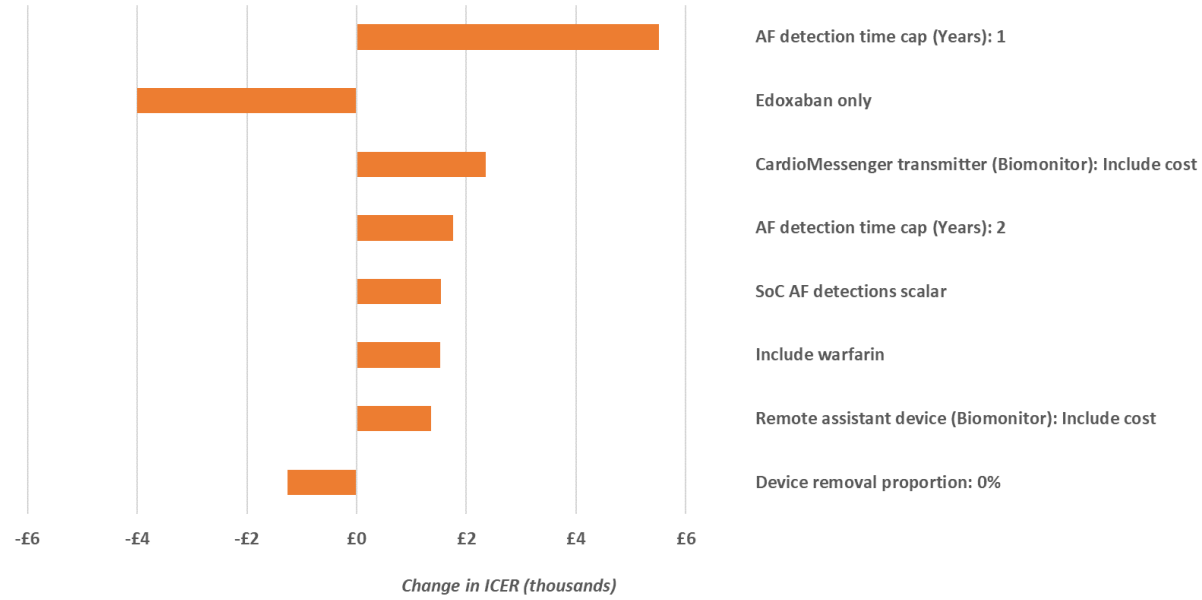
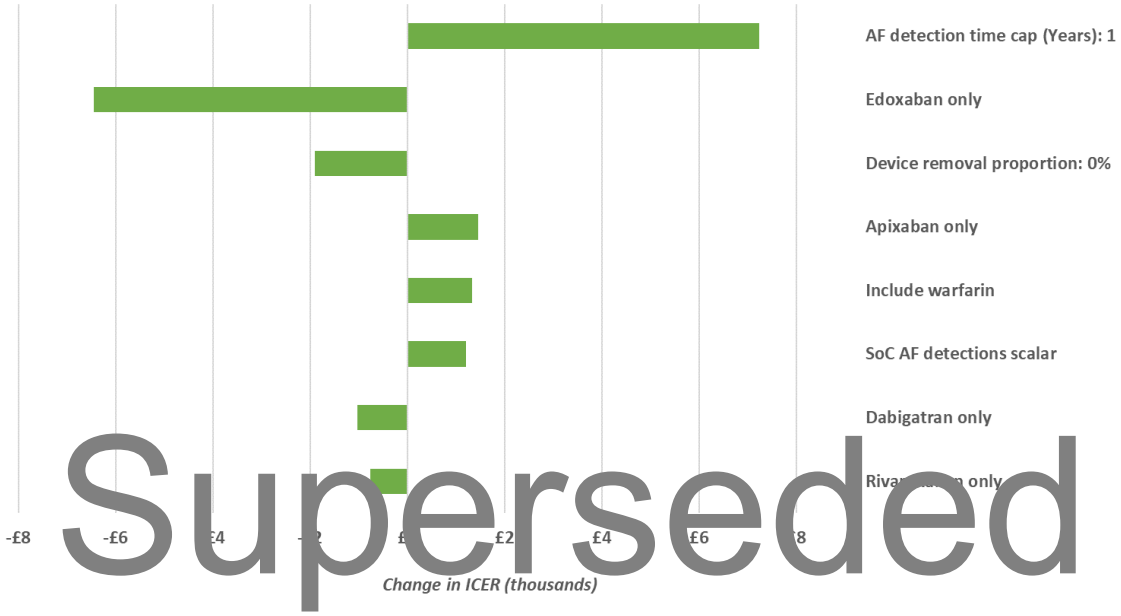


Figure 12. Tornado plot for scenarios with greatest impact (Confirm RX versus SoC)



5.1.3 Sensitivity analyses

5.1.3.1 One-way sensitivity analyses

The EAG conducted a number of sensitivity analyses around the cost inputs that were based on estimates (e.g. NHS reference costs), the outcomes applied from the long-term DOAC model, that is total costs and QALYs per cycle obtained from the long-term DOAC model, and the discount rate applied.

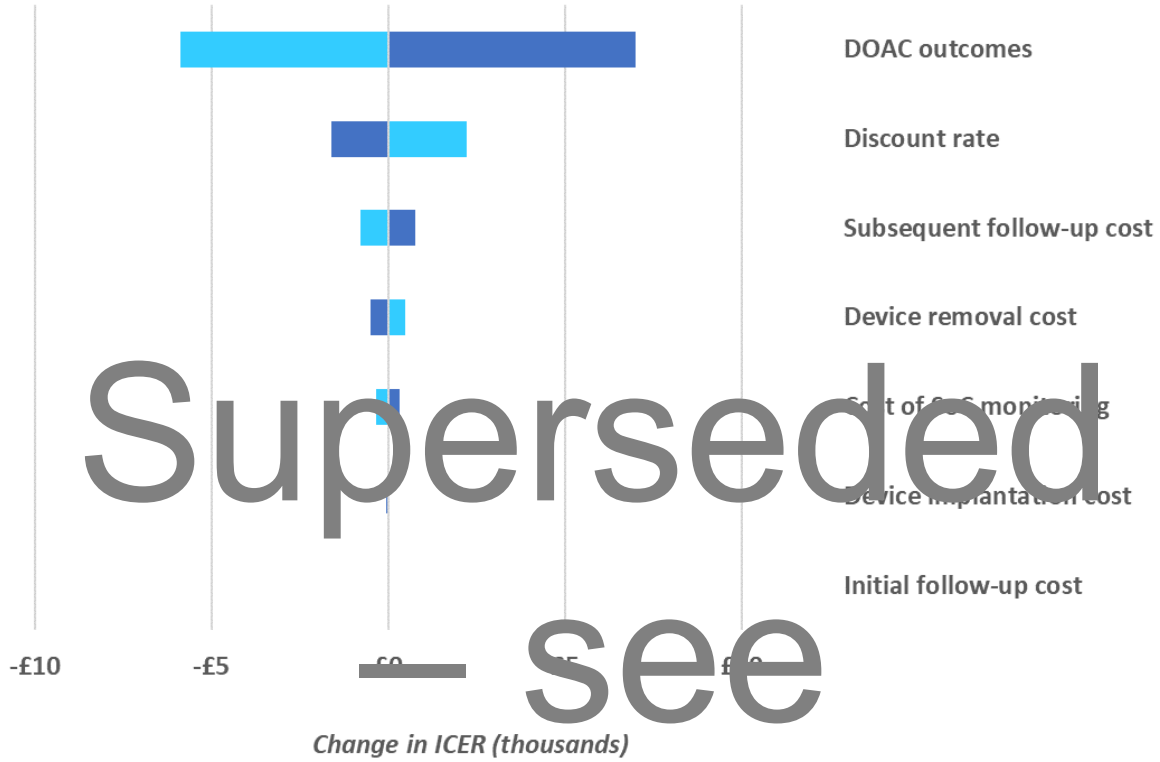
The most recent publication of NHS reference costs (2017-2018) no longer gives an inter-quartile range for the costs associated with each Healthcare Resource Group (HRG). Given the lack of data to inform the variation around the mean estimate, the EAG assumed a standard error of 20% of the mean value for each parameter. For DOAC outcomes, the 2.5th and 97.5th percentiles of the 10,000 samples for each cycle were used as the lower and upper limits, respectively, and the discount rate was lowered to 1.5% (as per the NICE Guide to the methods of technology appraisal 2013[123]), as well as increasing it to 6%. The summary of the inputs along with the results is given in Table 42.

Table 42. One-way sensitivity analyses (Discounted ICERs)

Parameter	Base case	Lower value	Upper value	Reveal LINQ		BIOMONITOR		CONFIRM-RX	
				Lower ICER	Upper ICER	Lower ICER	Upper ICER	Lower ICER	Upper ICER
Initial follow-up cost	£163	£99	£227	£14,983	£14,983	£10,464	£10,464	£17,092	£17,092
Device implantation cost	£24	£15	£34	[illegible]	[illegible]	[illegible]	[illegible]	£17,011	£17,173
Cost of SoC monitoring	£141	£85	[illegible]	[illegible]	£14,660	[illegible]	[illegible]	£17,564	£16,621
Device removal cost	£238	£145	£332	£14,489	£15,478	£9,969	£10,958	£16,346	£17,838
Subsequent follow-up cost	£128	£78	£178	£15,760	[illegible]	[illegible]	£9,687	£18,259	£15,925
Discount rate	3.5%	1.5%	6%	£13,373	[illegible]	[illegible]	£11,523	£15,107	£19,826
DOAC outcomes	Mean	2.5th percentile	97.5th percentile	£22,006	£9,102	£12,953	£6,688	£24,517	£10,338

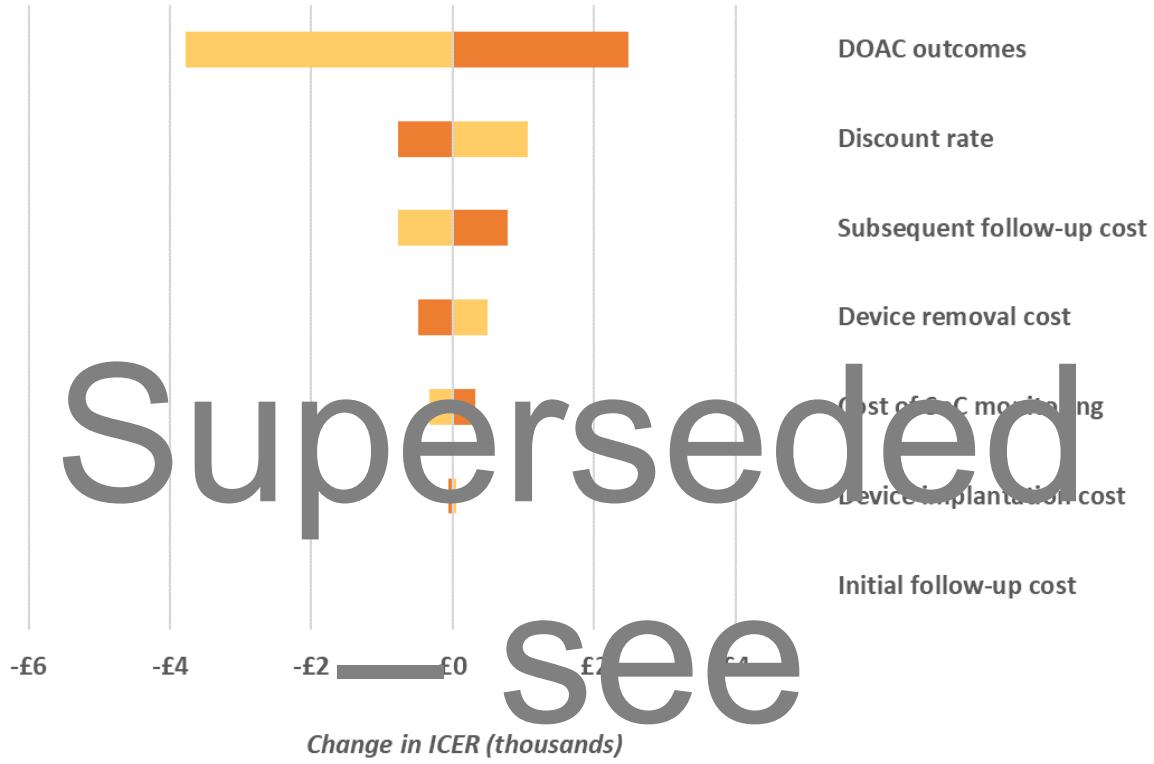
Abbreviations in table: DOAC, direct oral anticoagulant; ICER, incremental cost effectiveness ratio; SoC, standard of care.
Note: The ICERs correspond to the lower and upper parameter inputs and in some cases the "lower ICER" is a larger number than the "upper ICER".

Figure 13. Tornado plot showing OWSAs for Reveal LINQ versus SoC



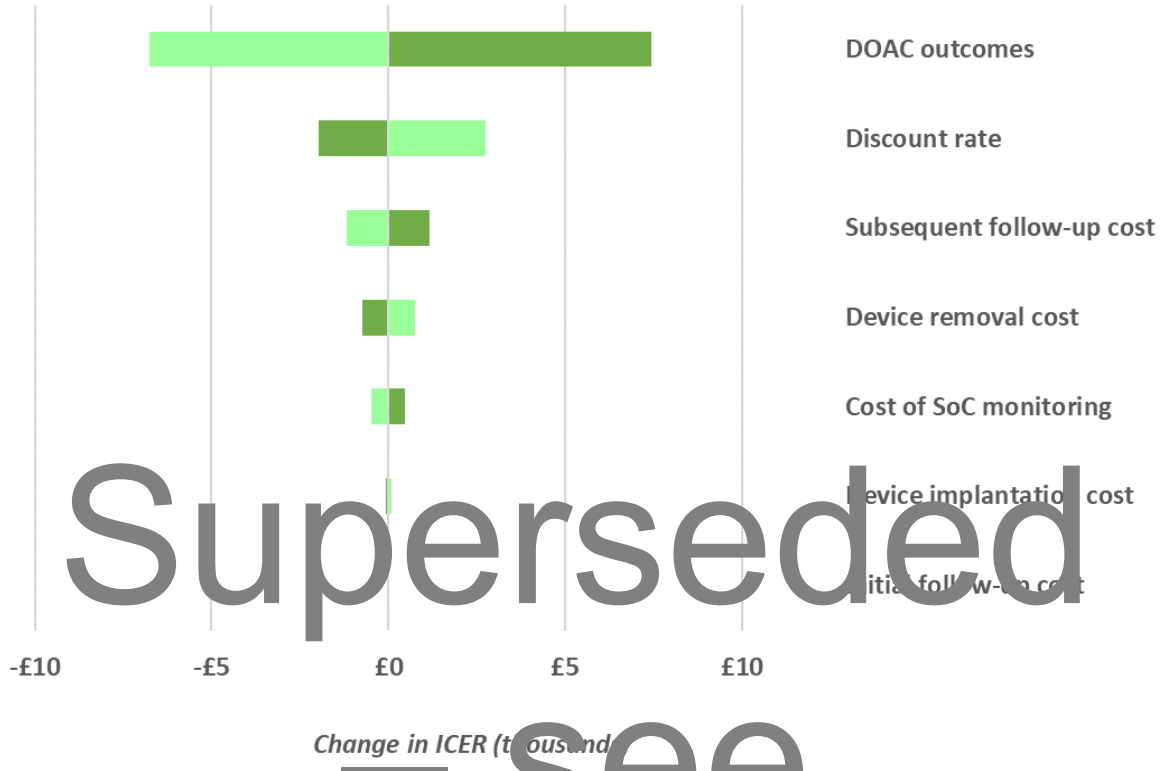
Abbreviations in figure: DOAC, direct oral anticoagulant; ICER, incremental cost effectiveness ratio; OWSA, one-way sensitivity analysis; SoC, standard of care.

Figure 14. Tornado plot showing OWSAs for BioMonitor 2-AF versus SoC



Abbreviations in figure: DOAC, direct oral anticoagulant; ICER, incremental cost effectiveness ratio; OWSA, one-way sensitivity analysis; SoC, standard of care.

Figure 15. Tornado plot showing OWSAs for Confirm-RX versus SoC



Abbreviations in figure: DOAC, direct oral anticoagulant; ICER, incremental cost effectiveness ratio; OWSA, one-way sensitivity analysis; SoC, standard of care.

5.1.3.2 Probabilistic sensitivity analysis

The AG conducted a probabilistic sensitivity analysis (PSA) to assess the impact of the combined uncertainty from all parameters in the model. This was performed by sampling from distributions of the uncertain parameters 10,000 times, to generate the equivalent number of sampled ICERs. The methods for the inclusion of parameter uncertainty are discussed for each parameter type in turn.

The key uncertainties in the model are captured in the long-term DOAC model (coded using R statistical software). This model is probabilistic and produced 10,000 per-cycle samples of costs and QALYs for each DOAC, warfarin and aspirin, respectively. These outcomes were pasted into separate tabs of the short-term Excel model, with each of 10,000 columns representing a single sample of per-cycle costs and QALYs over the lifetime horizon. These were sampled in the PSA using an offset parameter, which randomly selects a column-offset value between 0 and 9999 to apply to the first column of outcomes, i.e. to sample within columns 1 to 10,000, inclusively. This sampling is performed for each DOAC treatment (plus warfarin). The samples are then weighted according to the treatments that are included in the analysis and the usage proportions applied to weight them.

The usage proportions were sampled using the data from openprescribing.net[116], from which the mean estimates were derived. The total monthly usage values for each treatment between September 2017

and September 2018 (inclusive) were used to estimate correlated samples using the *mvrnorm* and *cov* functions from the *MASS* and *stats* packages in R, respectively.[124, 125] The *cov* function generates a covariance matrix (using Pearson's product moment correlation coefficient as the default) for the monthly usage totals of each treatment, which was inputted into the function, along with the mean monthly usage, to generate 10,000 sampled estimates of the monthly usage totals. These values were used to sample the weights applied to the DOAC treatment (plus warfarin) outcomes.

For cost estimates, gamma distributions were applied using 20% of the mean value to estimate standard errors. The cost estimates that were varied in the PSA are:

- SoC monitoring;
- Initial follow-up;
- Subsequent follow-up;
- Device implantation; and,
- Device removal.

The parameters used for the distribution of each variable are given in Table 43.

Table 43. Distribution and parameters of cost estimates

Variable	Mean cost	SE[a]	Distribution	Alpha[b]	Beta[c]
SoC monitoring	£141	£28	Gamma	25.00	5.62
Initial follow-up	£161	£33	Gamma	25.00	6.53
Subsequent follow-up	£126	£26	Gamma	25.00	5.12
Device implantation	£24	£5	Gamma	25.00	0.97
Device removal	£238	£48	Gamma	25.00	9.53

Abbreviations in table: SE, standard error; SoC, standard of care.
Notes:
a Assumed to be 20% of the mean cost.
b Calculated as *Mean/Beta*
c Calculated as $SE^2/Mean$

The results of the PSA for each ICM and SoC are given in Table 44, and a scatterplot showing the spread of results from the individual samples is given in Figure 16, Figure 17 and Figure 18, for Reveal LINQ, BioMonitor 2-AF and Confirm RX, respectively; each versus SoC. The incremental costs and QALYs relative to SoC are shown in the cost effectiveness planes in Figure 19, Figure 20, and Figure 21, respectively. In addition to these, cost effectiveness acceptability curves, showing the probability of each ICM being cost effective compared with SoC over a range of willingness to pay thresholds, are given in Figure 22, Figure 23, and Figure 24 for Reveal LINQ, BioMonitor 2-AF and Confirm RX, respectively. It should be noted that the cost and QALY results from the long-term DOAC model have

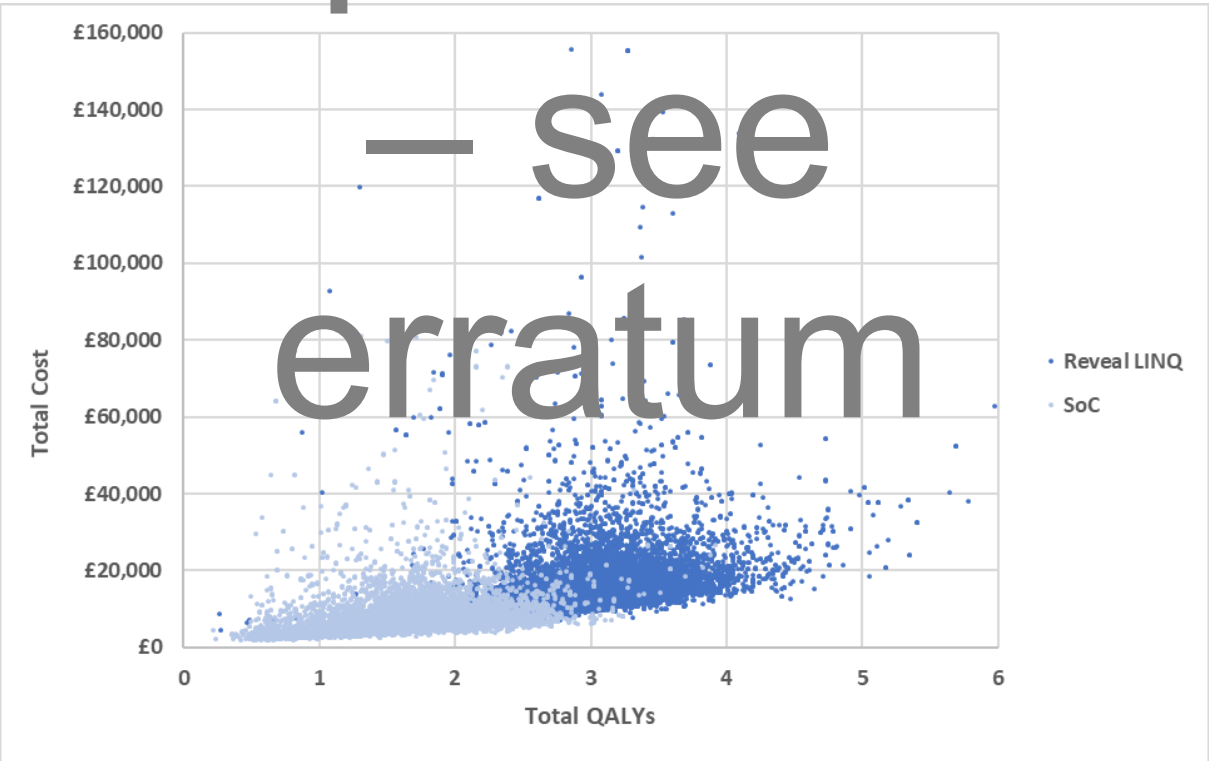
large ranges around the mean, with QALYs results positively skewed, and it is this that is driving the uncertainty in the PSA results.

Table 44. PSA results for each ICM compared with SoC (Discounted)

Intervention	Total Costs	Total QALYs	Incremental costs	Incremental QALYs	ICER
Standard of Care	£8,183	1.65	-	-	-
Reveal LINQ	£18,436	3.10	£10,253	1.45	£7,086
BioMonitor 2-AF	£17,666	3.10	£9,483	1.45	£6,554
Confirm RX	£15,545	2.69	£7,362	1.04	£7,085

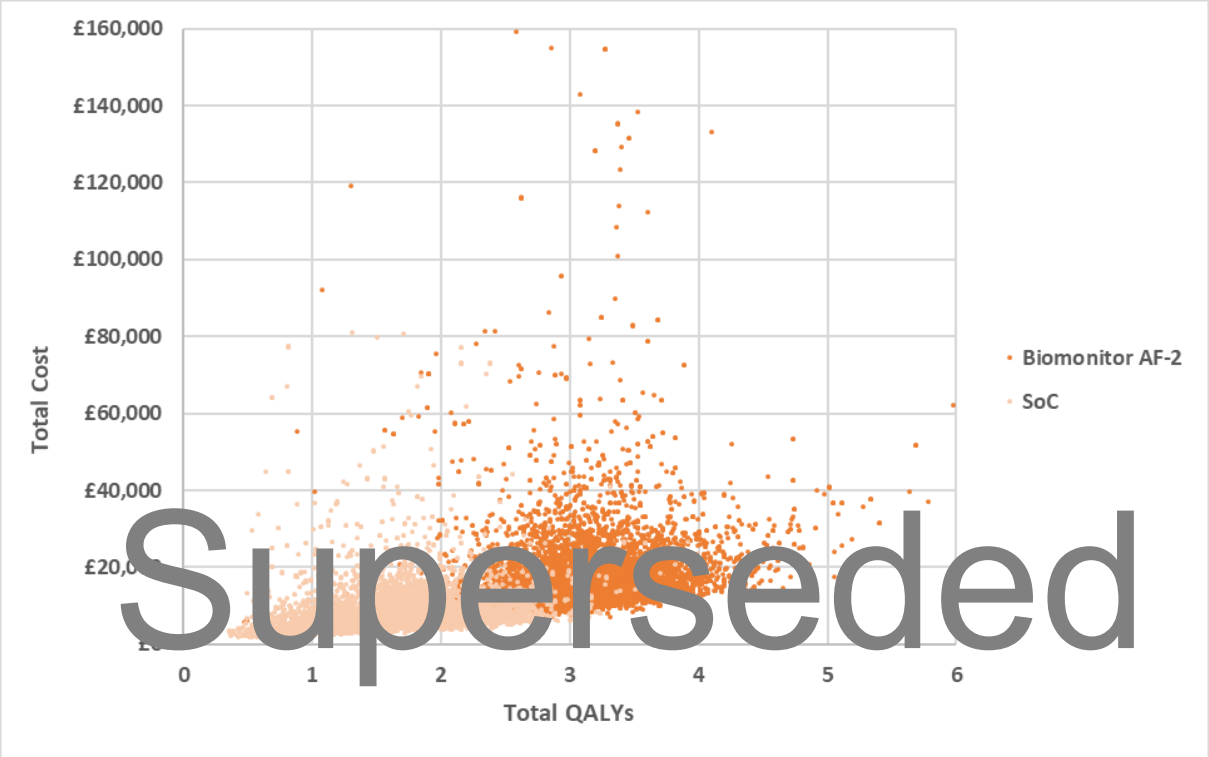
Abbreviations in table: ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life-year.

Figure 16. PSA scatterplot: Reveal LINQ versus SoC



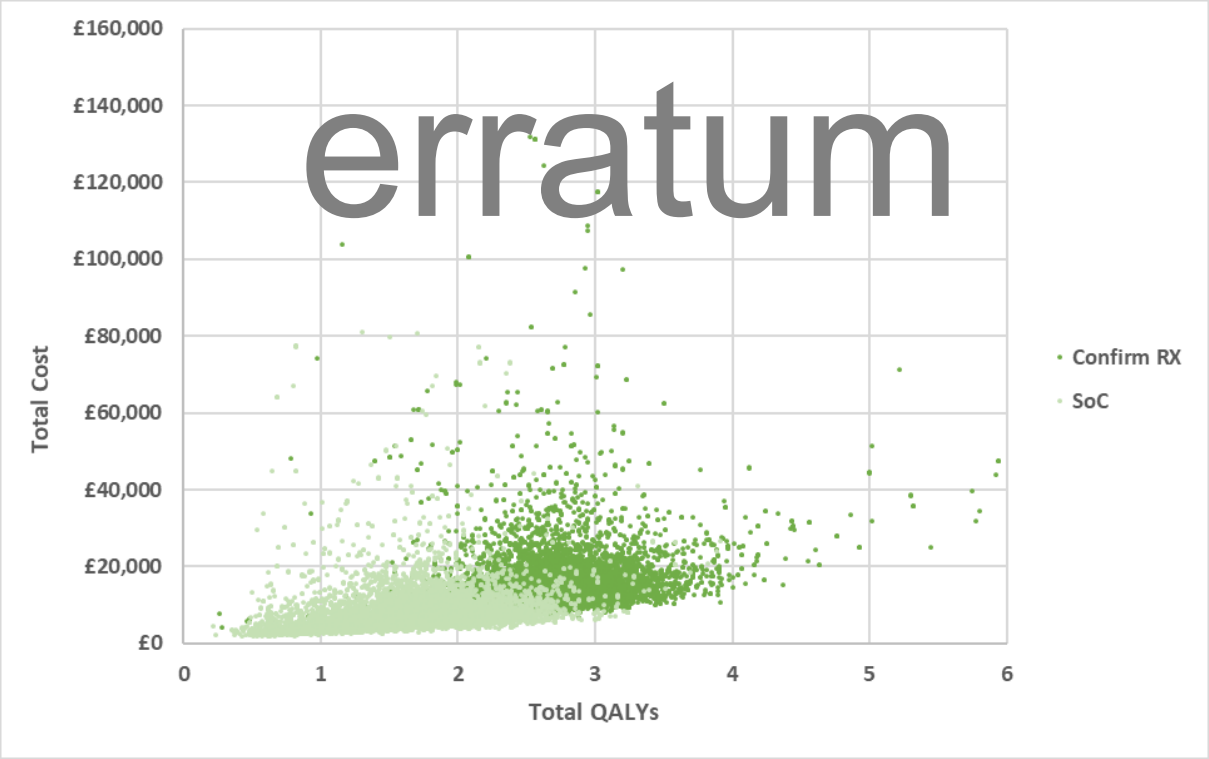
Abbreviations in figure: QALY, quality-adjusted life-year; SoC, standard of care.

Figure 17. PSA scatterplot for BioMonitor 2-AF versus SoC



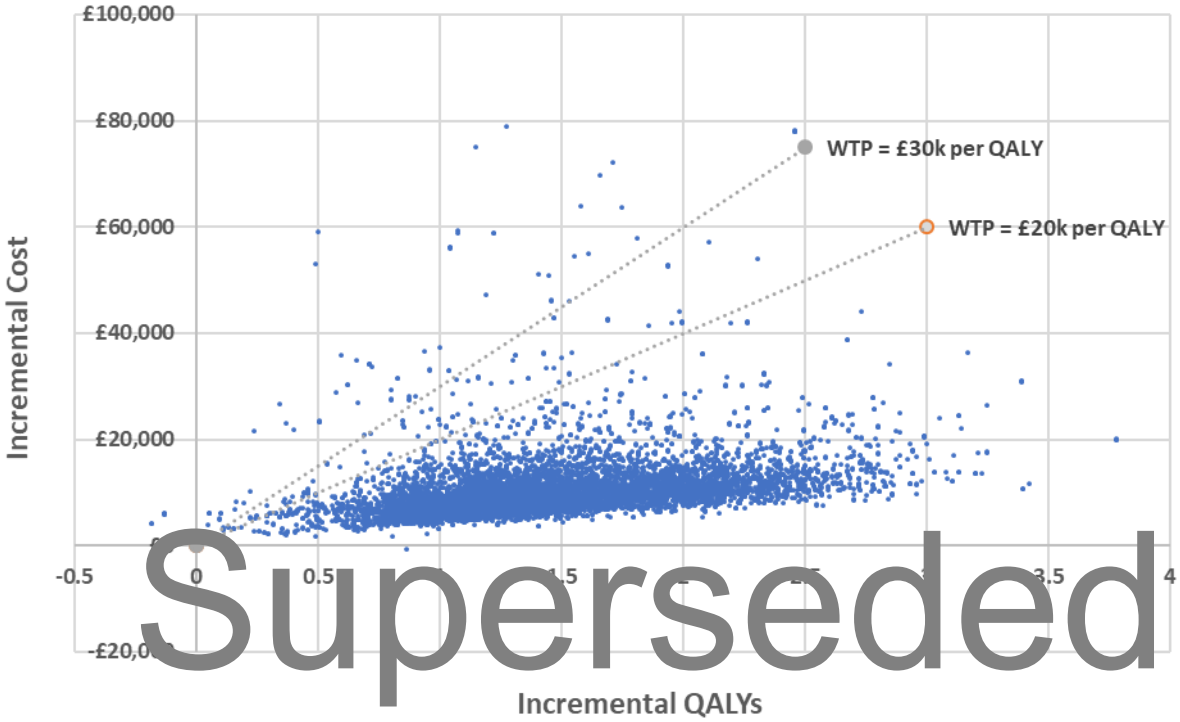
Abbreviations in figure: QALY, quality-adjusted life-year; SoC, standard of care.

Figure 18. PSA scatterplot for Confirm RX versus SoC



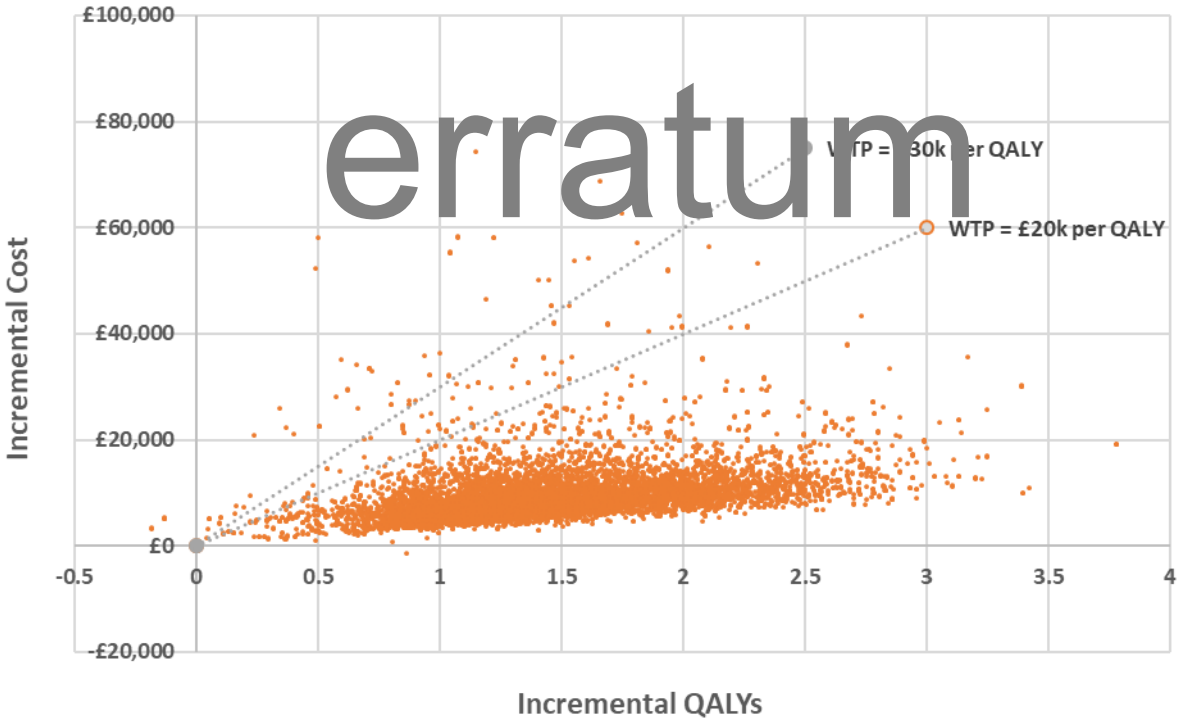
Abbreviations in figure: QALY, quality-adjusted life-year; SoC, standard of care.

Figure 19. Cost effectiveness plane for Reveal LINQ versus SoC



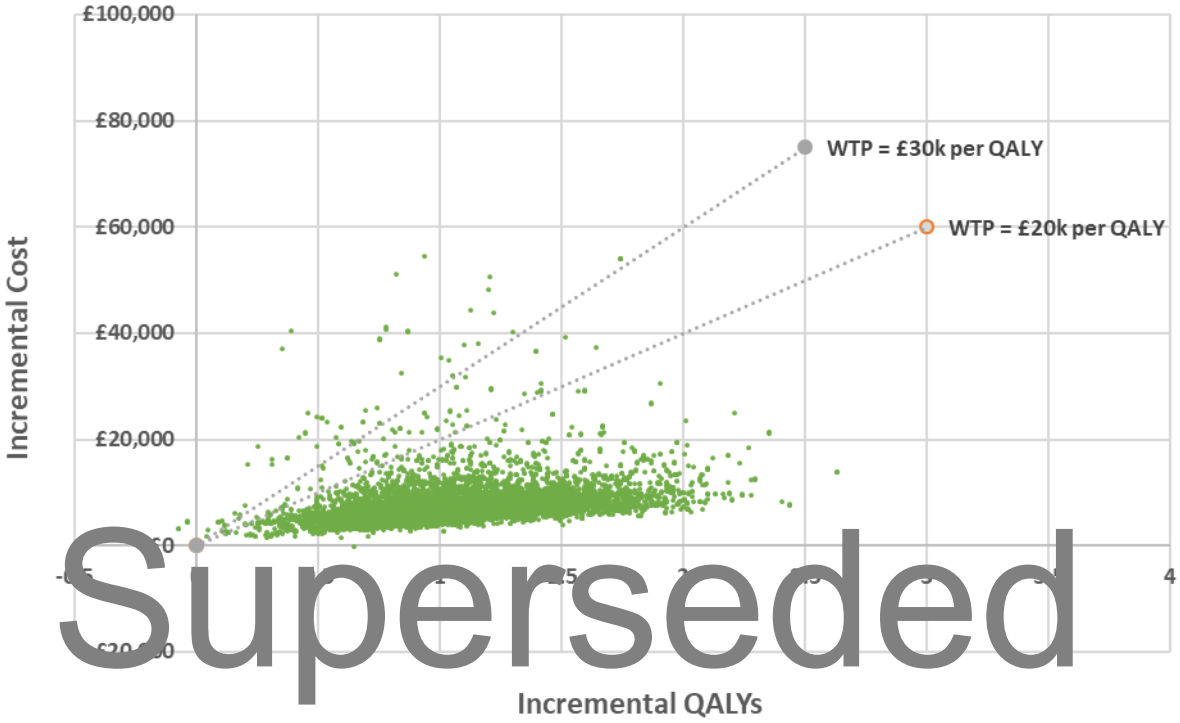
Abbreviations in figure: SoC, standard of care; WTP, willingness to pay.

Figure 20. Cost effectiveness plane for BioMonitor 2 AF versus SoC



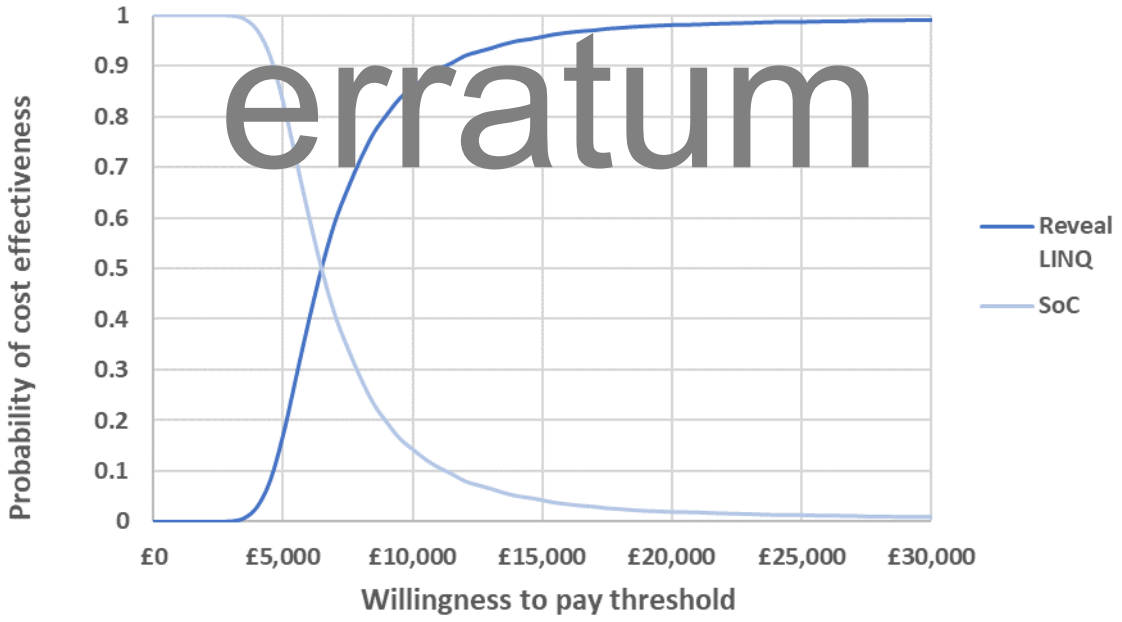
Abbreviations in figure: SoC, standard of care; WTP, willingness to pay.

Figure 21. Cost effectiveness plane for Confirm RX versus SoC



Abbreviations in figure: SoC, standard of care; WTP, willingness to pay.

Figure 22. Cost effectiveness acceptability curve for Reveal LINQ versus SoC



Abbreviations in table: SoC, standard of care.

Figure 23. Cost effectiveness accepatibility curve for BioMonitor 2-AF versus SoC

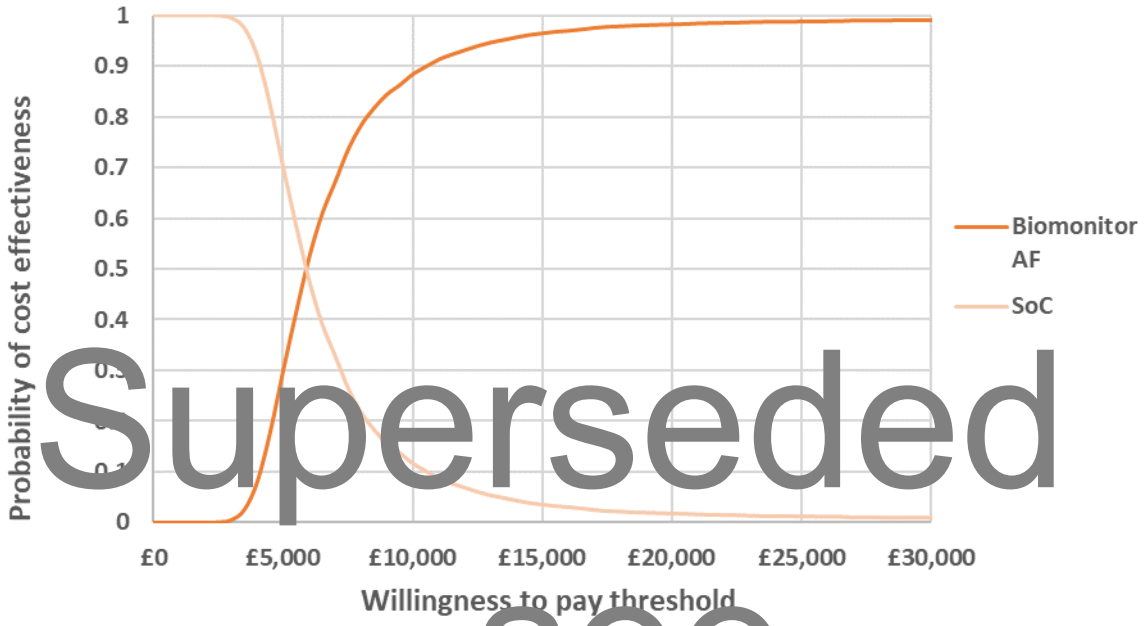
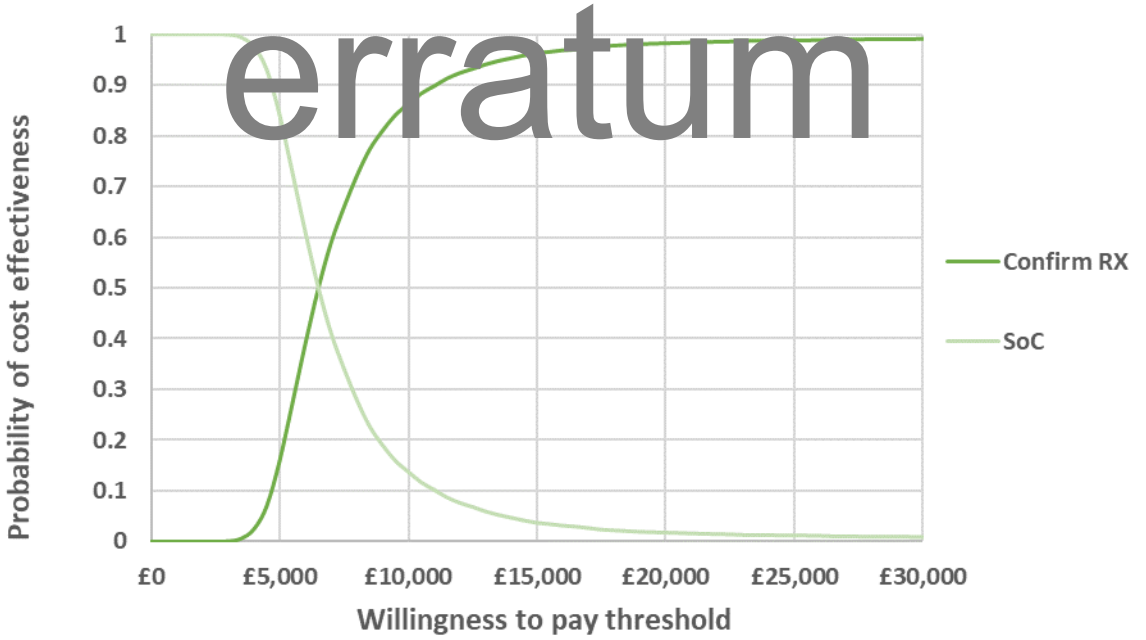


Figure 24. Cost effectiveness accepatibility curve for Confirm RX versus SoC



6 DISCUSSION

6.1 Statement of principal findings

6.1.1 Clinical

The clinical evidence systematic review sought to identify randomised controlled trials (RCTs) and comparative observational studies that compared any of the three devices (Confirm RX, Abbott; BioMonitor 2-AF, BIOTRONIK; and Reveal LINQ, Medtronic) with at least 24 hours of Holter (external ECG) monitoring to detect atrial fibrillation (AF) in people with cryptogenic stroke or transient ischaemic attack (hereafter referred to as CS). Only a single RCT assessing an earlier Medtronic Reveal model (XT rather than LINQ) met the original review eligibility criteria (CRYSTAL-AF),[35] and so the criteria were widened in an attempt to find evidence for the BioMonitor 2-AF, Confirm RX and Reveal LINQ. First, non-comparative observational studies were sought within the correct CS population, and then evidence was considered from studies of mixed populations submitted by each company. Only CRYSTAL-AF[35] falls within the eligibility criteria outlined in the original published protocol for this diagnostic assessment review, and so the additional evidence should be interpreted with caution. As such, CRYSTAL-AF[35] (n = 441) represents the most robust clinical evidence available to inform the decision problem, albeit assessing the Reveal XT.

CRYSTAL-AF was an open-label study that compared the Reveal XT ICM with conventional follow-up in a population with CS and no history of AF after extensive diagnostic workup. The study was conducted in North America and Europe and the population was considered by the The Evidence Assessment Group's (EAG's) clinical experts to be generally applicable to patients who would be eligible for an ICM in UK clinical practice.

Twenty-six single-arm observational studies were identified after widening the eligibility criteria to include non-comparative studies. The studies were conducted in North America and Western Europe (one in the UK) and all assessed the Reveal XT and Reveal LINQ in populations with CS; none provided evidence to assess the efficacy of BioMonitor 2-AF (other than a mixed device study that did not provide results by individual device) or Confirm RX for patients with CS. The observational studies represent a wide sample of patients who have received an ICM in practice (N = 3,414) and provide evidence for the Reveal LINQ and for additional outcomes specified in the NICE final scope that were not available from CRYSTAL-AF.

All of the observational studies were single-arm and therefore at high risk of bias, although three conducted within-patient comparisons of ICM versus other monitoring strategies.[14, 15, 60] Key sources of heterogeneity between the observational studies include patient demographics (mean or median age 52 to 72 years), rigor of stroke assessment, stroke risk score (CHA_2DS_2VASC score 3 to 5), definition and

adjudication of AF, and length of follow-up; published data and the EAG's clinical experts suggest that these are all likely to affect AF detection and other clinical outcomes.[1]

Mixed population studies recommended by the companies as having potential data for inclusion in the review have also been included as no data were identified for the Confirm RX or BioMonitor 2-AF in the CS population and only limited outcome data were identified in the CS population for the Reveal LINQ. A full systematic literature search was not conducted to validate their inclusion due to time constraints and concerns regarding the applicability of their results to the CS population.[1] The data presented from these studies may therefore be subject to study selection bias as well as clinical heterogeneity due to the variation in the patient populations of each of the studies. In total 1 study for Confirm RX (older model the Confirm DM2102), 5 studies of the BioMonitor 2-AF (all BioMonitor 2 but only one of which is specified as the '-AF' model) and 5 studies of the Reveal LINQ (3 studies Reveal LINQ and 3 studies Reveal XT [note: one study included both devices]). All of these mixed population studies are either single-arm observational studies or they provide diagnostic test accuracy (DTA) data for the ICM using Holter monitoring as the reference standard.

CRYSTAL-AF was designed to measure diagnostic yield rather than accuracy, and none of the observational studies provided comparative DTA between an ICM and standard monitoring. Two studies modelled patient AF detection data from CRYSTAL-AF (Choe 2015[14]) and a large patient registry (Ziegler 2017[15]) with repeated iterations (10,000) to estimate the number of patients whose AF would not have been detected should an intermittent monitoring strategy have been used (based on assumption that ICM has 100% sensitivity). The studies found that the best performing intermittent monitoring strategy detected less than a third of AF detected by the ICM (ranging from around 3% for a single 24-hour Holter monitor to 30% with a quarterly 7-day Holter monitor). Studies reporting false positive rates as the proportion of episodes detected by ICM algorithm that were not subsequently verified by a clinician were highly dependent on the ICM model and device programme settings.

The results of the mixed population DTA studies suggested that the enhancements over time to the AF diagnosis algorithm in the Reveal XT and Reveal LINQ ICMs has improved the DTA (sensitivity and specificity) of the ICMs. However, it should be noted that these data are not exclusively in the CS population and the data in the XPECT and Reveal LINQ Usability studies used to make some of these comparisons are heterogeneous due to differences in the way in which the reference standard was applied (Holter monitoring 48 hours vs 24 hours, respectively) and differences in the patient populations (e.g. reasons for ICM insertion). Nonetheless these data suggest that the Reveal LINQ is likely to be as effective if not better at detecting AF as the Reveal XT (as the Reveal LINQ has fewer false positives and false negatives). Therefore, the AF detection rate from CRYSTAL-AF is potentially a conservative estimate for the Reveal LINQ given that it was the Reveal XT that was used in CRYSTAL-AF.

A naïve comparison of the sensitivity and specificity data from non-CS or mixed populations in the studies flagged of relevance by the respective companies of the Confirm DM2102 (older model of Confirm RX) and Reveal LINQ suggests they both have 100% sensitivity for AF detection although specificity varies (85.7% and 99.0%, respectively); the BioMonitor 2 [redacted] However, it should be noted that the studies are subject to clinical heterogeneity in terms of the patient populations, interventions and study designs as well as the reference standards. The device related performance of ICMs is known to be dependent on the patient population and the incidence rate of AF as well as the reference standard and therefore this naïve comparison should be interpreted with caution as these data are not necessarily reflective of the respective ICMs performance in CS patients. In addition, they do not necessarily reflect the performance of the current device model / software, for example, the Confirm RX data are based on an earlier model.

AF detection rate was the primary outcome in CRYSTAL-AF (at 6 months), and all 26 observational studies. In CRYSTAL-AF, AF detection was higher with the Reveal XT compared to conventional follow-up at all timepoints. At the primary 6-month analysis, AF had been detected in 19 (8.6%) patients with an ICM and 3 (1.4%) patients in the conventional follow-up group. By 36 months, the number of patients detected were 42 (19%) with ICM and 5 (2.3%) with conventional follow-up, demonstrating the continued and increasing benefit of ICM monitoring. AF detection rates reported at the primary follow-up (6 to 24 months) across the 26 observational studies were highly variable, ranging from 6.7%[50] (Reveal LINQ and XT at 12 months) to 40.9%[56] (Reveal XT unknown follow-up). These data demonstrate that even within a CS population AF detection rates are highly variable, and it is impossible to make any meaningful comparison between the observational studies and CRYSTAL-AF. Observational studies reporting AF detection at different lengths of follow-up indicate that a minority of patients are diagnosed within the first month (mostly in the region of 10% of those detected by a year), around 70–80% by 6 months, and a small number beyond a year of monitoring.[15, 39, 46, 60, 62] In comparison, the 36-month data from the ICM arm of CRYSTAL-AF show higher proportions of AF diagnosed at 1-month (19.0%) and beyond 12-months (31.0%) and a lower proportion at 6-months (45.2%) compared to the observational studies. Where described, all or most AF detected was asymptomatic and so would not likely have been picked up without continuous ICM monitoring.

Time to AF detection was significantly shorter for patients with the Reveal XT in CRYSTAL-AF compared with conventional follow-up at 6 months (HR 6.4, 95% CI: 1.9 to 21.7, p<0.001), 12 months (HR 7.3 95% CI: 2.6 to 20.8, p<0.001) and 36 months (HR 8.8, 95% CI: 3.5 to 22.2, p<0.001). The benefit of the ICM increased with length of follow-up because very few patients in the conventional follow-up arm were diagnosed, whereas detection increased steadily in the group with an ICM. The observational studies showed highly variable median time to first AF detection, ranging from 21 to 217 days (average follow-up between 7 and 20 months) nevertheless the results are still broadly consistent

with the results from CRYSTAL-AF, where median time to AF diagnosis was 41 days (Interquartile range [IQR]: 4 to 84) at 6-months, 84 days (IQR: 18 to 265) at 12 months and 8.4 months (IQR not reported) at 36 months follow-up.

Three of the observational studies, primarily of the Reveal LINQ, suggest the proportion of patients in which the ICM detected other non-AF cardiac arrhythmias is in the region of 10% and they consisted mainly of bigeminy, pause and bradycardia. No information was presented about whether and how the detected arrhythmias were treated to prevent related complications, and data on detection of other arrhythmias were not available from CRYSTAL-AF. The value of this additional potential benefit of the ICMs is therefore unclear.

In CRYSTAL-AF, more than 90% of patients diagnosed with AF in the ICM arm started an oral anticoagulant (OAC). Data were only available for the conventional follow-up group irrespective of AF diagnosis, indicating 8.3% were on an anticoagulant by 36 months (24 patients, whereas 5 had been diagnosed with AF by that timepoint). These data, along with the data from the observational studies, suggest that most patients with ICMs diagnosed with AF go on to receive long-term OAC. Time to anticoagulation and AEs related to anticoagulant use were not reported in any of the identified evidence. Subsequent stroke or TIA rates in CRYSTAL-AF were reported to be 5.0% in the ICM arm versus 8.2% in the conventional follow-up arm at 6 months, 6.8% vs 8.6% at 12-months, and 9.0% vs 10.9% at 36-months ($p>0.05$). None of these data suggest statistically significant stroke prevention benefits of the Reveal XT vs conventional monitoring, although there is a trend to fewer events in the ICM arm. It was unclear how many recurrent strokes occurred in patients diagnosed with AF or on OACs, and no studies reported other thromboembolisms or related morbidities.

In CRYSTAL-AF, the overall rate of SAEs was similar between groups (around 25–30%) but more patients in the ICM group had non-serious AEs compared with conventional follow-up (18.6% vs 4.1%, respectively). CRYSTAL-AF reported that 5 devices were removed due to infection or pocket erosion (2.4%) which was in line with the premature removal rates seen in the observational studies (0.9% to 5.7%). At 12 months follow-up, 3.4% of ICMs had been removed in CRYSTAL-AF, in contrast in Ritter 2013[60] (Reveal XT), where removal after AF detection was offered in addition to removal for other reasons, 30% of patients had their ICM device removed during the study (median follow-up time in the study for all patients was 13 months). In the absence of further data, it is unclear why the removal rate was so high in Ritter 2013. However, device-related adverse events (AEs) such as pain and infection were consistently low in CRYSTAL-AF, the single-arm observational studies and mixed population studies suggest that ICMs are generally well tolerated.

The EQ-5D data collected throughout CRYSTAL-AF were [redacted]

[redacted]

[redacted] CRYSTAL-AF did not collect any other ease of use or patient acceptability data, and information from the observational studies was anecdotal. However, company submissions and the EAG's clinical experts reported that the newer models of the ICMs (e.g. Reveal LINQ and Confirm RX) were easier to insert and were suitable for insertion by trained nurses and cardiac physiologists.

Eight ongoing studies of potential relevance were identified, although only five (3 RCTs and 2 observational studies) reported details of their status and the ICM being studied. None of the ongoing studies include BioMonitor 2-AF. The three ongoing RCTs all include the Reveal LINQ but only one RCT in a discrete CS population; this is a Canadian trial comparing the clinical and cost-effectiveness of the Reveal LINQ ICM with external loop recording in 300 CS patients, which is estimated to complete in December 2019 (PERDIEM; NCT02428140). There was only one ongoing study identified relating to the Confirm RX: the SMART registry, a post-approval study planning to recruit at least 2,000 patients with Confirm RX (NCT03505801) across multiple indications, but with a planned subgroup analysis for CS; completion is expected during 2019. These studies may help to provide further clinical data for these two ICMs, although they will not address the lack of comparative data between the ICMs and do not provide any comparative data for the Confirm RX or BioMonitor 2-AF against either Holter monitoring or other ICMs.

6.1.2 Economic

As mentioned previously, only one RCT (CRYSTAL-AF) was identified in the clinical effectiveness SLR, which assessed the impact of using an ICM compared with SoC, in a CS population where there was a suspicion of paroxysmal AF. CRYSTAL-AF reported data on AF detection rates for SoC and the Reveal XT device, which is an earlier model of the Reveal LINQ device. No data were obtained for BioMonitor 2-AF or Confirm RX. As such, a strong assumption was made in the economic analysis, based on clinical expert opinion, that the effectiveness of ICMs are similar and thus the detection rates obtained from CRYSTAL-AF were used for all the ICM devices under assessment.

The results from the *de novo* economic model were incremental cost effectiveness ratios (ICERs), also known as cost per QALY gained. The results of the pairwise analysis, that is each ICM device compared with SoC, demonstrate ICMs could be considered cost-effective at a £20,000 – £30,000 threshold compared with SoC. When each device is compared incrementally, BioMonitor 2-AF dominates Reveal LINQ and Confirm RX. However, the results for BioMonitor 2-AF and Confirm RX should be viewed with caution, as no data were available for any version of these devices in the CS population and as such there is substantial uncertainty in the results.

The EAG conducted various scenario and sensitivity analyses and found that no scenarios tipped the cost-effectiveness results above £30,000. However, the scenario which caused the most substantial change in the ICER for all three devices was reducing the time-horizon for ICM monitoring to 1 year. From the one-way sensitivity analysis, the key driver of the cost-effectiveness results relates to outcomes (that is total costs and QALYs) obtained from the long-term DOAC model. However, even with the implementation of results from the 2.5th percentile for the DOAC outcomes, the ICERs for all three devices still remained below £30,000.

The EAG conducted an SLR to identify any published economic evaluations of ICM devices for the detection of AF in a CS population which could be used to inform the current analysis. One study was identified that assessed the cost-effectiveness of the Reveal XT ICM (a predecessor of the Reveal LINQ) compared with SoC in a CS population from the UK perspective.

The model was developed using a Markov structure with three main health states for AF status: AF-free, AF-detected, and AF-undetected. Patients start in the AF-free state, from which they can move to AF-undetected or AF-detected at any given model cycle. From the AF-undetected state, patients can either remain or move to the AF-detected state and patients remain in the AF-detected state unless the patient experiences a subsequent cerebrovascular event or bleeding event. Detection rates of AF were based on data from the CRYSTAL-AF trial.

Results of the deterministic base case analysis showed that the ICM was £2,587 more expensive than SoC and provided a benefit of 0.21 QALY, resulting in an ICER of £12,175 per QALY gained. This ICER is similar to the EAG's ICER of the Reveal LINQ (£14,783). The EAG's short-term model was informed by the model structure used by Diamantopoulos *et al*. 2016, as it includes the health states of AF-detected and AF-undetected, with data informing the proportions in each health state per model cycle based on the results from CRYSTAL-AF.[77] However, the approach to modelling long-term outcomes for patients with AF who are either detected and on anticoagulation treatment or undetected and on antiplatelet treatment, is based on a published DOAC cost-effectiveness model.[86] Table 45 presents a comparison of the results produced by each model.

It can be seen that the EAG's model produces incremental costs which are slightly lower, and this can be attributed to a difference in the way monitoring costs were estimated. The EAG used data on the monitoring tests performed per person per year in the control arm of CRYSTAL-AF, obtained from Diamantopoulos *et al*. 2016, to estimate costs for SoC in the current analysis. Minor differences in SoC costs between the two models are attributed to a change in the NHS reference cost used in the analysis (£137 in 2016, increased to £141 in 2018).[77, 118] In addition, the EAG used a different methodology of calculating the per cycle cost of SoC, by calculating the cost per year of the monitoring tests and

dividing the costs by number of model cycles per year. In the Diamantopoulos *et al*. 2016 model, the per cycle probability of each test was estimated and used to weight the unit cost per cycle.

In addition, the incremental QALY gained for the EAG model is slightly higher. The EAG considers that the difference in QALYs can be attributed to the inclusion of myocardial infarction (MI) outcomes, as well as the impact of multiple events (e.g. stroke and ICH, etc) in the long-term DOAC model.

It should be noted that in the model by Diamantopoulos *et al*. 2016, the entire cohort (No AF, AF-detected and AF-undetected) is modelled for clinical outcomes. However, the EAG considered that clinically outcomes for the No AF cohort would be the same in each arm of the model (ICM and SoC), so essentially cancel out, hence a focus on the overall incremental costs and QALYs between the two models.

Table 45. Comparison of cost-effectiveness results for the Reveal devices

Intervention	Incremental costs	Incremental QALYs	ICER
Reveal XT vs SoC (Diamantopoulos et al.2016[77])	£2,587	0.15	£17,175
Reveal LINQ vs SoC	£2,[illegible]	[illegible]7	£14,983

Abbreviations: ICER, incremental cost effectiveness ratio; QALY, quality adjusted life year; SoC, standard of care.

Clinical expert opinion suggests that an additional benefit of ICMs devices is the ability to detect non-AF arrhythmias, potentially preventing other events. However, data on incidental findings from ICMs was only found in single arm observational studies, as previously mentioned and are of poor quality. As such, it is unclear how detection of other non-AF arrhythmias differs between standard care and ICMs and furthermore how a patient's treatment pathway changes. Therefore, understanding the differences in costs and benefits for incidental findings for ICMs is problematic. However, the EAG considers that if without an ICM some of these arrhythmias remain undetected, then the impact on the cost-effectiveness estimates would be favourable towards ICMs, but the size of the impact is difficult to determine.

6.2 Strengths and limitations

6.2.1 Clinical

Despite extensive evidence searches, the clinical evidence for this DAR is based primarily on a single RCT for the older Medtronic Reveal XT device. Clinical expert opinion and evidence from a mixed population suggest that the Reveal LINQ may have better sensitivity and specificity for detecting AF than the XT and is likely to lead to fewer complications due to its size, but there are no head to head clinical trials to confirm these findings in a CS population.[28] In addition, no clinical or DTA data suitable for inclusion was identified for the BioMonitor 2-AF or Confirm RX devices, despite widening the eligibility criteria to include low quality non-comparative observational studies. Data for the BioMonitor 2-AF or Confirm RX devices was limited to mixed population diagnostic accuracy and

single-arm observational studies submitted by the companies. The EAG considers it important to highlight that there are data to suggest that the performance (e.g. PPV and NPV) of AF detection with ICM devices, is dependent on the patient population, incidence rate of AF, the duration of monitoring and the type of AF.[1] The mixed population studies were also not obtained through the robust and comprehensive searches that would ideally be used in a systematic review due to time constraints and concerns about the applicability of their findings in a CS population. The mixed population studies may therefore be subject to study selection bias as well as clinical heterogeneity due to the variation in the patient populations of each of the studies and so the results of any comparison between them should be interpreted with caution.

A further limitation of the review of the clinical effectiveness of the ICMs was that no evidence was found for any of the devices for the outcomes of mortality, hospital and outpatient care for AF, related morbidities, AEs related to anticoagulation, and information about the ease of using each device for clinicians. Their acceptability to patients was anecdotal or from mixed population studies. There were also no DTA data identified for the latest versions of any of the ICMs in CS patients and the DTA data that were identified did not use a consistent reference standard across the ICMs which limits the ability to compare the accuracy of any model of the ICMs even in non-CS populations.

Nonetheless there were high quality clinical data available for one of the ICMs (Reveal LINQ) from an RCT of an earlier model (Reveal XT) compared to conventional follow-up and the EAG's clinical experts considered CRYSTAL-AF generally reflective of UK clinical practice. The minor differences highlighted by the EAG's clinical experts between UK clinical practice and the CRYSTAL-AF study were that all UK patients receive a transthoracic echo (TTE) and then a minority may not go on to receive a transoesophageal ECHO (TOE) before receiving an ICM. They also considered that some patients who were excluded from the trial due to a recent myocardial infarction (MI) might still be considered for an ICM. Patients in CRYSTAL-AF were also slightly younger than would be expected and all patients would be expected to be on an antiplatelet agent in UK clinical practice.

The open-label design of CRYSTAL-AF introduces potential bias because the outcome assessor was aware of the intervention assignment and so would be able to influence the ECG or other assessment of AF. However, the ICM arm was unlikely to be affected by bias relating to the outcome assessor as all episodes of AF that qualified for analysis were adjudicated by an independent committee. Despite this, the open label design potentially biases the results in favour of the ICM over conventional follow-up compared to a double-blind design. However, there may also have been bias in the detection of AF due to the 2-minute analysis window used by the ICM. This is because the threshold for AF diagnosis in CRYSTAL-AF was defined as being at least 30 seconds but the ICM uses an automatic algorithm for AF detection that is based on R-wave interval variability within 2-minute analysis windows.[36, 37] It is therefore possible that some AF episodes between 30 seconds and 2 minutes in duration may have been

missed in the ICM arm[36, 38] and this may bias the results of CRYSTAL-AF in favour of conventional follow-up.

Most patients in CRYSTAL-AF had received a median 23 hours of Holter monitoring (71.2%), but the remainder received a median of 68 hours of inpatient telemetry monitoring (29.7%), which is not in line with the NICE final scope which requested outpatient monitoring for a minimum of 24 hours. In addition, it means that within the CRYSTAL-AF study the baseline monitoring was not consistent and there were no subgroup data reported to demonstrate whether the split between inpatient and outpatient ECG monitoring in establishing the diagnosis of a CS were consistent between the ICM and comparator arm. The EAG is also unable to comment on whether subsequent AF detection or other long-term clinical outcomes are influenced by whether patients received inpatient or outpatient ECG monitoring in the workup to receiving their diagnosis of CS as this was beyond the scope of this review. There were also other issues with CRYSTAL-AF noted by the EAG and its clinical experts, such as baseline differences (e.g. in the proportion of patients with patent foramen ovale and history of prior stroke), crossover between groups, insertion delays (11.5%) and withdrawals, although they are unlikely to have had an important impact on the results of CRYSTAL-AF.

The use of ICMs in CS patients is for the detection of AF in CS patients that may otherwise go undetected or be detected much later in standard follow-up so that treatment can be started to help reduce the risk of subsequent stroke or TIA. However, the AF detection rate in the ICM studies varies considerably between and within the types of evidence considered by the EAG, (i.e. CRYSTAL-AF, uncontrolled observational studies, mixed population studies) The EAG recommends caution in drawing conclusions from naïve comparisons between the additional studies due to the number of uncontrolled variables and inherent biases of their single-arm design. Sources of heterogeneity that likely contribute to the differences in AF detection include the episode threshold used (varying from 10 seconds to 2 minutes), population characteristics (such as stroke risk score), time from stroke to ICM insertion, length of follow up, and method of AF adjudication. As such, the EAG considers CRYSTAL-AF to provide the most robust evidence available on which to base conclusions of ICM efficacy and safety in this review.

Finally, it should be noted that there is evidence from the observational studies that the ICMs also detected some non-AF cardiac arrhythmias, although no data on this additional potential benefit of ICMs was available from CRYSTAL-AF or in comparison to external ECG monitoring. It is also unclear whether detecting these additional arrhythmias led to any change in the management of the patients in which they were identified. The actual benefit to patients of detecting non-AF cardiac arrhythmias is therefore unclear and requires further research to establish if there is a true benefit.

6.2.2 Economic

One of the main strengths of the economic analysis is that outcomes data were available from an RCT on the effectiveness of an ICM compared to SoC in the CS population. As such, reliable estimates of AF detection rates for an ICM (Reveal XT in this case) and SoC were used to estimate the long-term outcomes, costs and benefits of patients on anticoagulation therapy versus those that receive antiplatelet therapy, using a previously developed and established economic model.

Even though the strength of the economic analysis is data being available for an ICM device in the correct target population, data were not available for each of the devices in the NICE final scope of this diagnostic assessment review (i.e. Reveal LINQ, BioMonitor 2-AF and Confirm RX). However, for the Reveal LINQ, this is less of a limitation, as the data used in the analysis is based on an earlier model, the Reveal XT. The manufacturer of the Reveal devices advised that with each iteration of the device, improvements are made to the algorithm to improve sensitivity and specificity, such that the Reveal LINQ has been estimated to have 100% sensitivity. Furthermore, the EAG's clinical experts advised that the detection rates for each of the devices will be at least as good as the rates seen in CRYSTAL-AF. Though, caution should be applied when interpreting the cost-effectiveness results for BioMonitor 2-AF and Confirm RX, as the strong assumption of equivalence with the Reveal LINQ is not based on evidence of the performance of any version of these devices in the CS population, resulting in substantial uncertainty around the ICER.

7 CONCLUSIONS

7.1 Clinical effectiveness

There is extremely limited diagnostic test accuracy (DTA) or comparative clinical effectiveness evidence for the use of ICMs in the detection of atrial fibrillation (AF), particularly in the cryptogenic stroke (CS) population. There is also evidence to suggest that the performance (e.g. PPV and NPV) of AF detection in ICM devices, is dependent on the patient population, incidence rate of AF, the duration of monitoring and the type of AF[1] thus limiting the use of data in non-CS populations to draw meaningful conclusions.

Only the Reveal LINQ device has good quality clinical evidence upon which it is possible to draw conclusions in the CS population, albeit using RCT data from an older model, the Reveal XT. The clinical data for the Reveal XT suggests that it is significantly more effective at detecting AF compared to conventional follow-up, although it is also associated with a low risk of device-related adverse events. Clinical expert opinion and evidence from a mixed population suggest that the Reveal LINQ, the newer device that is under investigation in this review, is likely to have better sensitivity and specificity for detecting AF compared to the XT and that it is also likely to be associated with fewer complications due to its smaller size. Nonetheless, there are no clinical studies to confirm these findings in a CS population.

The limited clinical data available for the Confirm RX and BioMonitor 2-AF suggest they both have good sensitivity and specificity for detecting AF, although it is not possible to draw conclusions with how they perform in CS patients or how any of the devices compare with each other. [redacted]. As a rapidly evolving clinical diagnostic field, it makes it extremely difficult to enable any direct comparison between the diagnostic accuracy of the three devices (Reveal LINQ, BioMonitor 2-AF and Confirm RX). The absence of comparative clinical effectiveness data also limits the ability to draw any meaningful conclusions on the potential patient benefit of the ICMs but CRYSTAL-AF and the other clinical data for the Reveal devices suggest that cases of AF in CS patients that may otherwise go undetected are more likely to be identified using the Reveal LINQ than with no further monitoring.

7.2 Cost-effectiveness

The Evidence Assessment Group's (EAG's) economic evaluation assessed the cost-effectiveness of implantable cardiac monitors (ICMs) compared with no further monitoring, to detect AF in people who have had a CS and have received at least 24 hours of non-invasive external cardiac monitoring. The devices included in the scope of this assessment were the Reveal LINQ, BioMonitor 2-AF and Confirm

RX. As mentioned previously, clinical effectiveness data, in the form of AF detection rates, were only available for the Reveal XT device from the CRYSTAL-AF randomised controlled trial (RCT). As such, the entire economic analysis is based on the detection rates obtained from CRYSTAL-AF, under the assumption that all the devices are likely to have similar efficacy. Based on this strong assumption, the economic analysis found ICMs could be considered cost-effective at a £20,000 – £30,000 threshold compared with SoC. When each device is compared incrementally, BioMonitor 2-AF dominates Reveal LINQ and Confirm RX. However, the results for BioMonitor 2-AF and Confirm RX should be viewed with caution, as no data were available for any version of these devices in the CS population and as such there is substantial uncertainty in the results.

7.3 Suggested research priorities

High quality head-to-head clinical trials of the Reveal LINQ, BioMonitor 2-AF and Confirm RX in CS patients are required to enable a direct comparison between the ICMs in terms of clinical effectiveness. In addition, DTA studies for each of the three ICMs (Reveal LINQ, BioMonitor 2-AF and Confirm RX) using a consistent reference standard (which would ideally be a minimum of 24 hours of external ECG monitoring) are required in a CS population to both confirm the diagnostic accuracy of the ICM devices in detecting AF in CS patients and to also enable a robust comparison of diagnostic accuracy between the ICMs. The key important factor in any clinical or diagnostic studies of the ICMs will be to ensure that they use the latest model and version of the device software to ensure that they provide the most clinically relevant data, [redacted]

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9 APPENDICES

9.1 Appendix 1: PRISMA DTA checklist

Section/topic	#	PRISMA-DTA Checklist item	Reported on page #
TITLE/ABSTRACT			
Title	1	Identify the report as a systematic review (+/- meta-analysis) of diagnostic test accuracy (DTA) studies.	i
Abstract	2	Abstract: See PRISMA-DTA for abstracts.	iv-v
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	1-12
Clinical role of index test	D1	State the scientific and clinical background, including the intended use and clinical role of the index test, and if applicable, the rationale for minimally acceptable test accuracy (or minimum difference in accuracy for comparative design).	3-12
Objectives	4	Provide an explicit statement of question(s) being addressed in terms of participants, index test(s), and target condition(s).	13
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	13
Eligibility criteria	6	Specify study characteristics (participants, setting, index test(s), reference standard(s), target condition(s), and study design) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	13-16
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	16-17
Search	8	Present full search strategies for all electronic databases and other sources searched, including any limits used, such that they could be repeated.	146-148
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	17 and 54-55
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	17
Definitions for data extraction	11	Provide definitions used in data extraction and classifications of target condition(s), index test(s), reference standard(s) and other characteristics (e.g. study design, clinical setting).	13-17

Risk of bias and applicability	12	Describe methods used for assessing risk of bias in individual studies and concerns regarding the applicability to the review question.	17-18
Diagnostic accuracy measures	13	State the principal diagnostic accuracy measure(s) reported (e.g. sensitivity, specificity) and state the unit of assessment (e.g. per-patient, per-lesion).	18
Synthesis of results	14	Describe methods of handling data, combining results of studies and describing variability between studies. This could include, but is not limited to: a) handling of multiple definitions of target condition. b) handling of multiple thresholds of test positivity, c) handling multiple index test readers, d) handling of indeterminate test results, e) grouping and comparing tests, f) handling of different reference standards	18
Meta-analysis	D2	Report the statistical methods used for meta-analyses, if performed.	Not applicable
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	Not applicable
RESULTS			
Study selection	17	Provide numbers of studies screened, assessed for eligibility, included in the review (and included in meta-analysis, if applicable) with reasons for exclusions at each stage, ideally with a flow diagram.	19-22 and 54-60
Study characteristics	18	For each included study provide citations and present key characteristics including: a) participant characteristics (presentation, prior testing), b) clinical setting, c) study design, d) target condition definition, e) index test, f) reference standard, g) sample size, h) funding sources	22-28, 40-44, And 54-62
Risk of bias and applicability	19	Present evaluation of risk of bias and concerns regarding applicability for each study.	28-29, and 164-168
Results of individual studies	20	For each analysis in each study (e.g. unique combination of index test, reference standard, and positivity threshold) report 2x2 data (TP, FP, FN, TN) with estimates of diagnostic accuracy and confidence intervals, ideally with a forest or receiver operator characteristic (ROC) plot.	Not applicable
Synthesis of results	21	Describe test accuracy, including variability; if meta-analysis was done, include results and confidence intervals.	Not applicable
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression; analysis of index test: failure rates, proportion of inconclusive results, adverse events).	Not applicable
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence.	117-121
Limitations	25	Discuss limitations from included studies (e.g. risk of bias and concerns regarding applicability) and from the review process (e.g. incomplete retrieval of identified research).	123-125
Conclusions	26	Provide a general interpretation of the results in the context of other evidence. Discuss implications for future research and clinical practice (e.g. the intended use and clinical role of the index test).	127-128
FUNDING			
Funding	27	For the systematic review, describe the sources of funding and other support and the role of the funders.	Ii

Abbreviations: DTA, diagnostic test accuracy; FN, false negative; FP, false negative; ROC, receiver operator characteristic; TN, true negative; TP, true positive.
Adapted From: McInnes MDF, Moher D, Thombs BD, McGrath TA, Bossuyt PM, The PRISMA-DTA Group (2018). Preferred Reporting Items for a Systematic Review and Meta-analysis of Diagnostic Test Accuracy Studies: The PRISMA-DTA Statement. JAMA. 2018 Jan 23;319(4):388-396. doi: 10.1001/jama.2017.19163.

9.2 Appendix 2: PRISMA DTA for abstracts checklist

Section/topic	#	PRISMA-DTA for Abstracts Checklist item	Reported on page #
TITLE and PURPOSE			
Title	1	Identify the report as a systematic review (+/- meta-analysis) of diagnostic accuracy (DTA) studies.	iv
Objectives	2	Indication the research question, including components such as participants, index test, and target conditions.	iv
METHODS			
Eligibility criteria	3	Include study characteristics used as criteria for eligibility.	iv
Information sources	4	List the key databases searched and the search dates.	iv
Risk of bias and applicability	5	Indicate the methods of assessing risk of bias and applicability.	iv
Synthesis of results	A1	Indicate the methods for the data synthesis.	iv
RESULTS			
Included studies	6	Indicate the number and type of included studies and the participants and relevant characteristics of the studies (including the reference standard).	iv
Synthesis of results	7	Include the results for the analysis of diagnostic accuracy, preferably indicating the number of studies and participants. Describe test accuracy including variability; if meta-analysis was done, include summary results and confidence intervals.	Not Applicable
DISCUSSION			
Strengths and limitations	9	Provide a brief summary of the strengths and limitations of the evidence.	v
Interpretation	10	Provide a general interpretation of the results and the important implications.	v
OTHER			
Funding	11	Indicate the primary source of funding for the review.	v
Registration	12	Provide the registration number and the registry name.	v
Abbreviations: DTA, diagnostic test accuracy. Adapted From: McInnes MDF, Moher D, Thombs BD, McGrath TA, Bossuyt PM, The PRISMA-DTA Group (2018). Preferred Reporting Items for a Systematic Review and Meta-analysis of Diagnostic Test Accuracy Studies: The PRISMA-DTA Statement. JAMA. 2018 Jan 23;319(4):388-396. doi: 10.1001/jama.2017.19163.			

9.3 Appendix 3: Clinical search strategies

Table 46. MEDLINE search for clinical evidence

Ovid MEDLINE(R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Daily and Versions(R) <1946 to September 12, 2018> searched on 13 September 2018		
#	**Terms**	**Hits**
1	(Reveal adj2 LINQ$).tw.	35
2	(Reveal adj2 XT$).tw.	45
3	BioMonitor$.tw.	6297
4	(Confirm adj2 RX$).tw.	2
5	(SJM adj2 Confirm$).tw.	1
6	(insertable adj3 cardiac adj3 monitor$).tw.	80
7	(implantable adj3 cardiac adj3 monitor$).tw.	131
8	(insertable adj3 loop adj3 recorder$).tw.	35
9	(implantable adj3 loop adj3 recorder$).tw.	458
10	(ICM or ICMs).tw.	3782
11	or/1-10	10693
12	exp STROKE/	116275
13	(stroke$ or apoplexy$ or CVA or CVAS).tw.	218619
14	Ischemic Attack, Transient/	19490
15	(transient adj3 (ischemi$ or ischaemi$) adj3 attack$).tw.	12728
16	(TIA or TIAs or mini-stroke or ministroke or mini-strokes or ministrokes).tw.	7998
17	or/12-16	265082
18	11 and 17	137
19	animals/ not humans/	4461144
20	18 not 19	128
21	limit 20 to english language	123

Table 47. EMBASE search for clinical evidence

Embase <1974 to 2018 September 12> searched on 13 September 2018		
#	**Terms**	**Hits**
1	(Reveal adj2 LINQ$).tw.	96
2	(Reveal adj2 XT$).tw.	185
3	BioMonitor$.tw.	7678
4	(Confirm adj2 RX$).tw.	4
5	(SJM adj2 Confirm$).tw.	2
6	(insertable adj3 cardiac adj3 monitor$).tw.	187
7	(implantable adj3 cardiac adj3 monitor$).tw.	272
8	(insertable adj3 loop adj3 recorder$).tw.	51
9	(implantable adj3 loop adj3 recorder$).tw.	977
10	(ICM or ICMs).tw.	5864
11	implantable cardiac monitor/	11841
12	reveal.dv.	362
13	or/1-12	26150
14	exp cerebrovascular accident/	172589
15	(stroke$ or apoplexy$ or CVA or CVAS).tw.	341320

16	transient ischemic attack/	33423
17	(transient adj3 (ischemi$ or ischaemi$) adj3 attack$).tw.	19087
18	(TIA or TIAs or ministroke or mini-stroke or ministrokes or mini-strokes).tw.	17067
19	or/14-18	404456
20	13 and 19	791
21	nonhuman/ not human/	4201609
22	20 not 21	771
23	limit 22 to english language	758

Table 48. Cochrane Library search for clinical evidence

Cochrane Central Register of Controlled Trials (CENTRAL) and Cochrane Database of Systematic Reviews (CDSR) searched 13 September 2018		
#	**Terms**	**Hits**
1	(Reveal near/2 LINQ*):ti,ab,kw	14
2	(Reveal near/2 XT*):ti,ab,kw	27
3	BioMonitor*:ti,ab,kw	40
4	(Confirm near/2 RX*):ti,ab,kw	0
5	(SJM near/2 Confirm*):ti,ab,kw	1
6	(insertable near/3 cardiac near/3 monitor*):ti,ab,kw	31
7	(implantable near/3 cardiac near/3 monitor*):ti,ab,kw	254
8	(insertable near/3 loop near/3 recorder*):ti,ab,kw	1
9	(implantable near/3 loop near/3 recorder*):ti,ab,kw	101
10	ICM:ti,ab,kw	228
11	(OR #1-#10)	565
12	MeSH descriptor: [Stroke] explode all trees	7713
13	(stroke* or apoplexy* or CVA or CVAS):ti,ab,kw	42050
14	MeSH descriptor: [Ischemic Attack, Transient] explode all trees	645
15	(transient near/3 (ischemi* or ischaemi*) near/3 attack*):ti,ab,kw	2397
16	(TIA or TIAs or ministroke or mini-stroke or ministrokes or mini-strokes):ti,ab,kw	1185
17	(OR #12-#16)	43095
18	#11 and #17	72

Table 49. Centre for Reviews and Dissemination (CRD) search for clinical evidence

Database of Abstracts of Reviews of Effects (DARE) and Health Technology Assessment (HTA) database searched on 13 September 2018		
#	**Terms**	**Hits**
1	(Reveal NEAR2 LINQ*)	0
2	(Reveal NEAR2 XT*)	0
3	(BioMonitor*)	0
4	(Confirm NEAR2 RX*)	0
5	(SJM NEAR2 Confirm*)	0
6	(insertable NEAR3 cardiac NEAR3 monitor*)	0
7	(implantable NEAR3 cardiac NEAR3 monitor*)	0
8	(insertable NEAR3 loop NEAR3 recorder*)	5
9	(implantable NEAR3 loop NEAR3 recorder*)	9
10	(ICM*)	12
11	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10	25

12	MeSH DESCRIPTOR Stroke EXPLODE ALL TREES	1354
13	(stroke* or apoplexy* or CVA or CVAS)	3165
14	MeSH DESCRIPTOR Ischemic Attack, Transient EXPLODE ALL TREES	89
15	(transient NEAR3 (ischemi* or ischaemi*) NEAR3 attack*)	243
16	(TIA or TIAs or ministroke or mini-stroke or ministrokes or mini-strokes)	86
17	#12 OR #13 OR #14 OR #15 OR #16	3202
18	#11 AND #17	3
19	(#18) IN DARE, HTA	1

9.4 Appendix 4: Clinical excluded studies

Study/reference	Reason for exclusion
Assar M, Thijs V, Brachmann J, Morillo C, Passman R, Sanna T, et al. Predictors for detection of atrial fibrillation in cryptogenic stroke patients: Insights from insertable cardiac monitor data in the CRYSTAL AF study. Eur Heart J 2014; 1): 1109	No outcome data: CRYSTAL-AF, no unique data
Bernstein RA, Di Lazzaro V, Rymer MM, Passman RS, Brachmann J, Morillo CA, et al. Infarct topography and detection of atrial fibrillation in cryptogenic stroke: The CRYSTAL-AF study. Stroke Conference: American Heart Association/American Stroke Association 2015; 46.	No outcome data: CRYSTAL-AF, no unique data
Bernstein RA, Di Lazzaro V, Rymer MM, Passman RS, Brachmann J, Morillo CA, et al. Infarct Topography and Detection of Atrial Fibrillation in Cryptogenic Stroke: Results from CRYSTAL AF. Cerebrovasc Dis 2015; 40: 91-6.	No outcome data: CRYSTAL-AF, no unique data
Diamantopoulos A, Sawyer LM, Lip GYH, Witte KK, Reynolds MR, Fauchier L, et al. Cost-effectiveness of an insertable cardiac monitor to detect atrial fibrillation in patients with cryptogenic stroke. Int J Stroke 2016; 11: 302-12	No outcome data: CRYSTAL-AF, no unique data
Passman RS, Koehler JL, Ziegler PD. Atrial fibrillation begets atrial fibrillation in cryptogenic stroke patients: Results from the crystal-AF trial. Circulation Conference: American Heart Association's 2014; 130.	No outcome data: CRYSTAL-AF, no unique data
Passman RS, Rymer MM, Liu S, Ziegler PD. Incidence of atrial fibrillation among patients with an embolic stroke of undetermined source. Stroke Conference: American Heart Association/American Stroke Association 2017; 48.	No outcome data: CRYSTAL-AF, no unique data
Passman RS, Ziegler PD, Kwong C, Crawford MH, Koehler JL, Zhao SX. Validation of a clinical risk score for predicting atrial fibrillation in cryptogenic stroke patients with insertable cardiac monitors: insights from the crystal AF study. Stroke Conference: American Heart Association/American Stroke Association 2018; 49.	No outcome data: CRYSTAL-AF, no unique data
Sanna T, Bernstein R, Brachmann J, Diener HC, Di Lazzaro V, Morillo C, et al. Detection rates in patients with cryptogenic stroke: a comparison of the crystal-AF and embrace trials. European stroke journal 2016; Conference: 2nd European Stroke Organisation Conference, ESOC 2016. Spain. 1: 651	No outcome data: CRYSTAL-AF, no unique data
Thijs V, Brachmann J, Morillo C, Passman R, Sanna T, Bernstein R. Predictors for detection of atrial fibrillation in cryptogenic stroke patients: insights from insertable cardiac monitor data in the CRYSTAL AF study. Int J Stroke 2014; 9: 25.	No outcome data: CRYSTAL-AF, no unique data
Verma N, Ziegler PD, Liu S, Passman RS. Incidence of atrial fibrillation among patients with an embolic stroke of undetermined source: Insights from insertable cardiac monitors. Int J Stroke 2018: 1747493018798554.	No outcome data: CRYSTAL-AF, no unique data
Lambert AT, Ratajczek-Tretel B, Russell D, Halvorsen B, Sandset EC, Naess H, et al. Atrial fibrillation in cryptogenic stroke-the nordic atrial fibrillation and stroke study (nor-fib). European Stroke Journal 2017; 2 (1 Supplement 1): 336.	Ongoing study
Tancin Lambert A, Kong XY, Ratajczak-Tretel B, Bente Evy H, Skjelland M, Russell D, et al. Atrial fibrillation in cryptogenic stroke the nordic atrial	Ongoing study

fibrillation and stroke study (nor-fib. European Stroke Journal 2018; 3 (1 Supplement 1): 613-4.	
Tancin Lambert A, Kong XY, Ratajczak-Tretel B, Halvorsen B, Russell D, Bjerkeli V, et al. Atrial fibrillation in cryptogenic stroke: The Nordic Atrial Fibrillation and Stroke Study (NOR-FIB). Eur J Neurol 2018; 25 (Supplement 2): 60.	Ongoing study
Ratajczak-Tretel B, Aamodt AH, Johansen H, Atar D, Halvorsen B, Sandset EC, et al. Cryptogenic stroke in - The nordic and stroke study (NOR-FIB). European Stroke Journal 2016; 1 (1 Supplement 1): 778.	Ongoing study
Johansen H, Aamodt AH, Ratajczak-Tretel B, Atar D, Halvorsen B, Naess H, et al. Cryptogenic stroke in atrial fibrillation-the nordic atrial fibrillation and stroke study (NOR-FIB). European journal of neurology 2016; 23: 356-7.	Ongoing study
Toni D, Lorenzano S, Strano S. Detection of silent atrial fibrillation after ischemic stroke (SAFFO) guided by implantable loop recorder. A multicentre Italian trial based on neurocardiology unit network. Int J Stroke 2015; 10: 274.	Ongoing study
Toni D, Lorenzano S, Strano S. Detection of Silent Atrial Fibrillation aFter Ischemic StrOke (SAFFO) guided by implantable loop recorder: Multicentre Italian trial based on stroke unit network with paired cardio-arrhythmology units (Italian Neurocardiology Unit Network). Int J Stroke 2016; 11: 361-7.	Ongoing study
Ghrooda EM, Dobrowolski P, Basir G, Yaseen I, Khan N, Ahmad A, et al. Paroxysmal atrial fibrillation is common in patients with defined etiology for stroke: Prolonged monitoring of cardiac rhythm for detection of atrial fibrillation after a cerebral ischemic event (PEAACE) study. Stroke Conference 2014; 45.	"Wrong intervention: prolonged monitoring but not ICM
Dion F, Bonnaud I, Fauchier L, Friocourt P, Bonneau A, Poret P, et al. Unexpected low prevalence of atrial fibrillation in cryptogenic ischemic stroke: A prospective continuous monitoring study. Archives of Cardiovascular Diseases Supplements 2010; 2 (1): 73.	Wrong intervention: Reveal Plus 9526 with no AF detection algorithm
Dion F, Saudeau D, Bonnaud I, Friocourt P, Bonneau A, Poret P, et al. Unexpected low prevalence of atrial fibrillation in cryptogenic ischemic stroke: a prospective study. J Interv Card Electrophysiol 2010; 28: 101-7.	Wrong intervention: Reveal Plus 9526 with no AF detection algorithm
De Lera M, Bulnes LR, Cortijo E, Bombin S, Calleja AI, Garcia-Moran E, et al. Predictors of arrhytmic load in patients with cryptogenic stroke and covertatrial fibrillation detected by implantable loop recorders. European Stroke Journal 2017; 2 (1 Supplement 1): 115.	Wrong intervention: unknown device - abstract only
De Lera M, Largaespada G, Cortijo E, Sandin M, Calleja A, Garcia E, et al. Predictors of higher arrhytmic load in patients with cryptogenic stroke and covert detected by implantable loop recorders. European Stroke Journal 2016; 1 (1 Supplement 1): 641-2.	Wrong intervention: unknown device - abstract only
Evans N, Sobala C, Belham M, Pugh P, Warburton E. Age is an independent predictor of paroxysmal atrial fibrillation in embolic strokes of undetermined source. Int J Stroke 2016; 11 (4 Supplement 1): 9.	Wrong intervention: unknown device - abstract only
Giobbe D, Balducci A, Paglia G, Giobbe ML, Budano C, Alunni GL, et al. Detection of paroxysmal atrial fibrillation by implantable loop recorder in cryptogenic stroke. Eur J Neurol 2016; 2): 138.	Wrong intervention: unknown device - abstract only
Goetz N, Poli S, Haertig F, Bauer A, Duckheim M, Eick C, et al. Insertable cardiac monitors for detection of atrial fibrillation in patients with embolic stroke of undetermined source (ESUS) selected by risk factors. Eur Heart J 2015; 1): 988.	Wrong intervention: unknown device - abstract only
Heinrich J, Feil K, Kupper C, Wollenweber F, Sinner M, Kaab S, et al. Follow up in embolic stroke of undetermined source: New clinical treatment algorithm including longterm cardial monitoring and PFO closure in a prospective open-label observational study. European Stroke Journal 2018; 3 (1 Supplement 1): 317-8.	Wrong intervention: unknown device - abstract only
Jurjans K, Skarsta L, Miglane E, Millers A, Priede Z. Our experience of using implantable loop recorder devices to specify stroke etiology in Pauls Stradins clinical university hospital, Riga, Latvia from 2014 to 2017. Eur J Neurol 2018; 25 (Supplement 2): 219.	Wrong intervention: unknown device - abstract only

Kalejs O, Jurjans K, Jubele K, Kamzola G, Nikrus N, Nesterovics N, et al. Results of monitoring large artery cryptogenic embolic stroke survivors using implantable loop recorder device. Europace 2016; 18 (Supplement 1): i111.	Wrong intervention: unknown device - abstract only
Llerena Butron SI, San Roman Calvar JA, Sandin Fuentes M, Bulnes Garcia LR, Largaespada Perez G, Bombin Gonzalez S, et al. Implantable loop recorders and short episodes of rapid atrial rate: Relevant in the medical work-up of patients with embolic strokes of unknown source. Europace 2017; 19 (Supplement 3): iii143-iii4.	Wrong intervention: unknown device - abstract only
Llerena Butron SI, Sandin Fuentes M, Bombin Gonzalez S, Bulnes Garcia LR, Largaespada Perez G, Gomez Salvador I, et al. Rapid atrial rate and implantable loop recorders for embolic strokes of unknown source: Report of more than 2-years follow up in a single centre. Eur Heart J 2017; 38 (Supplement 1): 165.	Wrong intervention: unknown device - abstract only
Makimoto H, Kurt M, Gliem M, Jander S, Schmidt J, Blockhaus C, et al. High incidence of occult atrial fibrillation by insertable cardiac monitor in patients with cryptogenic stroke in the territory of vertebrobasilar system. Eur Heart J 2016; 37 (Supplement 1): 275.	Wrong intervention: unknown device - abstract only
Makimoto H, Kurt M, Gliem M, Lee JI, Schmidt J, Muller P, et al. High Incidence of Atrial Fibrillation After Embolic Stroke of Undetermined Source in Posterior Cerebral Artery Territory. Journal of the American Heart Association 2017; 6: 29.	Wrong intervention: unknown device - abstract only
Marzella F, Salek F, Calkins L, Welton M, Abou-Eid M, Choi M. Evaluation of medication therapy in cryptogenic stroke patients diagnosed with atrial fibrillation following loop recorder implantation. J Am Pharm Assoc (2003) 2018; 58 (3): e15.	Wrong intervention: unknown device - abstract only
Navarro Perez MP, Perez Lazaro C, Pelegrin Diaz J, Rodrigo Trallero G, Sanchez Val A, Garces Anton E, et al. Paroxysmal atrial fibrillation detection after cryptogenic stroke: A single center experience. European Stroke Journal 2018; 3 (1 Supplement 1): 460.	Wrong intervention: unknown device - abstract only
Noone I, Meagher MK, Mc Creery C, Cassidy T. The role of loop recorders in Embolic Stroke of Uncertain Source (ESUS). European Stroke Journal 2016; 1 (1 Supplement 1): 16.	Wrong intervention: unknown device - abstract only
Rafanelli M, Ceccofiglio A, Tesi F, Toffanello G, Chisciotti VM, Rivasi G, et al. Implantable loop recorder: A syncope unit experience. Eur Geriatr Med 2015; 1): S73.	Wrong intervention: unknown device - abstract only
Rafanelli M, Ceccofiglio A, Tesi F, Toffanello G, Chisciotti VM, Rivasi G, et al. Implantable loop recorder: A syncope unit experience. Europace 2015; 3): iii50.	Wrong intervention: unknown device - abstract only
Ramaiah G, Salahuddin H, Espinosa A, Zaidi S, Jumaa M, Tietjen G. Left atrial size is not a predictor for detection of atrial fibrillation in cryptogenic stroke. Stroke Conference: American Heart Association/American Stroke Association 2018; 49.	Wrong intervention: unknown device - abstract only
Ricci BA, Chang AD, Hemendinger M, Dakay K, Cutting SM, Burton T, et al. A simple score that predicts paroxysmal atrial fibrillation on outpatient cardiac monitoring after embolic stroke of unknown source. Stroke Conference: American Heart Association/American Stroke Association 2018; 49.	Wrong intervention: unknown device - abstract only
Scacciatella P, Jorfida M, Omede P, Budano C, Castagno D, Zema D, et al. Insertable cardiac monitor in older patients candidates to percutaneous PFO closure. Preliminary results of a perspective registry study. Eur Heart J 2017; 38 (Supplement 1): 1024-5.	Wrong intervention: unknown device - abstract only
Seiler A, Allred J, Biby S, Sethi P. Surveillance for atrial fibrillation in patients with cryptogenic stroke using an implantable loop recorder in a community hospital setting: Real world validation of Crystal AF. Eur J Neurol 2015; 1): 98.	Wrong intervention: unknown device - abstract only
Seiler A, Biby S, Sethi P, Allred J. Use of dedicated protocol and implantable loop recorder to evaluate for atrial fibrillation in cryptogenic stroke patients: Real world validation of crystal AF. Circulation Conference: American Heart Association's 2015; 132.	Wrong intervention: unknown device - abstract only

Sethi P, Allred J, Seiler A, Biby S. Surveillance for atrial fibrillation in patients with cryptogenic stroke using an implantable loop recorder in a community hospital setting : Real world validation of crystal atrial fibrillation trial. Cerebrovasc Dis 2015; 2): 30.	Wrong intervention: unknown device - abstract only
Sethi P, Biby S, Allred J, Seiler A, Xu J. Surveillance for atrial fibrillation in patients with cryptogenic stroke using an implantable loop recorder during an inpatient hospitalization in a community hospital setting. European Stroke Journal 2017; 2 (1 Supplement 1): 115-6.	Wrong intervention: unknown device - abstract only
Sethi P, Biby S, Xu J, Seiler A, Allred J. Lowincidence ofatrial fibrillation in recurrent strokes in a cohort of cryptogenic stroke patients on long term cardiac monitoring. European Stroke Journal 2018; 3 (1 Supplement 1): 459.	Wrong intervention: unknown device - abstract only
Summo CS, Riesinger L, Mehr M, Siebermair J, Fichtner S, Schuhmann C, et al. Potential role of PFO in patients after an esus eventand with implantable cardiac monitor. J Interv Card Electrophysiol 2018; 51 (1 Supplement 1): S41-S2.	Wrong intervention: unknown device - abstract only
Ungar A, Rieger G, De Melis M, Mangoni L, Reinke F, Bucx J, et al. Incidence of atrial fibrillation and medication changes in cryptogenic stroke patients with an implantable loop recorder. Cerebrovasc Dis 2014; 37 (Supplement 1): 517.	Wrong intervention: unknown device - abstract only
Ungar A, Rieger G, Puererfellner H, Duru F, De Melis M, Bonizzi T, et al. Incidence of atrial fibrillation and subsequent medication changes in cryptogenic stroke patients with an implantable loop recorder. Eur Heart J 2014; 1): 292.	Wrong intervention: unknown device - abstract only
Ungar A, Rieger G, West T, Purerfellner H, Bucx J, Topper RF, et al. Atrial fibrillation and treatment changes in cryptogenic stroke patients with an implantable loop recorder for continuous cardiac rhythm monitoring. Eur Heart J 2013; 1): 62.	Wrong intervention: unknown device - abstract only
Venzo S, Rafanelli M, Schipani E, Ceccofiglio A, Tesi F, Rivasi G, et al. Implantable loop recorder in cryptogenic stroke: A cardio-geriatric experience. Eur Geriatr Med 2016; 7 (Supplement 1): S169-S70.	Wrong intervention: unknown device - abstract only
Verbeet T, Castro J, Morissens M, Arbraud C, Knecht S. The Belgian Implantable Loop Recorder Database: Analysis of three years of activity. Acta Cardiol 2012; 67 (1): 115.	Wrong intervention: unknown device - abstract only
Weinstock J, Marks D, Andriulli JA, Collins J, Ortman ML, Russo AM. Subclinical atrial fibrillation identified in the setting of cryptogenic stroke: A real-world experience. Heart Rhythm 2018; 15 (5 Supplement 1): S71-S2.	Wrong intervention: unknown device - abstract only
Yasmeh B, Liu Z, Verdick C, DeMazumder D, Rajsheker S, Costea A. Clinical utility of implantable loop recorders for the diagnosis of paroxysmal atrial fibrillation in patients with cryptogenic stroke-a single large center retrospective analysis. Heart Rhythm 2018; 15 (5 Supplement 1): S72.	Wrong intervention: unknown device - abstract only
Yeneneh B, Munro J, Wilansky S, Behai J, Scott L. Predictors of atrial fibrillation detection in patients with implantable loop recorders for cryptogenic stroke. Europace 2017; 19 (Supplement 3): iii234.	Wrong intervention: unknown device - abstract only
Zeitzen T, Chan W. Loop recorder implantation: Keeping up with the guidelines with a single-centre experience. Heart Lung and Circulation 2017; 26 (Supplement 2): S185.	Wrong intervention: unknown device - abstract only
Rodriguez-Campello A, Cuadrado-Godia E, Ois A, Giralt-Steinhauer E, Jimenez-Conde J, Puig-Pijoan A, et al. Early detection of atrial fibrillation in embolic stroke of unknown origin (ESUS). Int J Stroke 2015; 2): 268-9.	Wrong intervention: unknown device - abstract only
Rodríguez-Campello A., Giralt-Steinhauer E., Ois A., Jiménez-Conde J., Avellaneda-Gómez C., Serra-Martínez M., Gómez-González A., Romeral G., Benito B., Vallès E., Ble M., Martí-Amor J., Roquer J., Cuadrado-Godia E. Atrial fibrillation detection and stroke recurrence in patients with early insertable cardiac monitor. A case-control study. European Stroke Journal (2018) 3:1 Supplement 1 (459).	Wrong intervention: unknown device - abstract only
Benito B, Valles E, Cuadrado E, Cabrera S, Ramos P, Ois A, et al. Improving AF detection in patients with cryptogenic stroke. Insights from a prospective cohort with insertable cardiac monitor. Eur Heart J 2015; 1): 164-5.	Wrong intervention: unknown device - Medtronic not involved in study

Benito B, Valles E, Cuadrado E, Ramos P, Cabrera S, Ois A, et al. Improving af detection in patients with cryptogenic stroke. Learning concepts from a prospective cohort with insertable cardiac monitor. Europace 2015; 3): iii205.	Wrong intervention: unknown device - Medtronic not involved in study
Maddox S, Hoskins M, Lloyd M, Mengistu A, Rangaraju S, Henriquez L, et al. High false positive rates of atrial fibrillation detection among stroke patients who receive medtronic implantable loop recorders. Stroke Conference: American Heart Association/American Stroke Association 2018; 47.	Wrong intervention: unknown device - Medtronic suggest Reveal XT and Non-TruRhythm Reveal LINQ based on timing/location of study.
Giralt-Steinhauer E, Cuadrado-Godia E, Soriano-Tarraga C, Ois A, Jimenez-Conde J, Rodriguez-Campello A, et al 2015 New-onset paroxysmal atrial fibrillation diagnosis in ischemic stroke patients Eur Neurol 74: 211-7	Wrong intervention: unknown device - not identified by companies and no reply from study authors
Miller DJ. Randomised controlled trial: Prolonged cardiac monitoring after cryptogenic stroke superior to 24 h ECG in detection of occult paroxysmal atrial fibrillation. Evid Based Med 2014; 19: 235	Wrong intervention/not comparison of interest/wrong publication type
Kanters, Tim A, et al. Cost comparison of two implantable cardiac monitors in two different settings: Reveal XT in a catheterization laboratory vs. Reveal LINQ in a procedure room. Europace (2015): euv217	Wrong outcome: cost comparison, no clinical outcomes
Gianatasio RM, Shams T, Aashish A, Abrol R, Thambidorai S, Janardhan V. Implanting longterm cardiac monitors by stroke interventionalists in a collaborative cryptogenic stroke program. Interventional Neurology 2016; 5 (Supplement 1): 54.	Wrong outcome: measuring increase in implants after stroke network initiated. No clinical outcomes.
Healy C, Burleson HD, Rivner H, Goyal V, Grevious S, Lambrakos LK, et al. Indications and utility of traditional, insertable, and smartphone-based ambulatory ECG monitoring systems. Heart Rhythm 2016; 1): S516-S7.	Wrong population
Katz JM, Eng MS, Carrazco C, Patel AV, Jadonath R, Gribko M, et al. Occult paroxysmal atrial fibrillation in non-cryptogenic ischemic stroke. J Neurol 2018; 24: 24.	Wrong population: described as non-cryptogenic stroke and limited information in abstract to check population characteristics
Katz JM, Gribko M, Jadonath R, Arora R, Salamon E, Garlitzki A, et al. Prevalence of occult paroxysmal atrial fibrillation in non-cryptogenic ischemic stroke patients. Stroke Conference: American Heart Association/American Stroke Association 2017; 48.	Wrong population: described as non-cryptogenic stroke and limited information in abstract to check population characteristics
De Ruvo E, Panuccio M, Sette A, Martino A, Fagagnini A, Grieco D, et al. Effectiveness of remote monitoring in patients implanted with a new miniaturized injectable cadiac monitor. Europace 2016; 18 (Supplement 1): i138	Wrong population: mixed diagnoses and not disaggregated
Iskandar S, Reddy M, Lavu M, Atoui M, Vodapally M, Neerumalla R, et al. Real world experience with medtronic reveal linq. Circulation Conference: American Heart Association's 2016; 134.	Wrong population: mixed diagnoses including only 9 with CS
Brahmbhatt DH, Chari A, Cotter PE, Martin P, Belham MRD, Pugh PJ. Atrial fibrillation detection algorithms alone are inadequate for identifying atrial arrhythmia by implantable loop recorder after ischaemic stroke. Eur Heart J 2013; 1): 738-9.	Wrong population: not cryptogenic stroke, related to Cotter 2013 which reports CS
Drak-Hernandez Y et al, Effectiveness and safety of remote monitoring of patients with an implantable loop recorder. Rev Esp Cardiol. 2013;66(12): 943-948.	Wrong population: not limited to stroke
Kipp R et al, Injectable loop recorder implantation in an ambulatory setting by advanced practice providers: Analysis of outcomes PACE 2017; 40:982-985	Wrong population: not limited to stroke
Maines M et al, Clinical impact, safety, and accuracy of the remotely monitored implantable loop recorder Medtronic Reveal LINQTM. Europace. 2017;0:1-8.	Wrong population: not limited to stroke
Musat DL, Deihl S, Preminger MW, Bhatt A, Sichrovsky TC, Ferrara M, et al. Understanding automatic connectivity limitations in patients undergoing long-term ECG monitoring with an implantable cardiac monitor. Heart Rhythm 2017; 14 (5 Supplement 1): S245.	Wrong population: not limited to stroke

Ching M, Lail N, Tirunagri D, Magun R, Kandel A, Deline C, et al. Predictors of paroxsymal atrial fibrillation in embolic stroke patients with insertable cardiac monitor-a comprehensive stroke center experience. Cerebrovasc Dis 2017; 43 (Supplement 1): 110.	Wrong population: stroke not cryptogenic
Ching MI, Zhang C, Vaughn C, Lail N, Leahy T, Kandel A, et al. Left atrial volume index and pr interval are independent predictors of atrial fibrillation in embolic stroke patients with insertable cardiac monitor. Stroke Conference: American Heart Association/American Stroke Association 2018; 49.	Wrong population: stroke not cryptogenic
Kamel H, Yaghi S, Passman R, Allred J, Sarkar S, Kohler J, et al. Comparison of atrial fibrillation diagnosis and oral anticoagulation utilization among ischemic stroke patients with vs. without insertable cardiac monitors. European Stroke Journal 2018; 3 (1 Supplement 1): 452-3.	Wrong population: stroke not cryptogenic, and unknown device model
Prakapenia A, Pallesen LP, Mayer J, Barlinn J, Barlinn K, Siepmann T, et al. Interactions detection rate of insertable cardiac monitors is not influenced by embolic pattern in neuroradiological imaging. European Stroke Journal 2017; 2 (1 Supplement 1): 113-4.	Wrong population: stroke population, not cryptogenic. Abstract only.
Diederichsen SZ, Haugan KJ, Hojberg S, Holst AG, Kober L, Pedersen KB, et al. Complications after implantation of a new-generation insertable cardiac monitor: Results from the LOOP study. Int J Cardiol 2017; 241: 229-34.	Wrong population: those at high risk of stroke, not limited to CS. Large ongoing RCT (LOOP)
Diederichsen SZ, Haugan KJ, Kober L, Hojberg S, Brandes A, Kronborg C, et al. Atrial fibrillation detected by continuous electrocardiographic monitoring using implantable loop recorder to prevent stroke in individuals at risk (the LOOP study): Rationale and design of a large randomized controlled trial. Am Heart J 2017; 187: 122-32.	Wrong population: those at high risk of stroke, not limited to CS. Large ongoing RCT (LOOP)
Velu S, et al. Remote monitoring of implantable loop recorders significantly improves diagnostic outcomes. Europace 2012;14 SUPPL. 4 (iv22-).	Wrong population: unexplained syncope
Sutton B, Zigler JD, Gopinathannair R, Deam AG, Graver R. Improved health outcomes and cost-savings with remote monitoring of cardiac implantable electronic devices. Heart Rhythm 2013; 1): S455.	Wrong population/not comparison of interest
Sethi A, Buescher M, Garberich R, Hoffman E, Sengupta J. An investigation of the evolution of implantable cardiac monitors: A comparison of reveal XTTM and reveal linqtm based on accuracy measurements and patient outcomes post-device implant. J Am Coll Cardiol 2017; 69 (11 Supplement 1): 518	Wrong population/wrong outcome/not comparison of interst
Healey JS. What do implanted cardiac monitors reveal about atrial fibrillation? JAMA Cardiology 2017; 2: 1128-9.	Wrong population/wrong study design
Miller DJ. Increasing the yield of atrial fibrillation detection in cryptogenic stroke using risk factor stratification: A more satisfying approach. Eur J Neurol 2016; 23: 239-40.	Wrong publication type: comment on Poli 2016
Wachter R, Weber-Kruger M, Groschel K. Letter by Wachter et al regarding article, "occult atrial fibrillation in cryptogenic stroke: detection by 7-day electrocardiogram versus implantable cardiac monitors". Stroke 2013; 44: e111.	Wrong publication type: letter
Healey JS. What do implanted cardiac monitors reveal about atrial fibrillation? JAMA Cardiology 2017; 2: 1128-9.	Wrong publication type: commentary
Abdul-Rahim A.H., Lees K.R. 2013 Paroxysmal atrial fibrillation after ischemic stroke: How should we hunt for it? Expert Review of Cardiovascular Therapy (2013) 11:4 (485-494)	Wrong publication type: narrative paper
Kamel H., Smith W.S. 2011 Detection of atrial fibrillation and secondary stroke prevention using telemetry and ambulatory cardiac monitoring Current Atherosclerosis Reports (2011) 13:4 (338-343)	Wrong publication type: narrative paper
Sundararajan K, Strbian D, Sundararajan S. Evaluation of patients for paroxysmal atrial fibrillation after ischemic stroke. Stroke 2013; 44: e168-e70.	Wrong publication type: narrative paper
Di Odoardo LAF, Ambrosini F, Giavarini A, Vicenzi M, Venturini F, Lombardi F. Reveal LINQ^{TM} experience out of the electrophysiology lab. J Cardiovasc Med 2017; 18: 550-2	Wrong intervention/not comparison of interest

Ellis D, Rangaraju S, Duncan A, Hoskins MH, Raza SA, Rahman H, et al. Measures of coagulation and hemostatic activation outperform left atrial structural parameters in identifying embolic stroke of undetermined source (ESUS) patients who may benefit from early anticoagulation. Stroke Conference: American Heart Association/American Stroke Association 2018; 49	Wrong intervention/not comparison of interest
Gladstone DJ, Spring M, Dorian P, Sanna T, Diener HC, Passman RS, et al. Ambulatory ECG monitoring for 30 d increased AF detection more than 24 h of ECG monitoring after cryptogenic stroke. Ann Intern Med 2014; 161: JC2-JC3.	Wrong intervention/not comparison of interest
Beinart et al. Real-world comparison of in-hospital Reveal LINQ insertion inside and outside of the cardiac catheterization or electrophysiology laboratory. Heart Rhythm 2016; 13:5 SUPPL 1 (S15)	Wrong intervention/not comparison of interest
Roebuck, A., et al. "Experiences from a non-medical, non-catheter laboratory implantable loop recorder (ILR) service." Br J Cardiol. 2015;22:36.	Wrong intervention/not comparison of interest
Wong Feasibility and safety of Reveal LINQ insertion in a sterile procedure room versus electrophysiology laboratory. Int J Cardiol 2016; 223:13-17	Wrong intervention/not comparison of interest
Muller P, Ivanov V, Kara K, Klein-Wiele O, Forkmann M, Piorkowski C, et al. PA-TDI interval to predict occult atrial fibrillation after cryptogenic stroke. Heart Rhythm 2016; 1): S263-S4.	Wrong intervention/not comparison of interest
Afzal M, Kanmanthareddy A, Gunda S, Atkins D, Reddy M, Atoui M, et al. Cryptogenic stroke and underlying atrial fibrillation: A systematic review and meta-analysis of randomized control trials. J Am Coll Cardiol 2015; 1): A360.	Wrong study design: systematic review
Afzal MR, Gunda S, Waheed S, Maybrook RJ, Pillarisetti J, Kanmanthareddy A, et al. Role of outpatient cardiac rhythm monitoring in cryptogenic stroke: A systematic review and meta-analysis of randomized trials and observational studies. Heart Rhythm 2015; 1): S528.	Wrong study design: systematic review
Afzal MR, Gunda S, Waheed S, Sehar N, Maybrook RJ, Dawn B, et al. Role of outpatient cardiac rhythm monitoring in cryptogenic stroke: A systematic review and meta-analysis. PACE - Pacing and Clinical Electrophysiology 2015; 38: 1236-45.	Wrong study design: systematic review
Bhatnagar UB, Sethi P, Gedela M, Thompson PA, Pham R, Pham S. Predictors of diagnostic yield of implanted loop recorder in patients with cryptogenic stroke: A systemic review and meta-analysis. Stroke Conference: American Heart Association/American Stroke Association 2018; 49	Wrong study design: systematic review
Burkowitz J, Merzenich C, Grassme K, Bruggenjurgen B. Insertable cardiac monitors in the diagnosis of syncope and the detection of atrial fibrillation: A systematic review and meta-analysis. European Journal of Preventive Cardiology 2016; 23: 1261-72	Wrong study design: systematic review
Dahal K, Chapagain B, Maharjan R, Farah HW, Nazeer A, Lootens RJ, et al. Prolonged Cardiac Monitoring to Detect Atrial Fibrillation after Cryptogenic Stroke or Transient Ischemic Attack: A Meta-Analysis of Randomized Controlled Trials. Annals of Noninvasive Electrocardiology 2016; 21: 382-8	Wrong study design: systematic review
Glotzer TV, Ziegler PD. Cryptogenic stroke: Is silent atrial fibrillation the culprit? Heart Rhythm 2015; 12: 234-41.	Wrong study design: systematic review
Korompoki E, Del Giudice A, Hillmann S, Malzahn U, Gladstone DJ, Heuschmann P, et al. Cardiac monitoring for detection of atrial fibrillation after TIA: A systematic review and meta-analysis. Int J Stroke 2017; 12: 33-45	Wrong study design: systematic review
Maylin E, Johnson D, Patel R, Hair C, Kraemer T, Lau M, et al. Predicting atrial fibrillation in ischaemic stroke: A systematic review. European Stroke Journal 2018; 3 (1 Supplement 1): 457	Wrong study design: systematic review
Musat DL, Milstein N, Mittal S. Implantable Loop Recorders for Cryptogenic Stroke (Plus Real-World Atrial Fibrillation Detection Rate with Implantable Loop Recorders). Card Electrophysiol Clin 2018; 10: 111-8	Wrong study design: systematic review

Thijs V, Bernstein RA, Morillo C, Diener HC, Rymer M, Di Lazzaro V, et al. Does neurological symptom duration affect the incidence of atrial fibrillation in patients monitored continuously following cryptogenic stroke? Int J Stroke 2016; 11 (Supplement 3): 226.	Wrong study design: systematic review
De Angelis G, Cimon K, Sinclair A, Farrah K, Cairns J, Baranchuk A, et al. Canadian Agency for Drugs and Technologies in Health CADTH Optimal Use Reports 2016; 03: 03	Wrong study design: systematic review/HTA
Rabinstein AA. Prolonged cardiac monitoring for detection of paroxysmal atrial fibrillation after cerebral ischemia. Stroke 2014; 45: 1208-14.	Wrong publication type: narrative paper
Raviele A. Asymptomatic atrial fibrillation after cryptogenetic stroke. Circulation: Arrhythmia and Electrophysiology 2015; 8: 249-51.	Wrong publication type: narrative paper
Kim Y, Lee SH. The optimal approach to detect atrial fibrillation in potential cardioembolic stroke. Eur J Neurol 2016; 23: e35-e	Wrong publication type: narrative paper
Lau YC, Lane DA, Lip GYH. Atrial fibrillation in cryptogenic stroke: Look harder, look longer, but just keep looking. Stroke 2014; 45: 3184-5	Wrong publication type: narrative paper
Jorfida M, Antolini M, Cerrato E, Caprioli MG, Castagno D, Garrone P, et al. Cryptogenic ischemic stroke and prevalence of asymptomatic atrial fibrillation: a prospective study. J Cardiovasc Med 2016; 17: 863-9.	Wrong intervention: Reveal PlusXT 9526 with no AF detection algorithm

9.5 Appendix 5: Clinical data extraction tables

Item	Details
Section 1: Reviewer and study information	
Study ID (Author name, year)	CRYSTAL-AF (Cryptogenic Stroke and Underlying AF)
Study details (journal, year, volume, page range)	1. Sanna T, Diener HC, Passman RS, Di Lazzaro V, Bernstein RA, Morillo CA, et al. Cryptogenic stroke and underlying atrial fibrillation. N Engl J Med 2014; 370: 2478-86 (plus online supplementary materials) [**PRIMARY**] 2. Brachmann J, Morillo CA, Sanna T, Di Lazzaro V, Diener HC, Bernstein RA, et al. Uncovering Atrial Fibrillation Beyond Short-Term Monitoring in Cryptogenic Stroke Patients: Three-Year Results From the Cryptogenic Stroke and Underlying Atrial Fibrillation Trial. Circulation: Arrhythmia and Electrophysiology 2016; 9: e003333 3. Sinha AM, Diener HC, Morillo CA, Sanna T, Bernstein RA, Di Lazzaro V, et al. Cryptogenic Stroke and underlying Atrial Fibrillation (CRYSTAL AF): design and rationale. Am Heart J 2010; 160: 36-41.e1 4. Brachmann J, Sanna T, Morillo CA, Passman RS, Di Lazzaro V, Bernstein RA, et al. Cryptogenic stroke and underlying atrial fibrillation (crystal AF): Long-term detection of clinically meaningful atrial fibrillation. Heart Rhythm 2014; 1): S15. 5. Choe WC, Passman RS, Brachmann J, Morillo CA, Sanna T, Bernstein RA, et al. A Comparison of Atrial Fibrillation Monitoring Strategies After Cryptogenic Stroke (from the Cryptogenic Stroke and Underlying AF Trial). Am J Cardiol 2015; 116: 889-93 6. Diener HC, Di Lazzaro V, Bernstein RA, Rymer MM, Sanna T, Brachmann J, et al. Cryptogenic stroke and underlying atrial fibrillation (CRYSTAL AF): Impact of arrhythmia monitoring on prescription of oral anticoagulation and risk of recurrent stroke. Cerebrovasc Dis 2014; 37 (Supplement 1): 192 7. Passman RS, Morillo CA, Brachmann J, Sanna T, Di Lazzaro V, Bernstein R, et al. A comparison of monitoring strategies for the detection of atrial fibrillation after cryptogenic stroke: Results from the crystal AF study. Heart Rhythm 2014; 1): S17. 8. Thijs VN, Brachmann J, Morillo CA, Passman RS, Sanna T, Bernstein RA, et al. Predictors for atrial fibrillation detection after cryptogenic stroke: Results from CRYSTAL AF. Neurology 2015; 86: 261-9.
Type of report (full paper//conference abstract)	Multiple full papers and abstracts
Section 2: Study information	
Location and number of sites	55 centres in 14 countries across Europe, Canada and the USA
Trial sponsor	Medtronic
Conflicts of interest	Various lead author conflicts including employment, grants and personal fees from Medtronic. The sponsor (Medtronic) had non-voting membership on the steering committee, assisted in the design of the study, data collection, and data analysis, proposed technical content for the manuscript, and contributed to manuscript review, but had no role in the decision to submit the manuscript for publication.
Patient enrolment (method and dates of enrolment)	Enrolled between June 2009 and April 2012
Trial design	Open-label parallel-group RCT
Trial duration (including any period of follow-up)	6 and 12 month primary follow-ups. Study closure was planned at 12 months after the last patient was randomised but long-term follow-up of 36 months reported for some patients.
Inclusion criteria	1. Recent episode (Protocol amendment from <60 days to <90 days) of cryptogenic symptomatic TIA or recent episode of cryptogenic ischemic stroke. Only TIAs with the following documented characteristics can be included: visible lesion on MRI or CT that fits the symptoms of the TIA and at least one of the following symptoms: speech problems, weakness of arm or leg, or hemianopsia. A stroke/TIA is considered to be cryptogenic if no possible cause can be determined despite extensive workup according to the standard protocol of the participating center.

	Before randomization, the following tests are minimally required as standard tests to establish the diagnosis of cryptogenic stroke: • MRI or CT • 12-lead ECG for AF detection • 24-h ECG monitoring for AF detection and PAC analysis (eg, Holter) • TEE • CTA or MRA of head and neck to rule out other causes of stroke pathologies 2. Patient or legally authorized representative is willing to sign patient consent form 3. Patient is ≥40 y old [Protocol amendment] Ultrasonography of cervical arteries and transcranial Doppler ultrasonography of intracranial vessels, in place of MRA or CTA of the head and neck, were allowed for patients older than 55 years of age
Exclusion criteria	The main exclusion criteria were a history of atrial fibrillation or atrial flutter, an indication or contraindication for permanent oral anticoagulant therapy at enrollment, and an indication for a pacemaker or implantable cardioverter–defibrillator. Full criteria from Sinha: 1. Patient has known etiology of the TIA or stroke (based on neuro-/cardiac/vascular imaging), such as: • Angiographic signs of large-artery atherosclerosis (MRA, CTA, or digital subtraction angiography) in the artery feeding the acute ischemic territory • Radiographic appearance consistent with acute small-artery occlusion, with lesion <1 cm in diameter (DWI or CT). • Evidence of a high-risk cardiac or aortic arch source of embolism (LV or LA thrombus or “smoke,” emboligenic valvular lesion or tumor, PFO with extant source of venous thromboembolism, aortic arch plaque >3 mm thick or with mobile components or any other high-risk lesion) • History of spontaneous deep vein thrombosis • Stroke of other determined cause such as presence of nonatherosclerotic vasculopathies, hypercoagulable states (must be tested in patients <55 y old) and hematologic disorders 2. Patient has untreated hyperthyroidism. 3. Patients had myocardial infarction <1 m before stroke/TIA. 4. Patient had coronary bypass grafting <1 m before stroke/TIA. 5. Patient has valvular disease requiring immediate surgical intervention. 6. Patient has documented history of AF or atrial flutter. 7. Patient has presence of a PFO, and PFO is/was an indication to start OAC in the patient according to the ESO guidelines. 8. Patient has permanent indication for anticoagulation at enrollment. 9. Patient has permanent OAC contraindication. 10. Patient is already included in another clinical trial that will affect the objectives of this study. 11. Patient's life expectancy is <1 y. 12. Patient is pregnant. 13. Patient is indicated for implant with a pacemaker, ICD, CRT device, or an implantable hemodynamic monitoring system 14. Patient is not fit, or is unable or unwilling to follow the required procedures of the Clinical Investigation Plan.
Subgroups evaluated	age, sex, race or ethnic group, type of index event, presence or absence of patent foramen ovale, and $CHADS_2$ score at baseline Nb. only type of index event relevant to NICE scope[2]
Stratification	within the study groups according to the type of index event (stroke or TIA) and the presence or absence of a patent foramen ovale
Definition of cryptogenic stroke or TIA	A stroke/TIA is considered to be cryptogenic if no possible cause can be determined despite extensive workup according to the standard protocol of the participating center. Before randomization, the following tests are minimally required as standard tests to establish the diagnosis of cryptogenic stroke: • 12-lead ECG

	• 24 hours or more of ECG monitoring • transesophageal echocardiography • screening for thrombophilic states (if <55 years of age) • MRA, CTA, or catheter angiography of the head and neck (or ultrasonography of cervical arteries and transcranial Doppler ultrasonography of intracranial vessels if > 55 years) Pre-enrollment screening for atrial fibrillation consisted of Holter monitoring with a median duration of 23 hours (interquartile range, 21 to 24) in 71.2% of patients (n=314, mean 31.0 +/-66.7 hours) and inpatient telemetry monitoring with a median duration of 68 hours (interquartile range, 40 to 96) in 29.7% of patients (n=131, mean 74.6 +/-51.4 hours).		
Definition of AF	Atrial fibrillation was defined as an episode of irregular heart rhythm, without detectable P waves, lasting more than 30 seconds. Episodes of atrial fibrillation that qualified for analysis were adjudicated by an independent committee.		
Treatment	**ICM - continuous monitoring**	**Conventional follow-up**	
Randomised or number in study, N	447 enrolled - 441 randomly allocated		
	221 [208 received device]	220	
Withdrawals (please specify reasons for withdrawal, including loss to follow-up; use different rows for different reasons), n (%)	At 6 months 12 (5.4%) Crossed over to control 12 (5.4%) Exited the study • 3 Died • 1 Was lost to follow-up • 5 Withdrew • 3 Were withdrawn by investigator	At 6 months 6 (2.7%) Crossed over to ICM 13 (5.9%) Exited the study • 2 Died • 1 Was lost to follow-up • 7 Withdrew • 3 Were withdrawn by investigator	
Details of follow-up for AF detection	Both groups: For patients in both groups, follow-up visits were scheduled at 1, 6, and 12 months and every 6 months thereafter until study closure, with unscheduled visits in the event of symptom occurrence or after the transmission of ICM data, if advised by the investigator. If patients reported an episode of atrial fibrillation since the previous visit, information was collected and source documentation was acquired for adjudication.		
	Patients assigned to the ICM group were scheduled to have the device inserted within 10 days after randomization. ICM settings were programmed in a standardized fashion. The ICM that was used (REVEAL XT, Medtronic) automatically detects and records atrial fibrillation, irrespective of heart rate or symptoms. The Medtronic CareLink Network was used to remotely transmit the device data.	Patients assigned to the control group underwent assessment at scheduled and unscheduled visits, with ECG monitoring performed at the discretion of the site investigator. Monitoring type, duration, and all results were recorded.	
Mean days from index event	To randomisation (SD): 38.1 (27.6)		
	To insertion of device: 184/208 (88.5%) within 10 days. Scheduling delays (22 patients) or medical justification 2 patients) accounted for delayed insertions (median delay, 6 days; interquartile range, 1 to 32).		
Mean duration/length of follow-up for AF detection **Number completing:** **6-month FU** **12-month FU** **24-month FU** **36-month FU**	20.3 +/- 9.4 months (407.4 patient-years) 205 194 88 24	19.2 +/-9.9 months (patient-years not reported) 208 185 89 24	
Baseline patient characteristics	**ICM - continuous monitoring (n = 221)**	**Conventional follow-up (n = 220)**	**p value**
Mean age, (with SD/SE if given), years (range)	61.6 (11.4)	61.4 (11.3)	0.84
Sex (M/F), n (%)	142 (64.3) male	138 (62.7) male	0.77

	79 (35.7) female	82 (37.3) female	
Ethnicity, n (%) Asian Black Hispanic or Latino White Other Not available	 3 (1.4) 7 (3.2) 2 (0.9) 194 (87.8) 0 15 (6.8)	 2 (0.9) 10 (4.5) 2 (0.9) 191 (86.8) 3 (1.4) 12 (5.5)	0.60
Geographic region, N (%) North America Europe	 83 (37.6) 138 (62.4)	 72 (32.7) 148 (67.3)	0.32
Patent foramen ovale, N (%)	52 (23.5)	46 (20.9)	0.57
Index event, N (%) Stroke TIA	 200 (90.5) 21 (9.5)	 201 (91.4) 19 (8.6)	0.87
Prior stroke/TIA, N (%) Stroke TIA	 37 (16.7) 22 (10.0)	 28 (12.7) 27 (12.3)	 0.28 0.45
Score on modified Rankin scale, N (%) 0 to 2 >2 (0 to 6, lower=better)	 184 (83.3) 36 (16.3)	 186 (84.5) 34 (15.5)	0.85
Mean (SD) NIH Stroke Scale (0 to 42, lower=better)	1.6 (2.7)	1.9 (3.8)	0.37
Hypertension, N (%)	144 (65.2)	127 (57.7)	0.12
Diabetes, N (%)	34 (15.4)	38 (17.3)	0.61
$CHADS_2$ score, N (%) 2 3 4 5 6	 69 (31.2) 92 (41.6) 50 (22.6) 9 (4.1) 1 (0.5)	 81 (36.8) 91 (41.4) 34 (15.5) 14 (6.4) 0	0.17
Hypercholesterolemia, N (%)	125 (56.6)	128 (58.2)	0.77
Current smoker, N (%)	43 (19.5)	44 (20.0)	0.91
Coronary artery disease, N (%)	16 (7.2)	9 (4.1)	0.22
Use of antiplatelet agent, N (%)	212 (95.9)	212 (96.4)	1.00
Section 3: Outcomes			
Outcome	**Definition**		
Diagnostic accuracy (sensitivity and specificity, and/or TP, TN, FP and FN)	Not defined/reported		
Diagnostic yield (number of AF diagnoses)	AF detected at 1, 6, 12, 24 and 36 months. Duration of AF, including median maximum and mean time in AF per day (with IQR), was reported by not extracted as not part of the NICE scope.[2]		
Detection of other cardiac pathologies or incidental findings (non-AF)	Not defined/reported		

Time to diagnosis of AF	Time to first detection of atrial fibrillation at 6 months (primary) and 12 months of follow-up (secondary). The rate of detection of atrial fibrillation was estimated with the use of the KM method and was compared between groups on an intention-to-treat basis with the use of a log-rank test. Data were censored at the time of death, study exit, or completion of 6 months of follow-up.
Time to initiation of anticoagulants	The time-to-event analytic methods used to analyze the primary end point were also used to analyze other time-to-event end points.
Uptake of anticoagulants	Change in use of oral anticoagulants. The between-group difference in the proportion of participants taking oral anticoagulants at follow-up visits was compared with the use of Fisher's exact test.
Incidences of device failure (such as inability to transmit data or battery life) and removal due to failure or AE	Not defined/reported
Hospitalisations for AF	Not defined/reported
Number of outpatient visits related to monitoring for AF	Not defined/reported
Ease of device use for clinicians (incl. insertion)	Not defined/reported
Mortality	Not defined/reported
Further strokes or TIAs, other thromboembolisms and heart failure	Recurrent stroke or TIA
Complications arising from preventative treatment, such as AE from anticoagulation	Not defined/reported
AE related to implanting or removing the device, such as infection or inflammation	Adverse events relating to ICM
Health-related quality of life	EQ5D and VAS
Acceptability of the device to patients	Not defined/reported

Section 4: Data extraction form

Outcome		**Intervention**		**Comparator**		
Dichotomous outcomes						
Diagnostic yield	**Months**	**n**	**N**	**n**	**N**	**Notes**
AF detection	1 m	8	221	1	220	
	6 m	19 (8.6%)	221 (208 with ICM)	3 (1.4%)	220	Control group AF from 88 ECGs (65 patients), 20 24-hour Holters (17 patients), and 1 event recording
	6-12 m	10	221 (189 with ICM and no AF before 6m)	1	220	Control group AF from 34 ECGs (33 patients) and 12 Holters (10 patients)

	12 m	29	221 (208 with ICM)	4	220	Control group AF from 122 ECGs, 32 Holters and 1 event recorder
	12-24 m	9	221 (208 with ICM)	1	220	Control group AF from 62 ECGs and 14 Holters
	24 m	38	221	5	220	
	24-36 m	4	221 (208 with ICM)	0	220	Control group AF from 19 ECGs and 6 Holters
	36 m	42	221	5	220	Control group AF from 256 AF monitoring tests
Asymptomatic AF detection (of all detected AF)	6 m	14	19	1	3	
	12 m	23	29	2	4	
	36 m	34	42	2	5	
AF detection by index event	Stroke TIA	6 m	7 (3.3%) 3 (15%)	200 21	3 (1.6%) 0	201 19	Index event numbers from baseline table. P-value for interaction, 0.99.
	Stroke TIA	12 m	23(11.6%) 4 (20.0%)	200 21	4 (2.2%) 0	201 19	
	Stroke TIA	36 m	(31.2%) NR	200 21	6.3%) 0.0%	201 19	
Time-to-event outcomes							
Time to event		**Median (IQR)**	**N**	**Median (IQR)**	**N**	**HR; 95% CI (p value)**
Time to AF detection, unadjusted	6 m	4 days (4 to 4)	19 detected	32 days (3 to 73)	3 detected	6.4; 1.9 to 21.7 (<0.001)
	12 m	84 days (18 to 265)	29 detected	53 days (17 to 212)	4 detected	7.3; 2.6 to 20.8 (<0.001)
	36 m	8.4 months (NR)	42 detected	2.4 months (NR)	5 detected	8.8; 3.5 to 22.2 (<0.001)
Time to AF detection, adjusted for PFO, hypertension and coronary artery disease	6 m	-	-	-	-	5.9; 1.7 to 19.8 (0.009)
Time to AF detection, censoring data at the time of crossover	6 m	-	-	-	-	6.1; 1.8 to 20.8 (0.009)
Other clinical outcomes	**Time**	**n**	**N**	**n**	**N**	**HR; 95% CI (p value)**
Ischemic stroke or TIA	6 m	11	221	18	220	NR
	12 m	15	221	19	220	0.63; 0.22 to 1.80 (0.39)
	36 m	20	221	24	220	0.77; 0.30 to 1.97 (0.59)
Use of oral anticoagulants	6 m	22 (10.1%)	221	10 (4.6%)	220	(0.0375)

	12 m	14.7% 29	197 (from CT.gov)	6.0% 11	185 (from CT.gov)	
	24 m	26.1%	88	5.6%	89	(0.0002)
	36 m	38.5%	26	8.3%	24	(0.0195)
Use of oral anticoagulants in patients diagnosed with AF	6 m	94.7%	19	NR	NR	
	12 m	96.6%	29	NR	NR	
	24 m	92.3%	39	NR	NR	
	36 m	90.5%	42	NR	NR	
Adverse events	**Time**	**n**	**N**	**n**	**N**	**Notes**
ICM removal due to infection or pocket erosion	36 m	5	208	NA	NA	
ICM no longer in situ	6 m	4	208	NA	NA	
	12 m	7	208	NA	NA	
AE: infection	unclear	3	208	NA	NA	
AE: pain	unclear	3	208	NA	NA	
AE: irritation or inflammation	unclear	4	208	NA	NA	
ICM still inserted	6 m	204 (98.1%)	208	NA	NA	
ICM still inserted	12 m	201 (96.6%)	208	NA	NA	
CV or stroke/TIA-related hospital admissions	12 m	10.5% 23	221	7.2% 16	220	From ct.gov
Patients with SAE	See note	68	221	58	220	From ct.gov., average FU was 19.7 +/- 9.7 m (range: 0 - 42.7).
Total patients with non-serious AE		41	221	9	220	
Health-related quality of life (Summary of EQ-5D domain responses provided by Medtronic)						
	[redacted]	[redacted]		[redacted]		
		[redacted]	[redacted]	[redacted]	[redacted]	
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	

[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
Continuous outcomes							
		Mean	SD	N	Mean	SD	N	Notes
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Section 5: Additional comments	
Additional comments	Denominators were unclear for some dichotomous outcomes (i.e. randomised group vs those inserted with ICM); some numbers don't match up when percentages are converted to events. AF detection with ICM vs conventional follow-up was consistent across all the prespecified subgroups (age, sex, race or ethnic group, index event, presence or absence of PFO, and $CHADS_2$), with no significant interactions. Subgroup analysis results at 12 months were consistent with those at 6 months. Passman 2014 and Choe 2015 include sensitivity and NPC data of ICM vs simulated intermittent monitoring strategies (single 24-hr to 30 days).
Further information that could be requested	HRQoL data as reported as an outcome in the study protocol.

Abbreviations used in table: AE, adverse events; AF, atrial fibrillation; CI, confidence interval; CT, computed tomography; CTA, CT angiogram; CV, cardiovascular; ECG, electrocardiogram; FU, follow-up; HR, hazard ratio; HRQoL, health-related quality of life; ICM, implantable cardiac monitor; KM, Kaplan–Meier; m, months; MRA, magnetic resonance angiogram; MRI, magnetic resonance imaging; n, number of patients with the outcome; N, number of patients assessed; NA, not applicable; NPV, negative predictive value; NR, not reported; PFO, patent foramen ovale; RCT, randomised controlled trial; SAE, serious adverse events; SD, standard deviation; SE, standard error; TEE, transesophageal echocardiography; TIA, transient ischemic event; USA, United States of America; VAS, visual analogue scale.

9.6 Appendix 6: CRYSTAL-AF quality assessment

Reference Sanna T, Diener HC, Passman RS, Di Lazzaro V, Bernstein RA, Morillo CA, et al. Cryptogenic stroke and underlying atrial fibrillation. N Engl J Med 2014; 370: 2478-86. [CRYSTAL-AF]

Study design

- ☑ Individually-randomized parallel-group trial
- ☐ Cluster-randomized parallel-group trial
- ☐ Individually randomized cross-over (or other matched) trial

Specify which outcome is being assessed for risk of bias	AF detection at 6, 12 and 36 months
Specify the numerical result being assessed. In case of multiple alternative analyses being presented, specify the numeric result (e.g. RR = 1.52 (95% CI 0.83 to 2.77) and/or a reference (e.g. to a table, figure or paragraph) that uniquely defines the result being assessed.	Time to first AF, ITT N=221 ICM, N=220 control *By 6 months* (primary analysis, unadjusted): Median 41 days (IQR 4 to 84) ICM vs 32 days (2 to 73) control; HR 6.4 (95% CI 1.9 to 21.7; p < 0.001) *By 12 months:* Median 84 days (18 to 265) ICM vs 53 days (17 to 212) control; HR 7.3 (95% CI 2.6 to 20.8; p < 0.001) *By 36 months:* HR 8.8 (95% CI 3.5 to 22.2; (p < 0.001)

Is the review team's aim for this result…?

- ☑ to assess the effect of *assignment to intervention* (the 'intention-to-treat' effect)
- ☐ to assess the effect of *adhering to intervention* (the 'per-protocol' effect)

Which of the following sources were <u>obtained</u> to help inform the risk-of-bias assessment? (tick as many as apply)

- ☑ Journal article(s) with results of the trial
- ☑ Trial protocol
- ☐ Statistical analysis plan (SAP)
- ☑ Non-commercial trial registry record (e.g. ClinicalTrials.gov record)
- ☐ Company-owned trial registry record (e.g. GSK Clinical Study Register record)
- ☐ "Grey literature" (e.g. unpublished thesis)
- ☑ Conference abstract(s) about the trial
- ☑ Regulatory document (e.g. Clinical Study Report, Drug Approval Package)
- ☐ Research ethics application
- ☐ Grant database summary (e.g. NIH RePORTER or Research Councils UK Gateway to Research)
- ☐ Personal communication with trialist
- ☑ Personal communication with the sponsor

Domain 1: Risk of bias arising from the randomization process

Signalling questions	Description	Response options
1.1 Was the allocation sequence random?	"Randomization lists were created with the use of permuted blocks of random size, with assignments made sequentially." (Sanna 2014)	Y / PY / PN / N / NI
1.2 Was the allocation sequence concealed until participants were enrolled and assigned to interventions?	"Randomization will use an interactive voice response telephone system." (Sinha 2010)	Y / PY / PN / N / NI
1.3 Did baseline differences between intervention groups suggest a problem with the randomization process?	All p values >0.05 although slightly higher rates of patent foramen ovale, hypertension, and coronary artery disease in the ICM group than in the control group at baseline. (Sanna 2014)	Y / PY / PN / N / NI
Risk-of-bias judgement		Low / High / Some concerns
Optional: What is the predicted direction of bias arising from the randomization process?	N/A	Favours experimental / Favours comparator / Towards null /Away from null / Unpredictable

Domain 2: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)

Signalling questions	Description	Response options
2.1. Were participants aware of their assigned intervention during the trial?	"Patients and physicians were aware of the study-group assignments, because patients in the ICM group underwent insertion of the device." (Sanna 2014)	Y / PY / PN / N / NI
2.2. Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?		Y / PY / PN / N / NI
2.3. If Y/PY/NI to 2.1 or 2.2: Were there deviations from the intended intervention that arose because of the experimental context?	12 (5.4%) patients assigned to ICM received standard care and 6 (2.7%) patients in standard care arm received ICM. (Sanna 2014) ICM insertion within 10 days of randomisation was not implemented in 24 patients in the ICM arm: "…scheduling delays (22 patients) or medical justification (2 patients) accounting for delayed insertions (median delay, 6 days; interquartile range, 1 to 32)." (Sanna 2014)	NA / Y / PY / PN / N / NI
2.4. If Y/PY to 2.3: Were these deviations from intended intervention balanced between groups?	Slightly higher cross over in ICM group: 12 (5.4%) patients assigned to ICM received standard care and 6 (2.7%) patients in standard care arm received ICM. (Sanna 2014) Delay in insertion of ICM not relevant to standard care arm.	NA / Y / PY / PN / N / NI
2.5 If N/PN/NI to 2.4: Were these deviations likely to have affected the outcome?	Only small numbers crossed over from assigned interventions: 5.4% in ICM group and 2.7% in standard care. Delay in insertion of ICM was mostly short (median 6 days) so the impact on AF detection is likely to be small. Delays to insertion are also expected to reflect clinical practice.	NA / Y / PY / PN / N / NI

2.6 Was an appropriate analysis used to estimate the effect of assignment to intervention?	"The rate of detection of atrial fibrillation was estimated with the use of the Kaplan–Meier method and was compared between groups on an intention-to-treat basis with the use of a log-rank test." (Sanna 2014) Only small numbers deviated from assigned interventions.	Y / PY / PN / N / NI
2.7 If N/PN/NI to 2.6: Was there potential for a substantial impact (on the result) of the failure to analyse participants in the group to which they were randomized?		NA / Y / PY / PN / N / NI
Risk-of-bias judgement	Lack of blinding unlikely to affect relative AF detection rates between groups. Only small numbers of patients received the alternative interventions (12 [5.4%] patients assigned to ICM and 6 [2.7%] patients in standard care arm). Results analysed for ITT population (Sanna 2014) so, by including patients who did not receive an ICM, received one late, or crossed over to standard care, the estimated benefit of receiving an ICM may be conservative. Delays in ICM insertion were mostly short and unlikely to impact this outcome.	Low / High / Some concerns
Optional: What is the predicted direction of bias due to deviations from intended interventions?	N/A	Favours experimental / Favours comparator / Towards null /Away from null / Unpredictable

Domain 3: Missing outcome data

Signalling questions	Description	Response options
3.1 Were data for this outcome available for all, or nearly all, participants randomized?	All patients included in analysis, only 12 (5.4%) in ICM arm and 13 (5.9%) in standard care arm withdrew from the study by 6 months. 194 (88.8%) patients in ICM arm and 185 (84.1%) in standard care arm completed 12 months follow-up. Only 88 patients completed 24 months follow-up in ICM arm and 89 in standard care arm, and this dropped to only 24 patients in each study arm by 36 months follow-up although an ITT analysis used.	6 months: Y / PY / PN / N / NI 12 months: Y / PY / PN / N / NI ≥24 months: Y / PY / PN / N / NI
3.2 If N/PN/NI to 3.1: Is there evidence that result was not biased by missing outcome data?	Although there were only 177 patients who completed 24 months follow-up and 48 patients that completed 36 months follow-up, there were similar patient numbers in each study arm and an ITT analysis was used. However, the reasons for loss to follow-up beyond 6 months are not reported and a large number of patients are censored in the analyses.	6 and 12 months: NA ≥24 months: NA / Y / PY / PN / N
3.3 If N/PN to 3.2: Could missingness in the outcome depend on its true value?	Unlikely given that balanced across treatment arms and adjucation panel used for the outcome assessment.	6 and 12 months: NA ≥24 months: NA / Y / PY / PN / N / NI
3.4 If Y/PY/NI to 3.3: Do the proportions of missing outcome data differ between intervention groups?		6 and 12 months: NA ≥24 months: NA / Y / PY / PN / N / NI

3.5 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value?		6 and 12 months: NA ≥24 months: NA / Y / PY / PN / N / NI
Risk-of-bias judgement		6 and 12 months: **Low** ≥24 months : **Some concerns**
Optional: What is the predicted direction of bias due to missing outcome data?		Favours experimental / Favours comparator / Towards null /Away from null / Unpredictable

Domain 4: Risk of bias in measurement of the outcome

Signalling questions	Description	Response options
4.1 Was the method of measuring the outcome inappropriate?	Patients assigned to the control group underwent assessment at scheduled and unscheduled visits, with ECG monitoring performed at the discretion of the site investigator. Monitoring type, duration, and all results were recorded. Patients assigned to the ICM group had the ICM settings programmed in a standardized fashion. The ICM (REVEAL XT, Medtronic) automatically detected and recorded episodes of suspected atrial fibrillation, irrespective of heart rate or symptoms.	Y / PY / PN / N / NI
4.2 Could measurement or ascertainment of the outcome have differed between intervention groups ?	The purpose of the study was to assess to different methods of measuring AF: ECG or ICM but the threshold/definition for diagnosing AF was consistent between the two treatment groups. “Episodes of atrial fibrillation that qualified for analysis were adjudicated by an independent committee.” (Sanna 2014) Adjudication committee were blinded to the treatment arm, where possible. (Sinha 2010)	Y / PY / PN / N / NI
4.3 Were outcome assessors aware of the intervention received by study participants?	“Patients and physicians were aware of the study-group assignments, because patients in the ICM group underwent insertion of the device.” (Sanna 2014) However, the adjudication committee were blinded to the treatment arm, where possible. (Sinha 2010)	Y / PY / PN / N / NI
4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?	There was a clear threshold and definition of AF applied by the adjudication panel.	NA / Y / PY / PN / N / NI
4.5 If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received?		NA / Y / PY / PN / N / NI
Risk-of-bias judgement		Low / High / Some concerns
Optional: What is the predicted direction of bias in measurement of the outcome?	N/A	Favours experimental / Favours comparator / Towards null /Away from null / Unpredictable

Domain 5: Risk of bias in selection of the reported result

Signalling questions	Description	Response options
5.1 Was the trial analysed in accordance with a pre-specified plan that was finalized before unblinded outcome data were available for analysis ?	Analysis plan reported in published trial protocol	(Y) / PY / PN / N
Is the numerical result being assessed likely to have been selected, on the basis of the results, from...		
5.2. ... multiple outcome measurements (e.g. scales, definitions, time points) within the outcome domain?	Discrete outcome of AF presence/absence assessed by adjudication committee	Y / PY / PN / (N) NI
5.3 ... multiple analyses of the data?		Y / PY / PN / (N) NI
Risk-of-bias judgement		(Low) / High / Some concerns
Optional: What is the predicted direction of bias due to selection of the reported result?		Favours experimental / Favours comparator / Towards null /Away from null / Unpredictable

Overall risk of bias

Risk-of-bias judgement		Low / High / (Some concerns)
Optional: What is the predicted direction of bias due to selection of the reported result?	Including patients who did not receive an ICM, received one late, or crossed over to standard care in the ITT analysis may give a conservative estimate of the true benefit of ICM, although these issues may reflect clinical practice. Incomplete follow-up at later that 24 months+ is likely to make these results less reliable than those at 6 and 12 months, although the direction of this bias is unpredictable.	Favours experimental / Favours comparator / Towards null /Away from null / (Unpredictable)

9.1 Appendix 7: Economic search strategies

9.1.1 Economic evaluations and cost and resource use evidence

Database: Embase <1974 to 2018 September 6>

Date of search: 7th September 2018

Terms (hits)
1 (Reveal adj2 LINQ$).tw. (96)
2 (Reveal adj2 XT$).tw. (184)
3 BioMonitor$.tw. (7669)
4 (Confirm adj2 RX$).tw. (4)
5 (SJM adj2 Confirm$).tw. (2)
6 (insertable adj3 cardiac adj3 monitor$).tw. (186)
7 (implantable adj3 cardiac adj3 monitor$).tw. (271)
8 (insertable adj3 loop adj3 recorder$).tw. (51)
9 (implantable adj3 loop adj3 recorder$).tw. (976)
10 (ICM or ICMs).tw. (5846)
11 implantable cardiac monitor/ (11836)
12 reveal.dv. (362)
13 or/1-12 (26118)
14 exp cerebrovascular accident/ (172215)
15 (stroke$ or apoplexy$ or CVA or CVAS).tw. (340745)
16 transient ischemic attack/ (33353)
17 (transient adj3 (ischemi$ or ischaemi$) adj3 attack$).tw. (19057)
18 (TIA or TIAs or ministroke or mini-stroke or ministrokes or mini-strokes).tw. (17043)
19 or/14-18 (403705)
20 exp "cost utility analysis"/ (8302)
21 exp "cost benefit analysis"/ (78398)
22 exp "cost effectiveness analysis"/ (134340)
23 exp "cost minimization analysis"/ (3169)
24 health economics.mp. (34419)
25 economic evaluation.mp. (20232)
26 statistical model/ (150051)
27 exp fee/ (37762)
28 exp budget/ (25710)
29 ("unit cost" or unit-cost or unit-costs or "unit costs" or "drug cost" or "drug costs" or "hospital costs" or "health-care costs" or "health care cost" or "medical cost" or "medical costs").tw. (46693)
30 (cost adj2 (util$ or effective$ or efficac$ or benefit$ or consequence$ or analys$ or minimi$ or allocation$ or control$ or illness$ or affordable$ or fee$ or charge$)).tw. (197333)

31 (decision adj1 (tree$ or analys$ or model$)).tw. (18116)
32 (econom$ or price$ or pricing or financ$ or fee$ or pharmacoeconomic$ or pharmaeconomic$ or pharmaco-economic$).tw. (1043164)
33 ((value or values or valuation) adj2 (money or monetary or life or lives or costs or cost)).tw. (8185)
34 Markov.tw. (23325)
35 or/20-34 (1514111)
36 13 and 19 and 35 (53)
37 (letter or editorial or comment or case reports or review).pt. (3946733)
38 nonhuman/ not human/ (4197535)
39 or/37-38 (7967184)
40 36 not 39 (37)

Database: Ovid MEDLINE(R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Daily and Versions(R) <1946 to September 06, 2018>

Date of search: 7th September 2018

Terms (hits)
1 (Reveal adj2 LINQ$).tw. (35)
2 (Reveal adj2 XT$).tw. (45)
3 BioMonitor$.tw. (6300)
4 (Confirm adj2 RX$).tw. (2)
5 (SJM adj2 Confirm$).tw. (1)
6 (insertable adj3 cardiac adj3 monitor$).tw. (79)
7 (implantable adj3 cardiac adj3 monitor$).tw. (131)
8 (insertable adj3 loop adj3 recorder$).tw. (35)
9 (implantable adj3 loop adj3 recorder$).tw. (459)
10 (ICM or ICMs).tw. (3783)
11 or/1-10 (10697)
12 exp STROKE/ (116324)
13 (stroke$ or apoplexy$ or CVA or CVAS).tw. (218734)
14 Ischemic Attack, Transient/ (19490)
15 (transient adj3 (ischemi$ or ischaemi$) adj3 attack$).tw. (12733)
16 (TIA or TIAs or mini-stroke or ministroke or mini-strokes or ministrokes).tw. (8006)
17 or/12-16 (265195)
18 Health economics.mp. (4003)
19 Economic evaluation.mp. (8421)
20 exp "Costs and Cost Analysis"/ (218208)
21 exp Cost-Benefit Analysis/ (74027)
22 exp Models, economic/ (13515)
23 exp "Fees and Charges"/ (29393)

24 exp Budgets/ (13358)

25 Cost Effectiveness Analysis.mp. (8807)

26 Cost Minimi?ation Analysis.mp. (623)

27 Cost Utility Analysis.mp. (2120)

28 (cost adj2 (util$ or effective$ or efficac$ or benefit$ or consequence$ or analys$ or minimi$ or allocation$ or control$ or illness$ or affordable$ or fee$ or charge$)).tw. (145093)

29 ("unit cost" or "unit-cost" or "unit-costs" or "unit costs" or "drug cost" or "drug costs" or "hospital costs" or "health-care costs" or "health care cost" or "medical cost" or "medical costs").tw. (30594)

30 (decision adj1 (tree$ or analys$ or model$)).tw. (12890)

31 (econom$ or price$ or pricing or financ$ or fee$ or pharmacoeconomic$ or pharmaeconomic$ or pharmaco-economic$).tw. (835398)

32 ((value or values or valuation) adj2 (money or monetary or life or lives or costs or cost)).tw. (6030)

33 Markov.tw. (18760)

34 or/18-33 (1125771)

35 11 and 17 and 34 (10)

36 (letter or editorial or comment or case reports or review).pt. (5630094)

37 animals/ not humans/ (4462509)

38 or/36-37 (8310735)

39 35 not 38 (7)

Database: Centre for Reviews and Dissemination
Date of search: 11th September 2018

Terms (hits)
1 (Reveal NEAR2 LINQ*) (0)
2 (Reveal NEAR2 XT*) (0)
3 (BioMonitor*)(0)
4 (Confirm NEAR2 RX*) (0)
5 (SJM NEAR2 Confirm*) (0)
6 (insertable NEAR3 cardiac NEAR3 monitor*) (0)
7 (implantable NEAR3 cardiac NEAR3 monitor*) (0)
8 (insertable NEAR3 loop NEAR3 recorder*) (5)
9 (implantable NEAR3 loop NEAR3 recorder*) (9)
10 (ICM*) (12)
11#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 (25)
12 MeSH DESCRIPTOR Stroke EXPLODE ALL TREES (1354)
13 (stroke* or apoplexy* or CVA or CVAS) (3165)
14 MeSH DESCRIPTOR Ischemic Attack, Transient EXPLODE ALL TREES (89)
15 (transient NEAR3 (ischemi* or ischaemi*) NEAR3 attack*) (243)
16 (TIA or TIAs or ministroke or mini-stroke or ministrokes or mini-strokes) (86)
17 #12 OR #13 OR #14 OR #15 OR #16 (3202)
18 #11 AND #17 (3)

Database: Cochrane library
Date of search: 11th September 2018

Terms (hits)
#1 MeSH descriptor: [Stroke] explode all trees (7713)
#2 MeSH descriptor: [Ischemic Attack, Transient] explode all trees (645)
#3 (stroke* or apoplexy* or CVA or CVAS):ti,ab,kw (42050)
#4 (transient near/3 (ischemi* or ischaemi*) near/3 attack):ti,ab,kw (2268)
#5 (TIA or TIAs or mini-stroke or mini-strokes or ministroke or ministrokes):ti,ab,kw (1185)
#6 (OR) #1-#5} (43047)
#7 (Reveal near/2 LINQ*):ti,ab,kw (14)
#8 (Reveal near/2 XT*):ti,ab,kw (27)
#9 BioMonitor*:ti,ab,kw (40)
#10 (Confirm near/2 RX*):ti,ab,kw (0)
#11 (SJM near/2 Confirm*):ti,ab,kw (1)
#12 (insertable near/3 cardiac near/3 monitor*):ti,ab,kw (31)
#13 (implantable near/3 cardiac near/3 monitor*):ti,ab,kw (254)
#14 (insertable near/3 loop near/3 recorder*):ti,ab,kw (1)
#15 (implantable near/3 loop near/3 recorder*):ti,ab,kw (101)
#16 ICM:ti,ab,kw (228)
#17 OR/ #7-#16 (565)
#18 #6 and #17 (72)
#19 MeSH descriptor: [Costs and Cost Analysis] explode all trees (9518)
#20 MeSH descriptor: [Cost-Benefit Analysis] explode all trees (6179)
#21 MeSH descriptor: [Fees and Charges] explode all trees (251)
#22 MeSH descriptor: [Budgets] explode all rees (33)
#23 MeSH descriptor: [Models, Economic] explode all trees (298)
#24 ("unit cost" or "unit-cost" or "unit-costs" or "unit costs" or "drug cost" or "drug costs" or "hospital costs" or "health-care costs" or "health care cost" or "medical cost" or "medical costs"):ti,ab (4117)
#25 (cost near/2 (util* or effective* or efficac* or benefit* or consequence* or analys* or minimi* or allocation* or control* or illness* or affordabl* or fee* or charge*)):ti,ab (20485)
#26 (decision near/1 (tree* or analys* or model*)):ti,ab (682)
#27 (econom* or price* or pricing or financ* or fee* or pharmacoeconomic* or pharmaeconomic* or pharmaco-economic*):ti,ab (50415)
#28 ((value or values or valuation) near/2 (money or monetary or life or lives or costs or cost)):ti,ab (578)
#29 Markov:ti,ab (903)
#30 OR/ #19-#29 (69869)
#31 #18 and #30 (5)

Database: EconLit <1886 to September 06, 2018>
Date of search: 11th September 2018

Terms (hits)
1 (Reveal adj2 LINQ$).tw. (0)
2 (Reveal adj2 XT$).tw. (0)
3 BioMonitor$.tw. (3)
4 (Confirm adj2 RX$).tw. (0)
5 (SJM adj2 Confirm$).tw. (0)
6 (insertable adj3 cardiac adj3 monitor$).tw. (0)
7 (implantable adj3 cardiac adj3 monitor$).tw. (0)
8 (insertable adj3 loop adj3 recorder$).tw. (0)
9 (implantable adj3 loop adj3 recorder$).tw. (0)
10 (ICM or ICMs).tw. (91)
11 or/1-10 (94)
12 (stroke$ or apoplexy$ or CVA or CVAS).tw. (365)
13 (transient adj3 (ischemi$ or ischaemi$) adj3 attack$).tw. (6)
14 (TIA or TIAs or ministroke or mini-stroke or ministrokes or mini-strokes).tw. (13)
15 or/12-14 (376)
16 11 and 15 (0)

9.1.2 Health-related quality of life evidence

Database: Embase <1974 to 2018 September 6>

Date of search: 10th September 2018

Terms (hits)
1 exp cerebrovascular accident/ (172439)
2 (stroke$ or apoplexy$ or CVA or CVAS).tw. (341008)
3 transient ischemic attack/ (33402)
4 (transient adj3 (ischemi$ or ischaemi$) adj3 attack$).tw. (19067)
5 (TIA or TIAs or ministroke or mini-stroke or ministrokes or mini-strokes).tw. (17054)
6 or/1-5 (404125)
7 ((quality adj2 life) or QOL).ti,ab. (373791)
8 (HRQL or HRQOL).ti,ab. (26321)
9 ("quality-adjusted life year$" or QALY or QALYs or "quality adjusted life year$").ti,ab. (19666)
10 exp quality adjusted life year/ (21653)
11 ("disability-adjusted life year$" or DALY or DALYs or "disability adjusted life year$").ti,ab. (3892)
12 (sf36 or sf-36 or "sf 36" or "short form 36" or "shortform 36" or "sf thirtysix" or "sf thirty six" or "shortform thirtysix" or "shortform thirty six" or "short form thirty six" or "short form thirtysix" or "short form thirty six").ti,ab. (36096)
13 (sf6 or "sf 6" or sf-6 or "short form 6" or "shortform 6" or "sf six" or sfsix or "shortform six" or "short form six").ti,ab. (2001)

14 (sf6d or "sf 6d" or sf-6d or "short form 6d" or "shortform 6d" or "sf six dimension" or "short form six dimension").ti,ab. (1281)
15 (sf12 or "sf 12" or sf-12 or "short form 12" or "shortform 12" or "sf twelve" or sftwelve or "shortform twelve" or "short form twelve").ti,ab. (7811)
16 (sf16 or "sf 16" or sf-16 or "short form 16" or "shortform 16" or "sf sixteen" or sfsixteen or "shortform sixteen" or "short form sixteen").ti,ab. (50)
17 (sf20 or "sf 20" or sf-20 or "short form 20" or "shortform 20" or "sf twenty" or sftwenty or "shortform twenty" or "short form twenty").ti,ab. (407)
18 (euroqol or "euro qol" or eq5d or "eq 5d" or eq-5d).tw. (15700)
19 (hye or hyes or "healthy year$ equivalent$").ti,ab. (133)
20 ("standard gamble" or SG).ti,ab. (12967)
21 ("time trade off" or "time tradeoff" or TTO or "time trade-off").ti,ab. (2356)
22 (utility adj3 value).ti,ab. (1308)
23 disutil$.ti,ab. (726)
24 ((quality adj3 wellbeing index) or QWB).ti,ab. (230)
25 ("health utilities index" or HUI).ti,ab. (2051)
26 or/7-25 (420375)
27 6 and 26 (12159)
28 (letter or editorial or comment or case reports or review).pt. (3949526)
29 nonhuman/ not human/ (4199086)
30 or/28-29 (7971522)
31 27 not 30 (10215)
32 limit 31 to english language (9614)
33 limit 32 to yr="1997 -Current" (9414)
34 limit 33 to (conference abstract and last 2 years) (1321)
35 limit 33 to conference abstract (4401)
36 33 not 35 (5013)
37 36 or 34 (6334)

Database: Ovid MEDLINE(R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Daily and Versions(R) <1946 to September 06, 2018>

Date of search: 10th September 2018

Terms (hits)
1 exp STROKE/ (116324)
2 (stroke$ or apoplexy$ or CVA or CVAS).tw. (218734)
3 Ischemic Attack, Transient/ (19490)
4 (transient adj3 (ischemi$ or ischaemi$) adj3 attack$).tw. (12733)
5 (TIA or TIAs or mini-stroke or mini-strokes or ministroke or ministrokes).tw. (8006)
6 or/1-5 (265195)

7 ((quality adj2 life) or QOL).ti,ab. (237735)
8 (HRQL or HRQOL).ti,ab. (16383)
9 ("quality-adjusted life year$" or QALY or QALYs or "quality adjusted life year$").ti,ab. (11707)
10 exp Quality-Adjusted Life Years/ (10391)
11 ("disability-adjusted life year$" or DALY or DALYs or "disability adjusted life year$").ti,ab. (3033)
12 (sf36 or sf-36 or "sf 36" or "short form 36" or "shortform 36" or "sf thirtysix" or "sf thirty six" or "shortform thirtysix" or "shortform thirty six" or "short form thirty six" or "short form thirtysix" or "short form thirty six").ti,ab. (22797)
13 (sf6 or "sf 6" or "sf-6" or "short form 6" or "shortform 6" or "sf six" or sfsix or "shortform six" or "short form six").ti,ab. (1887)
14 (sf6d or "sf 6d" or sf-6d or "short form 6d" or "shortform 6d" or "sf six dimension" or "short form six dimension").ti,ab. (717)
15 (sf12 or "sf 12" or sf-12 or "short form 12" or "shortform 12" or "sf twelve" or sftwelve or "shortform twelve" or "short form twelve").ti,ab. (4852)
16 (sf16 or "sf 16" or sf-16 or "short form 16" or "shortform 16" or "sf sixteen" or sfsixteen or "shortform sixteen" or "short form sixteen").ti,ab. (30)
17 (sf20 or "sf 20" or sf-20 or "short form 20" or "shortform 20" or "sf twenty" or sftwenty or "shortform twenty" or "short form twenty").ti,ab. (383)
18 (euroqol or "euro qol" or eq5d or "eq 5d" or eq-5d).tw. (8555)
19 (hye or hyes or "healthy year$ equivalent$").ti,ab. (70)
20 ("standard gamble" or SG).ti,ab. (9065)
21 ((quality adj3 wellbeing index) or QWB).ti,ab. (194)
22 ("time trade off" or "time tradeoff" or TTO or "time trade-off").ti,ab. (1646)
23 (utility adj3 value).ti,ab. (863)
24 disutil$.ti,ab. (382)
25 ("health utilities index" or HUI).ti,ab. (1447)
26 or/7-25 (267789)
27 6 and 26 (6061)
28 (letter or editorial or comment or case reports or review).pt. (5630094)
29 animals/ not humans/ (4462509)
30 or/28-29 (9858961)
31 27 not 30 (4450)
32 limit 31 to english language (4069)
33 limit 32 to yr="1997 -Current" (3933)

Database: Centre for Reviews and Dissemination
Date of search: 11th September 2018

Terms (hits)
1 (Reveal NEAR2 LINQ*) (0)
2 (Reveal NEAR2 XT*) (0)

3 (BioMonitor*) (0)

4 (Confirm NEAR2 RX*) (0)

5 (SJM NEAR2 Confirm*) (0)

6 (insertable NEAR3 cardiac NEAR3 monitor*) (0)

7 (implantable NEAR3 cardiac NEAR3 monitor*) (0)

8 (insertable NEAR3 loop NEAR3 recorder*) (5)

9 (implantable NEAR3 loop NEAR3 recorder*) (9)

10 (ICM*) (12)

11 #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 (25)

12 MeSH DESCRIPTOR Stroke EXPLODE ALL TREES (1354)

13 (stroke* or apoplexy* or CVA or CVAS) (3165)

14 MeSH DESCRIPTOR Ischemic Attack, Transient EXPLODE ALL TREES (89)

15 (transient NEAR3 (ischemi* or ischaemi*) NEAR3 attack*) (243)

16 (TIA or TIAs or ministroke or mini-stroke or ministrokes or mini-strokes) (86)

17 #12 OR #13 OR #14 OR #15 OR #16 (3202)

18 #11 AND #17 (3)

19 (quality NEAR2 life) OR (QOL) (11586)

20 (HRQL) OR (HRQOL) (198)

21 (QALY) OR (QALYs) (3263)

22 (quality-adjusted life year*) OR (quality adjusted life year*) (5265)

23 MeSH DESCRIPTOR Quality-Adjusted Life Years EXPLODE ALL TREES (3547)

24 (disability-adjusted life year*) OR (disability adjusted life year*) (174)

25 (DALY) OR (DALYs) (210)

26 (euroqol) OR (euro qol) (263

27 (eq5d) OR (eq 5d) OR (eq-5d) (661)

28 (hye) OR (hyes) OR (healthy year* equivalent*) (10)

29 (standard gamble) OR (SG) (455)

30 (TTO) (18)

31 (time trade off) OR (time tradeoff) OR (time trade-off) (372)

32 (utility NEAR3 value) (151)

33 (disutil*) (184)

34 (health utilities index) OR (HUI) (201)

35 (sf36 or sf-36 or "sf 36" or "short form 36" or "shortform 36" or "sf thirtysix" or "sf thirty six" or "shortform thirtysix" or "shortform thirty six" or "short form thirty six" or "short form thirtysix" or "short form thirty six") OR (sf6 or "sf 6" or "sf-6" or "short form 6" or "shortform 6" or "sf six" or sfsix or "shortform six" or "short form six") OR (sf6d or "sf 6d" or sf-6d or "short form 6d" or "shortform 6d" or "sf six dimension" or "short form six dimension") (439)

36 (sf12 or "sf 12" or sf-12 or "short form 12" or "shortform 12" or "sf twelve" or sftwelve or "shortform twelve" or "short form twelve") OR (sf16 or "sf 16" or sf-16 or "short form 16" or "shortform 16" or "sf sixteen" or sfsixteen or "shortform sixteen" or "short form sixteen") OR (sf20 or "sf 20" or sf-20 or "short form 20" or "shortform 20"

or "sf twenty" or sftwenty or "shortform twenty" or "short form twenty") (65)
37 #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32 OR #33 OR #34 OR #35 OR #36 (12312)
38 #17 AND #37 (805)
39 * IN DARE (45418)
40 #38 AND #39 (231)
41 * IN NHSEED (17613)
42 #38 AND #41 (516)
43 * IN HTA (17351)
44 #38 AND #43 (58)

Database: Cochrane library
Date of search: 11th September 2018

Terms (hits)
#1 MeSH descriptor: [Stroke] explode all trees (7713)
#2 MeSH descriptor: [Ischemic Attack, Transient] explode all trees (645)
#3 (stroke* or apoplexy* or CVA or CVAS):ti,ab,kw (42050)
#4 (transient near/3 (ischemi* or ischaemi*) near/3 attack):ti,ab,kw (2268)
#5 (TIA or TIAs or mini-stroke or mini-strokes or ministroke or ministrokes):ti,ab,kw (1185)
#6 OR/ #1-#5} (43047)
#7 (Reveal near/2 LINQ*):ti,ab,kw (14)
#8 (Reveal near/2 XT*):ti,ab,kw (27)
#9 BioMonitor*:ti,ab,kw (40)
#10 (Confirm near/2 RX*):ti,ab,kw (0)
#11 (SJM near/2 Confirm*):ti,ab,kw (1)
#12 (insertable near/3 cardiac near/3 monitor*):ti,ab,kw (31)
#13 (implantable near/3 cardiac near/3 monitor*):ti,ab,kw (254)
#14 (insertable near/3 loop near/3 recorder*):ti,ab,kw (1)
#15 (implantable near/3 loop near/3 recorder*):ti,ab,kw (101)
#16 ICM:ti,ab,kw (228)
#17 OR/ #7-#16 (565)
#18 #6 and #17 (72)

#19 MeSH descriptor: [Costs and Cost Analysis] explode all trees (9518)

#20 MeSH descriptor: [Cost-Benefit Analysis] explode all trees (6179)

#21 MeSH descriptor: [Fees and Charges] explode all trees (251)

#22 MeSH descriptor: [Budgets] explode all trees (33)

#23 MeSH descriptor: [Models, Economic] explode all trees (298)

#24 ("unit cost" or "unit-cost" or "unit-costs" or "unit costs" or "drug cost" or "drug costs" or "hospital costs" or "health-care costs" or "health care cost" or "medical cost" or "medical costs"):ti,ab (4117)

#25 (cost near/2 (util* or effective* or efficac* or benefit* or consequence* or analys* or minimi* or allocation* or control* or illness* or affordabl* or fee* or charge*)):ti,ab (20485)

#26 (decision near/1 (tree* or analys* or model*)):ti,ab (682)

#27 (econom* or price* or pricing or financ* or fee* or pharmacoeconomic* or pharmaeconomic* or pharmaco-economic*):ti,ab (50415)

#28 ((value or values or valuation) near/2 (money or monetary or life or lives or costs or cost)):ti,ab (578)

#29 Markov:ti,ab (903)

#30 OR/ #19-#29 (69869)

#31 #18 and #30 (5)

#32 MeSH descriptor: [Quality-Adjusted Life Years] explode all trees (1029)

#33 ("quality-adjusted life year*" or QALY or QALYs or "quality adjusted life year*"):ti,ab (2647)

#34 ("quality near/2 life" or QOL):ti,ab (11493)

#35 ("disability-adjusted life year*" or DALY or DALYs or "disability adjusted life years*"):ti,ab (148)

#36 (HRQL or HRQOL):ti,ab (4251)

#37 (sf36 or sf-36 or "sf 36" or "short form 36" or "shortform 36" or "sf thirtysix" or "sf thirty six" or "shortform thirtysix" or "shortform thirty six" or "short form thirty six" or "short form thirtysix" or "short form thirty six"):ti,ab (7486)

#38 (sf6 or "sf 6" or "sf-6" or "short form 6" or "shortform 6" or "sf six" or sfsix or "shortform six" or "short form six"):ti,ab (145)

#39 (sf6d or "sf 6d" or "sf-6d" or "short form 6d" or "shortform 6d" or "sf six dimension" or "short form six dimension"):ti,ab (219)

#40 (sf12 or "sf 12" or sf-12 or "short form 12" or "shortform 12" or "sf twelve" or sftwelve or "shortform twelve" or "short form twelve"):ti,ab (1395)

#41 (sf16 or "sf 16" or "sf-16" or "short form 16" or "shortform 16" or "sf sixteen" or sfsixteen or "shortform sixteen" or "short form sixteen"):ti,ab (4)

#42 (sf20 or "sf 20" or sf-20 or "short form 20" or "shortform 20" or "sf twenty" or sftwenty or "shortform twenty" or "short form twenty"):ti,ab (66)

#43 (euroqol or "euro qol" or eq5d or "eq 5d" or eq-5d):ti,ab,kw (4069)

#44 (hye or hyes or "health* year* equivalent*"):ti,ab (9)

#45 ("standard gamble" or SG):ti,ab (1039)

#46 ((quality near/3 wellbeing index) or QWB):ti,ab (107)

#47 ("time trade off" or "time tradeoff" or TTO or "time trade-off"):ti,ab (207)

#48 (utility near/3 value):ti,ab (106)

#49 disutil*:ti,ab (46)
#50 ("health utilities index" or HUI):ti,ab (190)
#51 OR/ #32-#50 (26945)
#52 #6 and #51 (909)

9.2 Appendix 8: Economic excluded studies

Excluded studies list, economic evaluations

Reference	Reason for exclusion
Bravo et al. 2012	Conference abstract published prior to the pre-specified cut-off date. Cost-consequence analysis
Merino et al. 2009	Conference abstract published prior to the pre-specified cut-off date. PAAF treatment beyond the scope.
Sadri et al. 2009	Conference abstract published prior to the pre-specified cut-off date. RCA treatment beyond the scope.
Steinhaus, et al. 2016	Irrelevant population (patients already diagnosed with AF). Irrelevant use of intervention (ICM used to guide anticoagulation treatment, rather than detect AF). Irrelevant comparison (ICM guided anticoagultion treatment vs. continuous anticoagulation treatment).

Excluded studies list, cost and resource use evidence

Reference	Reason for exclusion
Bravo et al. 2012	Non-UK
Maervoet, et al. 2017	Non-UK
Merino et al. 2009	Non-UK
Quiroz, et al. 2017	Non-UK
Sadri et al. 2009	Non-UK
Steinhaus et al. 2016	Non-UK
Thijs et al. 2018	Non-UK

Excluded studies list, HRQoL evidence

Reference	Reason for exclusion
Ali et al. 2016	Utility values not relevant to the pathway in the model
Aronsson et al. 2015	Not primary source
Ayis et al. 2015	SF-12 mapped to EQ-5D

Barclay-Goddard et al. 2011	Utility values not reported
Barreto et al. 2018	Conference abstract with insufficient detail
Bennaghmouch et al. 2018	Not available
Boehme et al. 2017	Conference abstract with insufficient detail
Bulkova et al. 2012	Irrelevant population. Utility values not reported
Cadilhac et al. 2017	Utility values not reported
Canestaro et al. 2013	Not primary source
Choi et al. 2017	Conference abstract with insufficient detail
Chun et al. 2018	Utility values not reported
Chun et al. 2017	Conference abstract with insufficient detail
Contreras et al. 2017	Text in Spanish
Cost et al. 2015	Not available
Davidson et al. 2013	Not primary source
De Caterina et al. 2018	Utility values not relevant to the pathway in the model
De Caterina et al. 2016	Conference abstract with insufficient detail
Demel et al. 2016	Conference abstract with insufficient detail
Dewilde et al. 2014	Conference abstract with insufficient detail
Dorman et al. 1997	Utility values not reported
Dorman et al. 1997	Utility values not reported
Dorman et al. 1998	Utility values not reported
Dorman et al. 1999	Utility values not reported
Dorman et al. 2000	Utility values not relevant to the pathway in the model
Dudink et al. 2018	Utility values not relevant to the pathway in the model
Duncan et al. 1997	EQ-5D not used to measure HRQoL
Eckman et al. 2014	Utility values not reported
Escolar-Albaladejo et al. 2016	Text in Spanish
Fadrna et al. 2017	Conference abstract with insufficient detail
Freeman et al. 2011	Not primary source
Freriks et al. 2018	Conference abstract with insufficient detail
Gage et al. 1995	Pre-1997. EQ-5D utility values not reported.
Gage et al. 1996	Pre-1997. EQ-5D utility values not reported.
Gage et al. 1998	Not primary source
Gall et al. 2017	Conference abstract with insufficient detail

Ganesh et al. 2017	Conference abstract with insufficient detail
Gupta et al. 2018	Conference abstract with insufficient detail
Hobbs et al. 2005	Not primary source
Jacobs et al. 2016	Not primary source
Janzic et al. 2015	Not primary source
Jones et al. 2016	Conference abstract with insufficient detail
Jonsson et al. 2014	Not available
Jowett et al. 2011	Utility values not reported
Kansal et al. 2012	Not primary source
Kamel et al. 2010	Not primary source
Kim et al. 2017	Conference abstract with insufficient detail
Kim et al. 2015	Utility values not reported
Kongnakorn et al. 2014	Not primary source
Kwon et al. 2018	Population unclear
Lafuente-Lafuente et al. 2012	Not primary source
Lahr et al. 2018	Conference abstract with insufficient detail
Lamy et al. 2017	Conference abstract with insufficient detail
Lanitis 2014	Not primary source
Lannin et al. 2017	EQ-5D not valued using standard methods
Leno Diaz et al. 2016	Not available
Levin et al. 2015	Not primary source
Lip et al. 2014	Not primary source
Lip et al. 2015	Not primary source
Lopez Espuela et al. 2017	Full-text in Spanish
Lowres et al. 2014	Not primary source
Mayer et al. 2013	Not primary source
Monreal et al. 2016	Conference abstract with insufficient detail
Monz et al. 2013	Irrelevant population
Moran et al. 2016	Not primary source
O'Brien et al. 2005	Not primary source
Patel et al. 2004	Utility values not reported
Phan et al. 2016	Conference abstract with insufficient detail
Phan et al. 2017	Conference abstract with insufficient detail

Phan et al. 2018	Conference abstract with insufficient detail
Puumalainen et al. 2016	EQ-5D not used to measure HRQoL
Quiroz et al. 2017	Conference abstract with insufficient detail
Radholm et al. 2015	Utility values not reported
Rangaraju et al. 2017	Utility values not relevant to the pathway in the model
Rudberg et al. 2018	Utility values not relevant to the pathway in the model
Savelieva et al. 2001	EQ-5D not used to measure HRQoL
Schleinitz et al. 2004	Not primary source
Schreuders et al. 2017	Utility values not relevant to the pathway in the model
Sorensen et al. 2009	Not primary source
Sprigg et al. 2013	Utility values not reported
Sullivan et al. 2006	Not primary source
Tengs et al. 2003	Not primary source. EQ-5D not used to measure HRQoL
Thijs et al. 2017	Conference abstract with insufficient detail
Thomson et al. 2000	EQ-5D not used to measure HRQoL
Van Den Berg et al. 2017	Conference abstract with insufficient detail
Verhoef et al. 2014	Not primary source
Walfridsson et al. 2014	Utility values not relevant to the pathway in the model
Wisloff et al. 2014	Not primary source
Wright et al. 2007	Not primary source

9.3 Appendix 9: Economic data extraction tables

Economic evaluations

Population, intervention and comparator	Perspective, discounting, cost year and model structure	Measures of diagnostic accuracy	Clinical effectiveness	Resource and cost use	HRQoL	Total costs and total QALYs	ICER and results of sensitivity analysis
De Angelis 2016 CADTH							
Population: Patients with a cryptogenic stroke or TIA within 90 days **Intervention:** ILR (Reveal XT) (3 years) **Comparator:** SoC (30% patients with at least one ECG and 8% patients with 24-hour Holter within 6 months)	**Perspective**: provincial Ministry of Health in Canada, public payer (societal considered in sensitivity analysis) **Discount rate:** costs and benefits 5% **Cost year:** 2015 **Model type**: Markov (monthly cycle length) **Heath states**: History of stroke only, history of stroke and MI, history of stroke and	Sanna et al. 2014 - Compared ILR with standard practice in 441 patients with an IS in the past 90 days and no history of AF - Prevalence of AF 30%, based on the proportion of patients diagnosed with AF after 36 months of continuous monitoring - Proportion of undiagnosed AF patients diagnosed	-When available, Canadian studies were given priority to ensure representativeness of the population. When Canadian studies were not available, studies from the US and Europe were selected - The baseline annual rate of death for a patient with a history of stroke, history of stroke and MI, and history of recurrent stroke was estimated from the Copenhagen Stroke Study - Mortality within 30	- According to the Ontario Ministry of Health and Long-Term Care, the cost of the Reveal XT device is $2,800 and the cost of physician time is $146, resulting in a total cost of $2,946 for surgical implantation. Physician monitoring costs were estimated to be $300 per year. 24-hour monitoring was	**Baseline Utilities** History of stroke 0.68 (Luengo-Fernandez 2013, Dorman et al. 2000, Mittmann et al. 1999, Nyman et al., 2007) History of MI 0.65 (Luengo-Fernandez 2013) History of ICH 0.62 (Luengo-Fernandez 2013 and Christensen et al. 2009) History of severe recurrent stroke 0.31 (Luengo-	SoC; ILR **Total costs when apixaban is the OAC treatment:** - Baseline $165,431; $166,158 - Testing $40; $3,474 - OAC $138; $402 - Acute events $11,469; $11,107 - TOTAL $177,078; $181,141 **Total costs when warfarin is the OAC treatment:** - Baseline $165,348; $165,914	**ICER, cost per QALY gained** - apixaban OAC treatment $273,815 - warfarin OAC treatment $414,732 **Results of SA** If diagnosis is followed by treatment with dabigatran or rivaroxaban, the ICER of 30-day ILR compared with 24-hour Holter is $420,062 per QALY gained and $390,578 per QALY gained, respectively. - Present OWSA for

	ICH, and history of recurrent stroke. Individuals transition to the state based on their most severe event to date (in the order of MI, ICH, and recurrent stroke). Patients remain undiagnosed or become diagnosed and receive OAC treatment, or other treatment for their diagnosis. **Time horizon**: lifetime Five possible OAC treatments were considered: none (Aspirin), warfarin, dabigatran, rivaroxaban, and apixaban.	in each month calculated using KM curves Proportion of undiagnosed AF patients ILR arm: - 12% in the first month of monitoring, 9% in the second month of monitoring, 6% in the third month of monitoring, 2% in the fourth through sixth months of monitoring, 3% in the seventh through 12th months of monitoring, and 7% per month thereafter. - This resulted in 8.9% of the total population being	days of an acute event was estimated using large observational cohort studies, including the Canadian Stroke Network - Based on the findings of a large insurance-based cohort (Fang et al. 2012), OAC therapy decreased the 30-day mortality recurrent ischemic stroke, but increased mortality from ICH. - Effect of AF on acute events (recurrent stroke HR 4.8 and MI HR 2.0) estimated from Wolf et al. 1991 and Soliman et al. 2014 - Acute event rates (annual per 100,000: recurrent stroke 10,700, MI 5,200, ICH 290, major non-briain	estimated to be $73; 7-day monitoring was $183. - Baseline age-specific public sector health care costs, including age-stratified average expenditures on hospitals, drugs, physician care, nursing homes, and residential care, were estimated based on national averages. Baseline costs were increased by a factor of 1.1 to account for the higher-than-average costs in patients with AF.	Fernandez 2013, Dorman et al. 2000, Gage et al. 1996, Smith et al. 2013, Pickard et al. 2004) **Utility Decrement** Warfarin –0.013 (Gage et al. 1996 and Singh et al. 2013) Dabigatran –0.006 (Singh et al. 2013) Rivaroxaban –0.006 Assumed Apixaban –0.006 Assumed **Event-Specific Disutility** (in the month it occurs) Non-fatal MI –0.01 (Bohmer et al. 2014) Non-fatal ICH –0.05 (Luengo-Fernandez 2013)	- Testing $40; $3,474 - OAC $41; $118 - Acute events $11,528; $11,283 - TOTAL $176,957; $180,789 **Total QALYs** - apixaban OAC treatment: 3.178; 3.193 - warfarin OAC treatment: 3.176; 3.185 **Discounted LYs:** - apixaban OAC treatment 4.818; 4.839 - warfarin OAC treatment 4.815; 4.832	warfarin, dabigatran, rivaroxaban and apixaban OAC treatments: results robust to changes in parameters - Only when the cost of the device and implantation was below $400 did the ICER fall below $100,000 per QALY gained - A one-time disutility of 0.005 associated with the outpatient implantation procedure greatly increases the ICERs such that they exceed $400,000 per QALY for any OAC. - ILR is more cost-effective in healthier patients, such as those with a lower baseline mortality rate, lower baseline costs, and higher baseline utilities, as well as in patients with a higher risk of recurrent

		diagnosed by six months, 12.6% diagnosed by 12 months, 23.2% by 24 months, and 27.4% of the total population being diagnosed by 36 months. SoC arm: - 0.8% per month in the first six months, 0.4% in months seven to 12, and 0.2% thereafter.	bleeding 1,056) estimated from Soliman et al. 2014, Hart et al. 2007, Stroke Risk in AF Working Group 2007, Xian et al. 2015, Mant et al. 2007, An et al. 2015, Go et al. 2003, The Stroke Prevention in AF Investigators 1996) - Effects of OACS on acute events (recurrent stroke, MI, ICH, major non-brain bleeding) estimated from Hart et al. 2007, Xian et al. 2015, Easton et al. 2012, Granger et al. 2011, Diener et al. 2010, Hankey et al. 2012 - Recurrent stroke severity (mild TIA 60% and moderate to severe 40%) estimated from	- Health care costs (annual) associated with specific medical history estimated from Singh et al. 2013, Mittmann et al. 2012 and Cohen et al. 2014 - AF treatment (OAC plus monitoring) costs taken from Ontario drug benefit programmes - Acute event costs (30 days in which the event occurs) for MI, ICH, recurrent stroke, TIA or mild IS, GI bleed estimated from Singh et al. 2013, Mittmann et al. 2012, Cohen et al. 2014 and the	Non-fatal recurrent stroke, TIA or mild –0.02 (Luengo-Fernandez 2013) Non-fatal recurrent stroke, severe –0.13 (Luengo-Fernandez 2013) GI bleed –0.03 (Bager et al. 2014)		stroke and a lower risk of bleeding - Increased OAC uptake increases the cost-effectiveness of ILR, but even at 100% uptake the most cost-effective OAC (apixaban) has an ICER above $175,000 per QALY gained **PSA** NR

			Saposnik et al. 2008 and Krueger et al. 2012 - Proportion who initiate OACs at diagnosis of AF, or after MI or recurrent stroke if AF is present (61%) taken from Bjorch et al. 2015	Canadian Institute for Health Information (CIHI) - The cost of death form other causes were estimated from Fassbender et al. 2009 and Tanuseputro et al. 2015			
Diamantopoulos et al. 2016							
Population Patients with a cryptogenic stroke or TIA **Intervention**: ICM (REVEAL XT) **Comparator:** SoC (ECG monitoring)	**Perspective:** UK NHS **Discount rate:** costs and benefits 3.5% **Cost year:** 2012/13 **Model type**: Markov (3-month cycle length) **Heath states**: - AF status (tracked throughout the model in all health states): AF free (patients receive aspirin), AF	- Data from the first 36 months of CRYSTAL-AF were used to model AF detection - AF detected by ICM at 3 months 8% and 3 years 30% - HR ICM vs SoC AF detection 8.78 (95% CI 3.47 to 22.2) - Per-cycle incidence of AF,	**Mortality** - Age-dependant mortality in the model was based on rates from ONS interim life tables for England and Wales and was adjusted, to exclude cerebrovascular events - Deaths due to cerebrovascular events were explicitly modelled and estimated from Dorian et al. 2014 and Lip et	Costs sourced from NHS Reference Costs - ICM device & insertion £1864 - ICM removal £491 - Cost of infection £532 - Unit cost of ECG £137 - Other ICH £2526 - GI bleed £1892 - Other major ECH £3999 - CRNM bleed	CRYSTAL-AF baseline 0.774 **Utilities sourced from Luengo-Fernandez et al. 2013** using the EQ-5D and UK population valuations: - History of AF 0.719 - Mild stroke (IS or HS) 0.730 - Moderate stroke (IS or HS) 0.500	**Total discounted costs per patient:** ICM; SoC -Total cost £19,631; £17,045 -Diagnostic costs £2,910; £666 -Health state costs £11,252; £10,610 -Event related costs £5,469; £5,769 -Total stroke event costs £3,958; £4,387 -Total bleed event costs £1,511; £1,382	**ICER, cost per QALY gained £17,175** **Other results:** -Cost per LY gained £15,354 -Cost per IS avoided £59,113 -Cost per stroke avoided (IS and HS) £61,319 -Cost per major bleed avoided (ICH, ECH) Dominated

	detected (patients receive NOACs in the absence of bleeds and may switch to aspirin in the event of bleeding), AF undetected (patients receive aspirin) - Temporary events: non-fatal ECH, non-fatal ICH, CRNMB - Events with permanent consequences: non-fatal IS, non-fatal HS, fatal IS, fatal HS, fatal ICH, fatal ECH - Post-event disability states (no further stroke or bleeding risks): post mild stroke, post moderate stroke, post severe stroke - Death **Time horizon**:	8.3% in the first cycle and 2.3% in subsequent cycles based on a diagnostic sensitivity of 96.1% (95% CI 91.7% to 100%) sourced fro Hendricks et al. 2010 - Per cycle probability of AF detection in the first and subsequent cycles (up to 3 years): 8% and 2.17% for ICM, 0.9% and 0.2% for SoC, respectively.	al. 2014 - Other ICH risk 0.13 - Major bleed risk 0.02 - Following a secondary non-fatal stroke, the mortality risk increases depending on the severity of the stroke (estimated from Huybrechts et al. 2008 and Brønnum-Hansen et al. 2001) and their treatment (estimated from Diener et al. 2012, Easton et al. 2012, Ntaois et al. 2012 and the EAFT Study Group 1993) - Mild stroke HR 2.56 - Moderate stroke HR 4.63 - Severe stroke HR 13.18 - Aspirin vs. placebo HR 0.91 - Warfarin vs. aspirin HR 1.09	£460 Event costs sourced from Luengo-Fernandez et al. 2013 and inflated to 2012/13 costs using the HCHS inflation indices: - Post-mild stroke (IS or HS) £2135 - Post-moderate stroke (IS or HS) £4165 - Post-severe stroke (IS or HS) £6324 - Mild IS £3401 - Moderate IS £17743 - Severe IS £24234 - Fatal IS £3059 - Mild HS £9903 - Moderate HS £25442 - Severe HS	- Severe stroke (IS or HS) 0.130 - Recurrent stroke 0.589 - Other ICH 0.700 - Post mild stroke (IS or HS) 0.727 - Post moderate stroke (IS or HS) 0.582 - Post severe stroke (IS or HS) 0.397 - Post recurrent stroke 0.659 **Utilities for temporary events** sourced from Dorian et al. 2014, Lip et al. 2014 and Sullivan et al. 2011 using a UK-based catalogue: - CRNM bleed 0.9997 - ECH 0.9942	**Total QALYs** ICM: 7.367 SoC: 7.216 **Total LYs**: ICM 10.500 SoC 10.332	**Sub-group analysis** -Substituting NOAC therapy with warfarin as the main anticoagulation treatment Cost per QALY gained £13,296 Cost per life year gained £12,862 -CHADS2 score: CHADS2 2; CHADS2 3; CHADS2 4, 5, 6 Cost per QALY gained £23,355; £17,950; £13,621 Cost per life year gained £22,068; £16,042; £11,223 **PSA** - ICM has probabilities 63.4% and 81% of being cost-effective at thresholds of £20,000 and £30,000 per QALY, respectively - Total costs: ICM £20,525; SoC £17,951

	lifetime This study was funded by Medtronic, Inc. and Medtronic, Switzerland		- NOAC vs. aspirin HR 0.98 **Risk of IS** - Estimated from several studies (Pister et al.2012, Diener et al. 2012, Easton et al. 2012, Gage et al. 2004, Mohan et al. 2009, Ntaiod et al. 2012) - Assumed to be related to AF status, virtual CHADS2 score, treatment, and age - Adjusted by a factor of 1.46 per decade according to Pisters et al. 2012 - AF free 0.0528 - AF undetected 0.0785 - AF detected (warfarin) 0.0310 - AF detected (NOAC) 0.0319	£43036 - Fatal HS £1592 Conventional SoC follow-up - Consists of (ECG), and Holter monitors (24 hour to 7 day) - Test frequencies were sourced from CRYSTAL-AF (Sanna et al. 2014) and unit costs from NHS Reference Costs: - SoC year 1 £29.74 - SoC year 2 £19.56 - SoC year 3+ £15.95 - ICM monitoring £49.50 Drug costs sourced from MIMS	**Disutilties applied in the model:** - History of AF -0.014 - Recurrent stroke (IS or HS) -0.15 - Post recurrent stroke (IS or HS) -0.068 - CRNM bleed -.0582 - ECH -.1511 - For strokes (IS or HS) and other ICH, the acute disutility was assumed to last for the duration of one cycle. For ECH, the acute disutility was assumed to last for 2 weeks and for CRNM bleeds, 2 days. - A utility decrement or multiplier was		- Total QALYs: ICM 7.343; SoC £7.182 **Tornado diagram illustrates the 8 most sensitive parameters:** -NOAC discontinuation -Baseline age -Cumulative detection by ICM at 3 years -CHADS2 score -Post-stroke health state utilities -OR of IS with NOAC vs. warfarin -HR of AF detection with ICM vs. SoC -Post-stroke costs

			Bleeding risks - Estimated from several studies (Ariesen et al. 2003, Easton et al. 2012, Granger et al. 2011, Hankey et al. 2012, Connolly et al. 2009) - Assumed to be treatment and age related - Adjusted by a factor of 1.97 per decade according to Ariesen et al. 2003 Risk of ICH - AF free 0.0055 - AF detected (Warfarin) 0.0119 - AF detected (NOAC) 0.0056 Risk of GI bleed - AF free 0.0115 - AF detected (Warfarin) 0.0111 - AF detected (NOAC) 0.134 CRNM bleed	Annual cost of warfarin INR monitoring sourced from Dorian et al. 2014, who estimated 18 monitoring visits per year £64.83	estimated based on the difference between the general population utility (by age and gender) and the utility of the health state or event reported by each study. - All utilities were adjusted to account for the age and sex of the population, according to Ara and Brazier 2010		

			- AF free 0.0756 - AF detected (Warfarin) 0.1012 - AF detected (NOAC) 0.0864 **Stroke severity** - Estimated from Dorian et al. 2014 and Lip et a. 2014: mild, moderate, severe, fatal - IS: 42%, 26%, 10%, 22% - HS: 28%, 23%, 12%, 37%				
Maervoet et al. 2017							
Population Patients with a cryptogenic stroke and suspected paroxysmal, silent AF **Intervention**: ICM (BioMonitor 2) **Comparator**:	**Perspective**: US payer (Medicare) **Discount rate**: applied, but rate NR **Cost year**: NR **Model type**: Markov (cycle length NR) **Heath states**: post cryptogenic stroke, MI, post mild/ moderate/severe	Diagnostic yield and accuracy based on RCTs and diagnostic accuracy studies, no further details reported.	NR	Clinical actions based on clinical expert's input, no further details reported.	NR (LYs measure of benefit)	**Total discounted cost per patient:** ICM US$90,100 SoC US$85,200 **Total QALYs:** NR (LYs measure of benefit)	**ICER, US$18,500 per LY gained** **Other results:** -ICM can avoid 48 strokes per 1000 patients, compared to the SoC. -Total discounted LYs per patient: ICM 9.7

conventional SoC, involving short-term, intermittent Holter monitoring	stroke and death. Other relevant clinical events modelled include: ischaemic and hemorrhagic stroke, transient ischaemic attack, MI, systemic embolism, other intra- or extracranial bleed, gastrointestinal bleed, minor bleed. **Time horizon**: lifetime Multiple drug treatment options included in the model (aspirin, new oral anticoagulants and warfarin)						SoC 9.5
Quiroz et al. 2017							
Population Patients with a cryptogenic stroke	**Perspective**: Dutch payer **Discount rate**: costs 4% and QALYs 1.5%	NR	NR	Costs were applied to each state according to occurrence of stroke, AF	Utilities were applied to each state according to occurrence of stroke, AF	NR	**ICER, €24,715 per QALY gained** **CHADS2 sub-group**

Intervention: ICM **Comparator**: conventional SoC	**Cost year**: NR **Model type**: Markov (3-month cycle length) **Heath states**: the presence and detection of AF, the occurrence of cerebrovascular and bleeding events and death **Time horizon**: lifetime			diagnosis and drug therapy use. Values and data sources NR	diagnosis and drug therapy use. Values and data sources NR		**analyses**: ICER ranged from €22,011 (CHADS2 score 4 to 6) to €29,795 (CHADS2 score 2) **PSA**: ICM had a probability of 91% of being cost-effective at a threshold of €80,000 per QALY gained
Thijs et al. 2018							
Population Patients with a cryptogenic stroke **Intervention**: long-term continuous monitoring with an ICM **Comparator**: conventional SoC	**Perspective**: Australian payer **Discount rate**: NR **Cost year**: NR **Model type**: Markov **Heath states**: NR **Time horizon**: lifetime	Used a linked evidence approach to estimate the rates of recurrent stroke when AF detection leads to initiation of oral anticoagulation, as detected using ICM during the lifetime of the device, or as detected using conventional care.	NR	Included all diagnostic and patient management costs. Values and data sources NR	Inputs determined by literature review, no further details reported.	NR	**ICER, A$29,570 per QALY gained** **CHADS2 sub-group analyses**: ICER ranged from A$26,342 (CHADS2 score 6) to A$42,967 (CHADS2 score 2). **PSA**: ICM had probabilities of 53.4% and 78.7% of being cost-effective at thresholds of $30 000 and $50 000 per QALY gained,

		Values and data sources NR.					respectively. PSA was undertaken to explore the effect of parameter uncertainty according to CHADS2 score and oral anticoagulation treatment effect

AF, atrial fibrillation; CRNM, clinically relevant non-major; ECH, extracranial haemorrhage; CI, confidence interval; GI, gastrointestinal; HR, hazard ratio HS, haemorrhagic stroke; ICM, insertable cardiac monitor; ICER, incremental cost-effectiveness ratio; ILR, implantable loop recorder; INR, international normalised ratio;
IS, ischemic stroke; KM, Kaplan Meier; ICH, intracerebral haemorrhage; NOAC, novel oral anticoagulant; NR, not reported; OAC, oral anticoagulant
PSA, probabilistic sensitivity analysis; QALY, quality-adjusted life year; RCT, randomised controlled trial; SoC, standard of care; TIA, transient ischemic attack;
LY, life years;

HRQoL evidence

Study	Elicitation method	Valuation method	Population	Health states and utility values
Alvarez-Sabin et al. 2016	Patients assessed their own HRQoL using the EQ-5D-3L 2 years post-stroke	NR	163 patients in Spain who suffered their first IS Mean (SD) age 67.5 (10.7) years Female n=83 (50.9%) 12.3% had AF	Mean (SD) utility 2 years after first IS: Total, 0.63 (0.28) Males, 0.67 (0.27) Females, 0.58 (0.29) Utility with AF: Males, 0.64 (0.27) Females, 0.53 (0.35)
Bach et al. 2011	Patients assessed their own HRQoL using the EQ-5D-3L (time NR)	Responses were converted into utilities using scoring algorithms for the German population (Greiner et al. 2003)	3,109 patients in Germany were included from the DETECT study. MI; stroke; MI and stroke Total number: 2,181; 783; 145 Mean (SD) age, years: 67.4 (10.2); 68.3 (10.8); 70.3 (8.4) Female, n(%): 640 (29.5%); 352 (44.0%); 37 (25.9%)	Mean (SD) utility In the AF population No stroke or MI: (n=1,504) 0.67 (0.18) Stroke: (n=113) 0.59 (0.22) MI: (n=218) 0.60 (0.21) MI and stroke: (n=25) 0.47 (0.26) Age, years: MI; stroke; MI and stroke 18 to 44: (n=58) 0.77 (0.18); (n=26) 0.68 (0.18); NR 45 to 64: (n=694) 0.67 (0.19); (n=226) 0.63 (0.19);(n=32) 0.61 (0.23) >64: (n=1,429) 0.66 (0.19);(n=531) 0.61 (0.20); (n=113) 0.56 (0.19)
Berg et al. 2010	Patients assessed their own HRQoL	Responses were converted into utilities	Patients with AF from 35 countries in the Euro heart survey.	Mean utility (SD) AF, baseline: 0.751 (0.269)

	using the EQ-5D-3L at baseline and 1-year post-AF	using UK population tariffs developed by Dolan 1997*	Baseline n=5,050; follow-up n=3,045 Mean age, years 66.4 (12.8); 66.6 (12.6) Male 58.1%; 59.8% Western and Northern Europe 23.7%; 26.2% AF type: AF symptoms, 69.5%; 34.2% First detected AF, 19.1%; 9.5% Paroxysmal AF, 29.1%; 29.8% Persistent AF, 22.7%; 14.4% Permanent AF, 29.1%; 40.5% AF considered cured, NA; 5.8%	AF, 1-year follow-up: 0.779 (0.253) Final model specification results for determinants of utility at follow-up, adverse events during follow-up CLAD; OLS, mean (95% CI) MI -0.181 (-0.298 to -0.073); -0.142 (-0.235 to -0.049) Stroke -0.229 (-0.429 to -0.144); -0.272 (-0.345 to -0.198) CHF -0.125 (-0.167 to -0.095); -0.149 (-0.177 to -0.121) Other major AEs -0.086 (-0.115 to -0.051); -0.108 (-0.135 to -0.082)
Bushnell et al. 2014	Patients assessed their own HRQoL using the EQ-5D-3L at 3 and 12 months post-stroke or post-TIA	Responses were converted into utilities using US population-based preference weights (Rockville 2005)	1,370 patients in the USA in the AVAIL Registry enrolled in the GWTG–Stroke hospitals. Median age, years 65 (IQR 56 to 75) Race, white 83.4%, black 10.7%, Hispanic 2.5% Stroke type, IS 77.4%, TIA 22.6% Previous stroke or TIA 23.0% AF/flutter 10.8%	Median (IQR) utility 3-months; 12-months Total (n=1,370): 0.83 (0.76 to 1.00); 0.83 (0.74 to 1.00) Female (n=634): 0.81 (0.71 to 0.85); 0.83 (0.71 to 1.00) Male (n=736): 0.84 (0.76 to 1.00); 0.84 (0.76 to 1.00)
Chang et al. 2016	Patients assessed their own HRQoL using the EQ-5D-3L 6 months post-stroke	Responses were converted into utilities using Kang 2006	First-time stroke patients included in the KOSCO study IS n=2,289 (80.1%) HS n=568 (19.9 %) Mean age 64.3 years Ratio of males to females 1.48:1	Mean (SD) utility Total: 0.82488 (0.18644) IS: 0.82411 (0.18660) HS: 0.82818 (9.18595)
Christensen et al. 2009	Patients assessed their own HRQoL	Responses were converted into utilities	621 patients included in the FAST trial from 22 countries.	Mean (SD) utility after ICH 0.62 (0.3)

	using the EQ-5D-3L 3 months post-stroke	using US population-based preference weights (Shaw et al. 2005 and Luo et al. 2005)	Mean age 64 years (range, 23 to 97 years) 60% male 68% white, 21% Asian, and 9% black.	
Ghatnekar et al.2013	Patients assessed their own HRQoL using the EQ-5D-3L 3 months post-stroke	Responses were converted into utilities using UK population tariffs developed by Dolan 1997*	Patients included in the Ris-Stroke registry in Sweden Used two time periods with patients who had experienced their first haemorrhagic or ischaemic stroke (ICD-10: I61, I63 and I64)	Mean (SD) utility 2006 sample: (n=105) 0.57 (0.42) 2009 sample: (n=439) 0.61 (0.38)
Golicki et al. 2015	Patients assessed their own HRQoL using the EQ-5D-3L and EQ-5D-5L during their index hospitalisation (median 8 days since admission)	To obtain 3L index values, the Polish EQ-5D-3L value set based on the TTO valuation technique (Golicki et al. 2010). To obtain 5L index values, the Polish interim EQ-5D-5L value set (Golicki et al. 2014) estimated with crosswalk methodology developed by van Hout et al 2012	408 patients with cerebral infarction, intracranial or subarachnoid hemorrhage (I63, I61 or I60, according to the ICD-10 classification) Patients had to be Polish language native speakers Male 51.5 % males Mean age 69.0 years	Mean (95% CI) EQ-5D-3L values by stroke type (ICD-10) I60 SAH: (n=8) 0.390 (0.016 to 0.764) I61 ICH: (n=35) 0.399 (0.222 to 0.576) I63 Cerebral infarction: (n=342) 0.545 (0.506 to 0.583) Utility by age, years 0 to 60: (n=95) 0.595 (0.527 to 0.663) 61 to 70: (n=104) 0.612 (0.542 to 0.681) 71 to 80: (n=111) 0.473 (0.405 to 0.542) >80: (n=81) 0.422 (0.322 to 0.523)

				mRS 5 (n=65) -0.027 (-0.098 to 0.044) 4 (n=56) 0.271 (0.181 to 0.360) 3 (n=71) 0.597 (0.550 to 0.644) 2 (n=108) 0.705 (0.668 to 0.742) 1 (n=68) 0.828 (0.793 to 0.863) 0 (n=19) 0.884 (0.829 to 0.939)
Golicki et al. 2015	Patients assessed their own HRQoL using the EQ-5D-3L and EQ-5D-5L 1 week and 4 months post-stroke	To obtain 3L index values, the Polish EQ-5D-3L value set based on the TTO valuation technique (Golicki et al. 2010). To obtain 5L index values, the Polish interim EQ-5D-5L value set (Golicki et al. 2014) estimated with crosswalk methodology developed by van Hout et al 2013	Adult patients with primary ICH or cerebral infarction (I61 or I63 according to ICD- 10 classification). Individuals had to be Polish language native speakers. 112 patients at baseline Mean (SD) age 70.6 years (11.0) Female n=58 (51.8%) ICH n=8 (7.1%) Cerebral infarction n=104 (92.9%)	Mean (SD) EQ-5D-3L utility values Baseline: 0.584 (0.353) Follow-up: 0.694 (0.281) mRS: Improved n=43; Stable n=50; Deteriorated n=19 Baseline: 0.531 (0.382); 0.595 (0.357); 0.674 (0.253) Follow-up: 0.769 (0.174); 0.691 (0.286); 0.530 (0.150) Barthel index-based external criterion: Improved n=37; Stable n=60; Deteriorated n=15 Baseline: 0.323 (0.377); 0.731 (0.248); 0.637 (0.293) Follow-up: 0.634 (0.228); 0.796 (0.198); 0.434 (0.445)
Haacke et al. 2006	Patients assessed their own HRQoL using the German version of the EQ-5D-3L 4 years post-stroke	NR	77 patients in Germany experiencing IS, TIA, or HS Age, years n=77 71.7 (11.3) HS n=5 73.9 (8.6) Infarct n=34 70.6 (7.9) TIA n=18 63.1 (17.0) TIA and Infarct n=20 69.6 (11.0) mRS, independence n=47 1.1 (0.8)	Mean utility (SD) Total: 0.73 (0.32) Haemorrhage: (n=5) 0.74 (0.39) Infarct, Infarct+TIA: (n=54) 0.68 (0.33) TIA: (n=18) 0.90 (0.16) Male: (n=35) 0.75 (0.31) Female: (n=42) 0.72 (0.32) Age 50 to 65: 0.90 (0.16)

			mRS, severe disability n=30 3.6 (0.7)	Age 65 to 75: 0.68 (0.34) Age >75: 0.64 (0.33) mRS “independence”: (n=47) 0.86 (0.21) mRS "severe disability": (n=30) 0.44 (0.34)
Hallinen et al. 2016	Patients with AF assessed their own HRQoL using the EQ-5D-3L (time NR)	NR	5,690 Finnish inhabitants with AF who participated in the Health 2000 study (Methodology report, Health 2000 Survey 2008).	In the regression model the constant term was 1.068, the disutility associated with AF was −0.045, and the decrease in QoL per year of age was −0.004. The, AF equals 0.743 (=1.068 − 0.004 × 70 − 0.045, where 70 is the average age of patients Mean disutility Mild IS -0.087 Moderate IS -0.198 Severe IS -0.644 Mild HS -0.071 Moderate HS -0.352 Severe HS -0.578 Systemic embolism -0.084 Other intracranial bleeds, per episode -0.168 (applied for 6 weeks) Other major bleeds -0.168 (applied for 14 days) CRNMB -0.0582 (taken from Sullivan et al. 2011, applied for 2 days) MI -0.005
Lindgren et al. 2008	Patients assessed their own HRQoL using the EQ-5D-3L 3, 6, 9 or 12 months	Responses were converted into utilities using UK population tariffs developed by Dolan 1997*	275 patients with IS or HS included in the Ris-stroke registry in Sweden Mean (SD) age 64.4 years (9.3) First stroke 79.3%	Mean (SD) utility 3 months: (n=57) 0.65 (0.31) 6 months: (n=60) 0.75 (SD 0.23) 9 months: (n=53) 0.62 (0.29)

	post-stroke		IS 76.3% Female 40.4%	12 months: (n=55) 0.66 (0.28) All patients: (n=225) 0.67 (0.28)
Lopez-Bastida et al. 2012	Patients assessed their own HRQoL using the EQ-5D-3L, 1,2 or 3 years post-stroke	Responses were converted into utilities using UK population tariffs developed by Dolan 1997*	448 patients in the Canary Island diagnosed with stroke Year 1 n=94 Year 2 n=205 Year 3 n=149 Mean age 67.1 years (12.2) Female 43.3%	Mean (SD) utility Total: 0.4708 (0.4388) Year 1: 0.4961 (0.4246) Year 2:.4674 (0.4407) Year 3: 0.4596 (0.4475)
Luengo-Fernandez et al. 2013	Patients assessed their own HRQoL using the EQ-5D-3L over five years	Responses were converted into utilities using UK population tariffs developed by Dolan 1997*	TIA patients and stroke patients included in the OXVASC study from 9 general practices across Oxfordshire, UK. Stroke (n=748); TIA (n=444) Mean age, years (SD): 75 (12); 73 (13) Males n (%): 370 (49%); 194 (44%) Stroke severity by NIHSS score, n(%): Minor, 436 (59%) Moderate,169 (23%) Severe, 133 (18%) Stroke type, n(%): IS, 618 (83%) ICH, 54 (11%) SAH, 38 (5%) Unknown, 38 (3%)	Month: 1; 6; 12; 24; 60 Mean utility (SD) TIA: (n=314) 0.78 (0.25); (n=244) 0.76 (0.27); (n=305) 0.78 (0.26); (n=173) 0.76 (0.26); (n=210) 0.80 (0.22) All stroke: (n=445) 0.64 (0.33); (n=339) 0.70 (0.29); (n=368) 0.70 (0.27); (n=235) 0.66 (0.29); (n=241) 0.68 (0.31) Stroke severity by NIHSS score Minor stroke: (n=314) 0.73 (0.25); (n=244) 0.76 (0.25); (n=302) 0.74 (0.25); (n=190) 0.70 (0.27); (n=207) 0.73 (0.27) Moderate stroke: (n=98) 0.50 (0.37); (n=69) 0.62 (0.32); (n=88) 0.65 (0.25); (n=53) 0.60 (0.30); (n=46) 0.56 (0.38) Severe stroke: (n=32) 0.13 (0.32); (n=23) 0.38 (0.37); (n=26) 0.41 (0.38); (n=20) 0.45 (0.33); (n=14) 0.38 (0.39)

				Stroke type Ischemic: (n=404) 0.64 (0.33); (n=301) 0.70 (0.29); (n=382) 0.70 (0.27); (n=246) 0.66 (0.29); (n=244) 0.67 (0.31) Primary ICH: (n=23) 0.56 (0.37); (n=18) 0.65 (0.32); (n=17) 0.67 (0.36); (n=6) 0.81 (0.18); (n=11) 0.79 (0.25) SAH: (n=9) 0.70 (0.28); (n=12) 0.81 (0.14); (n=13) 0.73 (0.26); (n=9) 0.83 (0.17); (n=12) 0.85 (0.21) Unknown: (n=9) 0.56 (0.42); (n=8) 0.66 (0.35); (n=6) 0.62 (0.34); (n=2) 0.46 (0.36); (n=2) 0.32 (0.38)
Lunde et al. 2013	Patients assessed their own HRQoL using the EQ-5D-3L 6 months post-stroke	Responses were converted into utilities using UK population tariffs developed by Dolan 1997*	408 patients suffering from IS, HS, or TIA admitted to the stroke unit of a large Norwegian hospital. Mean (SD) age 68.74 years (12.93) Male 64% IS 42%, HS 26%, TIA 36%	Mean (SD) utility (n=345) 0.70 (0.30)
Mar et al. 2005	Patients assessed their own HRQoL using the EQ-5D-3L 1-year post-stroke	NR	100 patients in Spain with a first diagnosis of stroke (IS, HS, TIA or undetermined) Mean age 70.9 years (SE 12.29)	Mean (SE) utility <95 Barthel Index: (n=51) 0.2208 (0.0547) >=95 Barthel Index: (n=49) 0.7729 (0.0347) Total: (n=100) 0.4913 (0.0427) Autonomous 0.736 (0.069) Disabled 0.4013 (0.2213)
Mar et al. 2015	Patients assessed their own HRQoL using the EQ-5D-3L	Responses were converted into utilities using general Spanish	321 patients in Spain with first IS (90.7%) or HS (9.3%) Mean (SD) age 72.1 years (13.2)	Mean (SD) utility Discharge: 0.57 (0.32) 3 months: 0.62 (0.30)

	at admission, 3 and 12 months post-stroke	population (Badía et al. 1999)	Male 54.8% AF 50.2% Stroke recurrence at 1 year 7.8%	12 months: 0.65 (0.28)
Pickard et al. 2004	Patients assessed their own HRQoL using the EQ-5D-3L at admission and 6 months post-stroke	Responses were converted into utilities using UK population tariffs developed by Dolan 1997*	124 patients with IS in Canada Mean (SD) age 68.3 years (14.6) Gender, female/male 47/53	Mean (SD) utility Baseline: (n=124) 0.31 (0.38) Month 1: (n=102) 0.55 (0.36) Month 3: (n=99) 0.61 (0.30) Month 6: (n=95) 0.62 (0.34)
Pickard et al. 2005	Patients assessed their own HRQoL using the EQ-5D-3L at baseline and 6 months post-stroke	Responses were converted into utilities using UK population tariffs developed by Dolan 1997*	98 patients with IS in Canada Mean age 67 years (15) Male 52% Previous stroke 14%	Mean (SD) utility n=98 Baseline 0.31 (0.38) 6 months 0.62 (0.33) Barthel index: stable (n=34); some improvement (n=35); large improvement (n=27) Baseline: 0.41 (0.40); 0.33 (0.38); 0.15 (0.31) 6 months: 0.52 (0.42); 0.65 (0.28); 0.74 (0.21) mRS: stable (n=19); some improvement (n=26); large improvement (n=49) Baseline: 0.13 (0.34); 0.30 (0.42); 0.37 (0.34) 6 months: 0.29 (0.34); 0.58 (0.31); 0.80 (0.19)
Roalfe et al. 2012	Patients assessed their own HRQoL using the EQ-5D-3L (time NR)	NR	1,762 patients with AF in the UK included in the BAFTA study Mean age 82 years (range 75-99) Males (n=888); females (n=778) History of MI 108 (13%); 68 (9%) TIA: 84 (10%); 66 (9%)	Mean (SD) utility Males (n=867) 0.77 (0.22) Females (n=737) 0.68 (0.26)

			Stroke: 66 (8%); 42 (6%)	
Sullivan et al. 2011	Patients assessed their own HRQoL using the EQ-5D-3L (time NR)	Responses were converted into utilities using UK population tariffs developed by Dolan 1997*	79,522 individuals taken from the US-based MEPS OLS, Tobit, and CLAD regression methods were used to estimate the 'marginal disutility' of each condition (ICD-9 codes, CCC codes) controlling for covariates.	EQ-5D (UK-Dolan) Scores by CCC CCC 100 Acute MI N=496 Mean age 63.1 years Mean EQ-5D 0.605 SE 0.022 95% CI 0.561 to 0.648 Disutility of condition -0.0557 CCC 109 Acute Cerebrovascular Disease (stroke) N=709 Mean age 68.3 years Mean EQ-5D 0.523 SE 0.019 95% CI 0.485 to 0.561 Disutility of condition -0.1009
van Eeden et al. 2015	Patients assessed their own HRQoL using the Dutch EQ-5D-3L 2, 6 and 12 months post-stroke	Responses were converted into utilities using Dutch tariffs (Lamers et al. 2005)	352 patients with first ever or recurrent stroke Mean age (SD) 66.8 years (12.27) Male 64.8% IS 93%	Mean (SD) utility 2 months: 0.73 (0.24) 6 months: 0.74 (0.25) 12 months: 0.74 (0.24)
Wang et al. 2017	Patients assessed their own HRQoL at 3-month intervals for up to 48 months.	Responses were converted into utilities using an algorithm developed for the US	10,706 patients included in the ENGAGE AFTIMI 48 trial from 46 counties to asses the prevention of stroke or systemic embolism in AF	Mean (SD) utility Major GI Bleeding Event: 0.821 (0.166), no event 0.837 (0.152) Major Non-GI Bleeding (extracranial) Event: 0.843

	Authors estimated the impact of different categories of bleeding events on health-state utility over 12 months following the event.	population (EuroQol 1990)	Major GI Bleeding Event (N=207) Mean age, years (SD) 74.6 (8.6), male 61.4% Prior MI, 13.5%; Prior stroke, 16.4%; Prior TIA, 11.1% Major Non-GI Bleeding (extracranial) Event (N=152) Age 73.6 (8.8), male 64.5% Prior MI, 11.8%; Prior stroke, 17.8%; Prior TIA, 12.5% CRNM Bleeding Event (N=1419) Age 72.1 (9.2), male 60.2% Prior MI, 11.6%; Prior stroke, 18.3%; Prior TIA, 13.5% Minor Bleeding Event (N=714) Age 72.3 (9.2), male 61.9% Prior MI, 10.8%; Prior stroke, 17.1%; Prior TIA 14.8%	(0.159), no event 0.837 (0.152) CRNM Bleeding Event: 0.843 (0.147), no event 0.836 (0.110) Minor Bleeding Event: 0.833 (0.163), no event 0.837 (0.152)
Xie et al. 2006	Patients (26% proxy) assessed their own HRQoL using the EQ-5D-3L (time NR)	Responses were converted into utilities using US population-based preference weights (Shaw et al. 2005)	1,040 patients in the US who “had ever been diagnosed as having had a stroke or transient ischemic attack.” Data obtained from the Household Component of the MEPS Age, years :18 to 49, 12.6%, 50 to 64, 26.4%; 65 to 74, 25.6%; 75 to 84, 27.7%; 85 or older,	Mean (SE) utility Age, years 18 to 49: 0.73 (0.02) 50 to 64: 0.67 (0.01) 65 to 74: 0.72 (0.01) 75 to 84: 0.70 (0.01) >84: 0.60 (0.03) Total 0.69 (0.01)

			7.8% Male 43.9% Race: White, 78.0%; Black, 17.7%; Other, 4.3%	 Male 0.72 (0.01) Female 0.67 (0.01)

AF, atrial fibrillation; AVAIL, The Adherence eValuation After Ischemic stroke–Longitudinal; BAFTA, Birmingham Atrial Fibrillation Treatment of the Aged; CCC, Clinical Classification Categories; CLAD censored least absolute deviations; DETECT, Diabetes Cardiovascular Risk Evaluation: Targets and Essential Data for Commitment of Treatment; ENGAGE AF-TIMI 48, Effective Anticoagulation with Factor Xa Next Generation in Atrial Fibrillation–Thrombolysis in Myocardial Infarction 48; OXVASC, Oxford Vascular Study; OLS Ordinary least squares; FAST, Factor Seven for Acute Haemorrhagic Stroke; HRQoL, health-related quality of life; HS, haemorrhagic stroke; ICD, International Statistical Classification of Diseases; ICH, intracerebral haemorrhage; IQR, interquartile range; IS, ischemic stroke; KOSCO, Korean Stroke Cohort for Functioning and Rehabilitation Study; MEPS Medical Expenditure Panel Survey; MI, myocardial infarction; mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale; NR, not reported; SD, standard deviation; SE, standard error; SAH, Subarachnoid haemorrhage; TIA, transient ischemic attack; TTO, time trade-off; VISTA, Virtual International Stroke Trials Archive

*Health states valued by the general public using the TTO