National Institute for Health and Care Excellence

DIAGNOSTICS ASSESSMENT PROGRAMME

Evidence overview

Implantable cardiac monitors to detect atrial fibrillation after cryptogenic stroke

This overview summarises the key issues for the diagnostics advisory committee's consideration. This document is intended to be read with NICE's final scope for the assessment and the diagnostics assessment report. A glossary of terms is in appendix B. Academic-in-confidence information is marked [redacted]. Commercial-in-confidence information is marked [redacted].

1 Background

1.1 Introduction

The purpose of this assessment is to evaluate the clinical and cost effectiveness of implantable cardiac monitors (BioMonitor 2-AF, Confirm Rx and Reveal LINQ) to detect atrial fibrillation after cryptogenic stroke.

Implantable cardiac monitors are also known as implantable loop recorders or insertable cardiac monitors. The devices monitor heart rhythm for longer than heart rhythm monitors which are worn externally (for example, Holter monitors). Implantable cardiac monitors can identify atrial fibrillation and could be particularly helpful for identifying atrial fibrillation that is not always present (intermittent or paroxysmal atrial fibrillation) in people who have had a cryptogenic stroke. The devices might improve detection of intermittent atrial fibrillation in people who have had a cryptogenic stroke, that is, an ischaemic stroke with no identified cause. This includes transient ischaemic attack (TIA).

If atrial fibrillation is diagnosed, anticoagulant therapy can be offered to reduce the risk of having another stroke or TIA.

The monitors are implanted under the skin of a person's chest using a small incision under local anaesthetic. They continuously monitor heart rhythm for up to several years and record information if the device detects an arrhythmia. The devices contain algorithms that detect potential atrial fibrillation. These algorithm parameters can be varied to adjust the electrocardiogram (ECG) features identified and flagged as potential atrial fibrillation. Recorded ECGs are remotely transmitted to clinicians, who determine if atrial fibrillation has occurred and make clinical decisions about continued monitoring or treatment.

Provisional recommendations on the use of these technologies will be developed by the diagnostics advisory committee at the committee meeting on 16 April 2019.

1.2 Scope of the assessment

Table 1 Scope of the assessment

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 transient ischaemic attack [TIA])for whom there is a suspicion of paroxysmal atrial fibrillation, and who have had at least 24 hours of outpatient external ambulatory ECG monitoring that has not detected atrial fibrillation. Potential subgroups: • people with varying lengths of previous outpatient external ambulatory ECG monitoring that has not detected atrial fibrillation (for example 1, 2, 7, 14 or 30 days) • people with a cryptogenic TIA • people with a cryptogenic stroke (excluding TIA).
Interventions	• BioMonitor 2-AF • Confirm RX • 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: • diagnostic accuracy • diagnostic yield (number of atrial fibrillation diagnoses) • detection of other cardiac pathologies or incidental findings (non-atrial fibrillation) • time to diagnosis of atrial fibrillation • time to initiation of anticoagulants • uptake of anticoagulants • incidences of device failure (such as inability to transmit data or unexpectedly short battery life) and device removal because of failure or adverse events • hospitalisations caused by atrial fibrillation • number of outpatient visits related to monitoring for atrial fibrillation • ease of use of devices for clinicians (including insertion).
	Clinical outcomes for consideration may include: • mortality • morbidity (including further strokes or TIAs, other thromboembolisms and heart failure, any complications arising from preventative treatment, such as adverse effects of anticoagulation treatment, and any adverse events related to implanting or removing the devices, such as infection or inflammation).
	Patient-reported outcomes for consideration may include: • health-related quality of life • 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.

Further details including descriptions of the interventions, comparator, care pathway and outcomes can be found in the final scope.

2 The evidence

This section summarises data from the diagnostics assessment report compiled by the external assessment group (EAG).

2.1 Clinical effectiveness

The EAG did a systematic review to identify evidence on the clinical effectiveness and diagnostic accuracy of the implantable cardiac monitors to detect suspected atrial fibrillation after cryptogenic stroke. The devices reviewed were BioMonitor 2-AF, Confirm Rx and Reveal LINQ. Details of the systematic review start on page 13 of the diagnostics assessment report.

Studies were included if they assessed the devices in a population of people with a cryptogenic stroke or cryptogenic transient ischaemic attack (TIA) when there was suspected paroxysmal atrial fibrillation. Because of the small number of studies identified, the requirement for at least 24 hours of outpatient external ambulatory electrocardiogram (ECG) monitoring without atrial fibrillation detection before the devices were implanted (as per current practice) was not applied. Also, data from earlier versions of the devices were considered.

Because only 1 study (the CRYSTAL-AF randomised controlled trial) met the EAG's initial eligibility criteria, the EAG relaxed the study inclusion criteria to consider single-arm observational studies. The EAG chose not to change the population inclusion criteria because it considered that data from non-cryptogenic stroke populations would not represent the device's performance in people with cryptogenic stroke or TIA. This is because non-cryptogenic stroke populations will have different incidence rates of atrial fibrillation. However, the EAG provided a summary of studies highlighted by the device manufacturers that were not done in a cryptogenic stroke population. The EAG further highlighted that the patient population, duration of monitoring and the type of atrial fibrillation would affect estimates of device performance. Results of the clinical effectiveness review start on page 19 of the diagnostics assessment report.

Comparative studies

There was 1 study identified (reported in 6 publications) that compared the effectiveness of using 1 of the devices to conventional follow up: the CRYSTAL-AF study. This was an open-label, parallel group randomised controlled trial that used Reveal XT (an earlier version of the Reveal LINQ). The XT model is larger. The EAG commented that evidence from diagnostic accuracy studies (discussed later) suggests that the Reveal LINQ has better specificity than the previous XT model, is easier to implant and causes fewer complications. Table 2 on page 7 of the diagnostic assessment report compares the 2 devices.

People 40 years or older who had a recent episode of cryptogenic symptomatic TIA or recent episode of cryptogenic ischaemic stroke had the Reveal XT (n=221) or conventional follow-up care (n=220). Follow up in the control group was ECG monitoring at the discretion of the site investigator. The study was done in 55 centres across 14 countries in Europe (none in the UK), Canada and the USA. The EAG commented that there were similar numbers of withdrawals between the 2 arms (except for crossovers, discussed below). Data were collected for up to 36 months follow up, but

relatively few people reached this point (24 in each arm). Mean duration of follow up was 20.3 months for Reveal XT and 19.2 months for conventional follow up.

Baseline characteristics of enrolled patients are in table 5 in the diagnostics assessment report (page 27). The EAG noted that although there were no significant differences between study arms, there were differences in the numbers of people with patent foramen ovale and history of prior stroke; however, these were small and unlikely to be because of systematic issues with randomisation. Clinical experts commented that the population was slightly younger than people expected to be eligible for an implantable cardiac monitor in the UK. Also, a higher proportion of TIA (rather than stroke) would be expected in clinical practice (closer to 20%, instead of about 9% seen in each of the study arms). All patients would be expected to be taking an antiplatelet agent (about 96% in each arm were using an antiplatelet agent at baseline).

Pre-planned subgroup analyses were age, sex, race or ethnic group, type of index event, presence or absence of patent foramen ovale, and $CHADS_2$ score (a predecessor to the CHA_2DS_2VASc score).

The EAG's clinical experts commented that the tests used in the trial to define a stroke as cryptogenic were broadly the same as what would be done in the NHS. Pre-enrolment screening for atrial fibrillation was Holter monitoring for 71.2% of people (median duration of 23 hours, interquartile range 21 to 24 hours), and the remaining people had inpatient telemetry monitoring only. The EAG commented that this meant almost 30% of people did not have any outpatient ECG monitoring (as specified in the scope) and that not all patients who did have outpatient ECG monitoring had it for at least 24 hours.

The EAG commented that this trial was sponsored by Medtronic, manufacturers of the device used in the study. The EAG also commented that authors of publications for this study reported employment, grants and personal fees from this company.

A full description of the CRYSTAL-AF study is in the diagnostics assessment report, starting on page 22. The EAG considered that this to be the most robust clinical evidence for the Reveal LINQ, even though it relates to an earlier version of the device.

Non-comparative studies

Comparative data were not identified for the BioMonitor 2-AF, Confirm Rx or the current Reveal LINQ version. Therefore, the EAG reviewed single-arm observational studies in cryptogenic stroke (including TIA) populations to identify available data on these devices.

There were 26 observational studies (reported in 60 publications) found. All but 1 study assessed either the Reveal LINQ or the Reveal XT. In 1 study (Israel et al. 2017), 13% of people used the BioMonitor (an earlier version of the BioMonitor 2-AF), but results were not reported by device. The EAG commented that these studies therefore do not provide any data for the BioMonitor 2-AF or Confirm Rx, but that they did supplement data from the CRYSTAL-AF trial.

Sample sizes in the studies ranged from 14 to 1,247. Only 1 study (Cotter et al. 2013) was done in the UK. Most studies (17) were prospective single-arm observational studies. There were 5 retrospective studies (Asaithambi et al. 2018, Chalfoun et al. 2016, Heckle et al. 2018, Li et al. 2018 and Salahuddin et al. 2015) and 1 did not report a clear methodology (Cotter et al. 2013). Ritter et al. (2013) did a within-patient comparison of the Reveal XT and 7-day Holter ECG monitoring. Choe et al. (2015) used the CRYSTAL-AF data set to predict how many cases of atrial fibrillation detected by the Reveal XT would have been detected by shorter length intermittent ECG monitoring strategies using simulations. Ziegler et al. 2017 presented data from a registry of people who had the Reveal LINQ and used simulations to predict how many people with atrial fibrillation detected by the device would have been identified by shorter (non-continuous) ECG monitoring.

Further details on the observational studies are in the diagnostics assessment report, starting on page 40.

Quality assessment of studies

Randomised controlled trials

CRYSTAL-AF was assessed using the Cochrane risk of bias 2.0 tool. The full quality assessment is in the diagnostics assessment report starting from page 28. There was some concern about risk of bias because the trial was open-label and not all people had the randomised intervention required by the study protocol (5.4% of people assigned to Reveal XT got conventional follow up; 2.7% of people assigned conventional follow up got Reveal XT). Also, device implantation was delayed for 11.5% of people who had the Reveal XT (median length of delay was 6 days, interquartile range 1 to 32 days). The EAG noted that results were analysed by intention-to-treat population and by including patients who did not have Reveal XT, received it late, or crossed over to conventional follow up. This means the estimated benefit of having the device may be conservative. Delays in implanting the Reveal XT were mostly short and unlikely to affect outcomes. The EAG commented that the lack of blinding was unlikely to affect relative atrial fibrillation detection rates between groups. It noted that only a small number of people were followed up after 12 months, so the 24 and 36 month results are likely to be less reliable than results from 6 and 12 months, but the direction of this bias is unclear.

Observational studies

The EAG stated that formal quality assessment of the 26 additional, non-RCT studies identified was not possible. However, it considered them all to be at high risk of bias because of their single-arm designs. Because of heterogeneity between the studies the EAG did not consider it appropriate to pool results from these studies. This included the model of device used, detection settings, patient characteristics, rigor of stroke assessment, severity of index stroke, definition and adjudication of atrial fibrillation, and length of follow up.

Evidence on ability to detect atrial fibrillation

Diagnostic yield (atrial fibrillation detection rate)

Atrial fibrillation detection rate at 6 months was CRYSTAL-AF's primary outcome (episodes had to last more than 30 seconds). At 6 months, 19 people were diagnosed with atrial fibrillation in the Reveal XT arm, compared with 3 people in the conventional follow-up arm. Increased atrial fibrillation detection with the Reveal XT was seen across all time points (see table 2). The increased detection of atrial fibrillation by the Reveal XT was consistent across all pre-specified subgroups (age, sex, race or ethnic group, index event, presence or absence of patent foramen ovale, and $CHADS_2$ score), with no significant interactions. Most people who had atrial fibrillation detected by the Reveal XT were asymptomatic (34 out of the 42 detected by 36 months).

Table 2 Atrial fibrillation detection in CRYSTAL-AF

Months	Number of patients with atrial fibrillation detected (cumulative)	
	Reveal XT [n (% ITT)]	**Conventional follow up** [n (% ITT)]
1	8 (3.6%)	1 (0.5%)
6	19 (8.6%)	3 (1.4%)
12	29 (13.1%)	4 (1.8%)
24	38 (17.2%)	5 (2.3%)
36	42 (19.0%[a])	5 (2.3%)[a]

Abbreviation: ITT: intention to treat

[a] Proportions are based on the intention-to-treat population. Estimated detection rates are higher in the 36-month Kaplan–Meier analysis because of the non-informative censoring of patients lost to follow up (atrial fibrillation detection rate estimated as 30% with the Reveal XT and 3% with conventional follow up).

All 26 observational studies reported atrial fibrillation detection rate. Detection rates varied widely; ranging from 6.7% to 40.9% (length of monitoring varied between studies). Full details of the included studies are in table 17 of the diagnostics assessment report, starting on page 48.

Several studies reported atrial fibrillation detection rates over multiple time points (see table 3). The EAG commented that the studies generally show that a minority of patients are diagnosed in the first month (about 10% of those detected by 1 year), around 70 to 80% (of the total number of people with atrial fibrillation detected in a study) are diagnosed by 6 months, and a small number after a year of monitoring.

Table 3 Atrial fibrillation detection rates in observational studies reporting follow-up time points

Study	Device	Atrial fibrillation threshold	Follow up (months)	Atrial fibrillation detection rate (%)
Asaithambi et al. 2018	Reveal LINQ	NR	1	9.0
			6	20.1
			18 (median)	29.1
Chalfoun et al. 2016	Reveal LINQ	NR	0.5	7.3
			1	9.4
			6	17.2
Seow et al. 2018	Reveal LINQ	2 minutes or more	6	12.7
			12	15.5
Ziegler et al. 2017	Reveal LINQ	2 minutes or more	1	4.1
			24	19.1
Poli et al. 2016	Reveal LINQ (51.4%) or XT (48.6%)	2 minutes or more	6	28.0
			12	33.3
Muller et al. 2017	Reveal XT	30 seconds or more	1	8.9
			11	17.8
Ritter et al. 2013	Reveal XT	30 seconds or more	0.25 (7 days)	5.0
			3	11.7
			13 (median)	16.7
Israel et al. 2017	Reveal XT (87%) or BioMonitor (13%)	2 minutes or more	3	12.2
			9	22.8
			13	23.6

All or most detected atrial fibrillation in the observational studies (when stated) was asymptomatic, as was also seen in CRYSTAL-AF.

There were 2 observational studies that estimated how many atrial fibrillation episodes would have been detected by intermittent ECG monitoring. These used data sets generated by the Reveal XT (in CRYSTAL-AF; Choe et al. 2015) or Reveal LINQ (from a large registry of patients with the device [n=1,247]; Ziegler et al. 2017). The studies assumed the Reveal devices had 100% sensitivity. The studies estimated that even the best intermittent ECG monitoring strategies would detect less than a third of atrial fibrillation detected by the Reveal devices.

Diagnostic yield: Other (non-atrial fibrillation) cardiac pathologies

CRYSTAL-AF did not report any results for the detection of other cardiac pathologies.

There were 5 non-comparative observational studies that reported incidental detection of other arrhythmias. The EAG commented that the proportion of patients detected with other arrhythmias is about 10% of the total number of people in a study. This mainly consists of bigeminy, pause and bradycardia. There were 2 studies that reported the breakdown of arrhythmias and gave rates of 1% (atrial flutter, cardiac arrest, sick sinus node, bigeminy, ventricular tachycardia) to 7% to 8% (atrioventricular block and ventricular extra systole). Full details are on page 51 of the diagnostics assessment report.

The studies did not state if the other detected arrhythmias were treated, or if outcomes were improved because these arrhythmias were identified. Also, because these were non-comparative studies, the extent of any increase in detection compared with conventional follow up couldn’t be determined.

Diagnostic accuracy

No data relevant to this outcome were reported in CRYSTAL-AF.

There were 2 non-comparative observational studies that reported the proportion of episodes detected by the devices that were not verified as atrial fibrillation by a clinician. Li et al. (2018) reported 79.7% for the Reveal LINQ and Israel et al. (2017) reported that over 90% of detected episodes were not

confirmed by review (Reveal XT and BioMonitor). The EAG noted that Medtronic had stated that the number of false positive alerts will vary depending on the device model used, and the configuration for detection (including episode duration) that is programmed by the operator.

Data on device accuracy (for all devices) in non-cryptogenic stroke populations from studies identified by manufacturers is presented later in this overview.

Evidence on clinical outcomes

Time to diagnosis of atrial fibrillation

The EAG commented that only 5 people with atrial fibrillation were detected in the conventional follow-up arm of CRYSTAL-AF (and none after 24 months; see table 2). This means it is difficult to make any conclusions about the effect of using the Reveal XT from the median time to atrial fibrillation detection data. The number of people with atrial fibrillation detected increased with longer follow up, and therefore the median time to detection also increased. There was a greater increase in the median time to atrial fibrillation detection with the Reveal XT compared with conventional follow up across all time points. The EAG stated that the low detection rate of atrial fibrillation in the conventional follow-up arm was the likely cause of this difference. Full data on time to diagnosis in this trial starts from page 32 of in the diagnostics assessment report.

There were 18 observational studies that reported time from device insertion to atrial fibrillation detection. Average follow up ranged from 7 to 20 months, and median time to first atrial fibrillation detection had a wide range, from 21 to 217 days. When reported, interquartile ranges also showed high variability within studies. Full details are in the diagnostics assessment report, starting on page 51.

Atrial fibrillation-related hospitalisation

No data were reported in CRYSTAL-AF or the observational studies.

Incidence of outpatient monitoring

No data were reported in CRYSTAL-AF or the observational studies.

Uptake of anticoagulants

Most people diagnosed with atrial fibrillation using the Reveal XT started having an oral anticoagulant (more than 90%; see table 4) in CRYSTAL-AF. The reasons people did not start on anticoagulants after being diagnosed with atrial fibrillation were not clear. The EAG noted that some people who were not diagnosed with atrial fibrillation in the trial were also started on anticoagulants. Reasons for this were not provided.

Table 4 Anticoagulants for people diagnosed with atrial fibrillation in CRYSTAL-AF

Months	Number of people on anticoagulants after diagnosis of atrial fibrillation	
	Reveal XT	Conventional follow up
6	18 (n=19; 94.7%)	Not reported
12	28 (n=29; 96.6%)	Not reported
24	36 (n=39; 92.3%)	Not reported
36	38 (n=42; 90.5%)	Not reported

There were 7 observational studies (Asaithambi et al. 2018, Carrazco et al. 2018, Christensen et al. 2014, Etgen et al. 2013, Li et al. 2018, Merce et al. 2013 and Seow et al. 2018) that reported that uptake of anticoagulants for people with atrial fibrillation detected by the Reveal XT or LINQ was high; between 83.3% and 100%.

Time to start of anticoagulants

No data were reported in CRYSTAL-AF or the observational studies.

Incidences of device failure and removal

No incidence of Reveal XT failure was reported in CRYSTAL-AF. Early removal of the device because of infection or pocket erosion occurred in 5 out of the 208 (2.4%) people with the device by 36 months.

There were 3 non-comparative observational studies that reported numbers of devices removed during follow up. In Christensen et al. (2014), the Reveal XT was removed prematurely in 5.7% people (because of skin reactions and discomfort). A further 3.4% of people chose to have the device removed after more than 1 year without atrial fibrillation being detected. In Asaithambi et al. (2018), 2.6% of people chose to have the Reveal LINQ removed, and for 0.9% of people the devices migrated or fell out. In Ritter et al. (2013), removal of the Reveal XT was offered once atrial fibrillation was detected, but it was not reported how many of the 30% of removals were because of this or other reasons such as discomfort.

Ease of use of devices for clinicians

No data were reported in CRYSTAL-AF or the observational studies.

Mortality

No data were reported in CRYSTAL-AF or the observational studies.

Further strokes or TIAs

In CRYSTAL-AF, a non-significant trend of fewer recurrent events (stroke or TIA) in the Reveal XT arm was reported (see table 5). The study was not powered for this outcome. It is not clear if the recurrent stroke or TIA events occurred in people who were diagnosed with atrial fibrillation or not.

Table 5 Cumulative incidence of further strokes or TIAs in CRYSTAL-AF

Months	**Number of people having a further stroke or TIA**		**Hazard ratio** (95% CI)
	Reveal XT (n=221)	**Conventional follow up** (n=220)	
6	11 (5.0%)	18 (8.2%)	Not reported
12	15 (6.8%)	19 (8.6%)	0.63 (0.22 to 1.80)
36	20 (9.1%)	24 (10.9%)	0.77 (0.30 to 1.97)
TIA: transient ischaemic attack; CI: confidence interval			

Of the studies, 6 non-comparative observational studies reported variable incidences of secondary stroke or TIA in people with an implantable cardiac monitor (see table 6).

Table 6 Incidence of recurrent stroke or TIA in observational studies

Study	Device	Follow up (months)	Incidence of recurrent stroke or TIA
Poli et al. 2016	Reveal LINQ (51.4%) or XT (48.6%)	12	1.4% secondary stroke
Pedersen et al. 2018	Reveal XT (72.4%) LINQ (27.6%)	12.5	2.9% secondary stroke 6.7% secondary TIA
Christensen et al. 2014	Reveal XT	18.7	4.6% secondary stroke
Etgen et al. 2013	Reveal XT	12	0% secondary stroke
Ritter et al. 2013	Reveal XT	12.5	0% secondary stroke
Israel et al. 2017	Reveal XT (87%) or BioMonitor (13%)	12.7	14.6% secondary stroke
Abbreviation: TIA, transient ischaemic attack			

Other thromboembolisms

No data were reported in CRYSTAL-AF or the observational studies.

Device-related adverse events

The EAG commented that that the incidence of device-related adverse effects (such as pain and infection) was relatively low for people who had the Reveal XT implanted in CRYSTAL-AF. However, adverse events did lead to the device being removed in 2.4% of patients. The proportion of people with serious adverse events was slightly higher for Reveal XT (30.8%) than conventional follow up (27.9%). More people had non-serious adverse events in the Reveal XT arm (18.6%) than in the conventional follow-up arm (4.1%). No details of these events were reported, and the EAG commented that it was unclear why there was a difference between the study arms. A full list of the incidence of adverse events reported in CRYSTAL-AF is in the diagnostics assessment report on page 38. As noted above, the Reveal XT is larger than the Reveal LINQ.

For 5 non-comparative observational studies there were no complications from the procedure or insertion site reported at follow up (length of follow up was not specified). These were Merce et al. (2013), Reinke et al. (2018) and Ritter et al. (2013) for Reveal XT; Poli et al. (2016) for Reveal LINQ and XT; and Israel et al. (2017) for Reveal XT and BioMonitor.

Anticoagulant-related adverse events

No data were reported in CRYSTAL-AF or the observational studies.

Evidence on patient-reported outcomes

Health-related quality of life

Health-related quality of life data were collected in CRYSTAL-AF using the EuroQol 5-Dimensions (EQ-5D) tool. Unpublished data were provided by the company. The EAG commented that these data [redacted]

Acceptability of the devices to patients

No data were reported in CRYSTAL-AF or the observational studies.

Evidence from non-cryptogenic stroke populations

The EAG provided a narrative summary of studies in non-cryptogenic stroke populations identified by manufacturers of the devices. These studies were not done in populations who had had a cryptogenic stroke or TIA, or in a 'mixed population' (less than 50% of the study population had a cryptogenic

stroke or TIA and subgroup analysis was not provided). All studies were either single-arm observational studies or assessed the diagnostic accuracy of the devices compared with Holter monitoring.

The EAG highlighted that the performance of the devices is dependent on the patient population, incidence rate of atrial fibrillation and the type of atrial fibrillation. Therefore, the results from these studies are not necessarily representative of the devices' performance in people with cryptogenic stroke.

The EAG did not do a full systematic literature search to validate the inclusion of the studies. This was because of time constraints and concerns about the applicability of results to the cryptogenic stroke population. The EAG stated that the data may have study selection bias as well as clinical heterogeneity caused by the variation in the patient populations of each of the studies.

Abbott Medical

The company highlighted the Detect AF study (Nölker et al. 2016) as potentially relevant for assessing the Confirm Rx. The EAG noted that the device used in Detect AF was the Confirm ICM, Model DM2102. This is an older and larger model of the Confirm Rx. The EAG was unsure how the software in this earlier version compared with the current Confirm Rx.

Detect AF was a prospective observational study. It assessed the diagnostic accuracy of the Confirm ICM in detecting atrial fibrillation compared with Holter monitoring (reference standard) with simultaneous use of the devices. In per-patient analysis, sensitivity of the Confirm ICM was 100%, positive predictive value was 64.0%, specificity was 85.7% and negative predictive value was 100%. Most of the episodes of atrial fibrillation detected by the Confirm ICM but not confirmed by the Holter monitor were because of irregular sinus rhythms. No adverse events associated with the device were reported. Full details of the study are in the diagnostics assessment report, starting on page 55.

Biotronik SE & Co

The EAG discussed 5 single-arm prospective observational studies (in 8 publications) provided by Biotronik. An overview of the studies is in table 22 (page 58) of the diagnostics assessment report. [redacted]

[redacted]

[redacted]

Reinsch et al. (2018) reported that the BioMonitor 2 was successfully implanted in a catheterisation laboratory with a median time from first cut to final suture of 8 minutes (interquartile range 7 to 10 minutes). Ooi et al. (2017) reported that all insertions of the device were made on first attempt in a catheterisation laboratory with a median time of 9 minutes (interquartile range 5 to 14 minutes). [redacted]

[redacted]

Ooi et al. reported that 1 pocket infection occurred when using the device. Reinsch et al. reported that no devices implanted in the study migrated, and 1 person needed the device removing because of device-related pocket infection. Another patient complained of slight discomfort. [redacted]

Reinsch et al. reported results from patient satisfaction surveys. Of the respondents, 7% reported moderate to severe pain and 20% reported mild pain within 24 hours of device insertion. A moderate impairment in daily life was reported by 1 person. Of the respondents, 63% said that the cosmetic result was very satisfying and 30% said satisfying.

Medtronic Limited

The EAG provided discussion of 5 studies highlighted by the company. Of the studies, 2 assessed the diagnostic accuracy of Reveal devices (per-patient analysis) to detect atrial fibrillation compared with Holter monitoring (Hindricks et al. 2010 and Sanders et al. 2016). In Hindricks et al. (2010), the Reveal XT was used (the XPECT trial). A further study (Puerefellner et al. 2014) used data from this trial and recalculated accuracy estimates when changes were made to the atrial fibrillation detection algorithm. This incorporated data on P-waves when classifying patients, and this algorithm change was applied in the Reveal LINQ. Sanders et al. (2016) used the Reveal LINQ. A subsequent study was published using this data set (and the XPECT data) to calculate the accuracy of a modified algorithm for detecting atrial fibrillation (using the TruRhythm algorithm that has now been incorporated in the device). Further

details of these studies are in the diagnostics assessment report, starting on page 60. Data on the diagnostic accuracy reported in these studies are shown in table 7.

Table 7 Diagnostic accuracy estimates for the Reveal XT and Reveal LINQ

	Study			
	XPECT study Hindricks et al. 2010	**XPECT dataset** Puerefellner et al. 2014	**LINQ usability study** Sanders et al. 2016	**LINQ usability dataset** Puerefellner et al. 2018
Device	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
Positive predictive value (%)	79.3	84.9[a]	92.5	97.4
Negative predictive value (%)	97.4	97.5[a]	99.0	100
Accuracy (%)	89.3	92.2[a]	97.1	99.3
[a] Calculated by the external assessment group using data in Puerefellner et al. 2014				

The EAG commented that the studies showed improved detection of atrial fibrillation by the Reveal LINQ compared with the Reveal XT. Changes made to the algorithm also improved detection, but caution should be taken because these studies were not done in a cryptogenic stroke population. However, the EAG stated that these data suggest that the Reveal LINQ is likely to be as effective as the Reveal XT, if not better, at detecting atrial fibrillation. Therefore, the clinical data from CRYSTAL-AF (which uses the XT) could be a conservative estimate of the clinical effectiveness of the device.

Mittal et al. (2015) reported adverse event data from 2 observational studies that used the Reveal LINQ. An infection occurred in 1.5% of people, an adverse event in 4.0% and a serious adverse event in 1.1%.

Ongoing studies

The EAG identified 8 potentially relevant ongoing studies from searches of trial registries and electronic databases, in addition to company submissions. Full details are in the diagnostics assessment report, starting from page 21. There are 3 ongoing RCTs assessing the Reveal LINQ. Of these, 1 is in a cryptogenic stroke population. This is a Canadian randomised trial comparing the clinical and cost effectiveness of the Reveal LINQ with external loop recording in 300 cryptogenic stroke patients. It is estimated to complete in December 2019 (PERDIEM; NCT02428140). One ongoing study identified is assessing the Confirm Rx: the SMART registry (NCT03505801). This is a post-approval study planned for at least 2,000 patients with Confirm Rx across multiple indications, with a planned subgroup analysis for cryptogenic stroke. Completion is expected during 2019.

2.2 Costs and cost effectiveness

The EAG did a search to identify existing studies investigating the cost effectiveness of implantable cardiac monitors (BioMonitor 2-AF, Confirm Rx and Reveal LINQ) to detect suspected atrial fibrillation after cryptogenic stroke (including TIA). The EAG also constructed a de novo economic model to assess the cost effectiveness of the devices.

Systematic review of cost-effectiveness evidence

The EAG did a systematic review to identify any published economic evaluations of implantable cardiac monitors to detect atrial fibrillation in people with cryptogenic stroke. Full details of the review are in the diagnostics assessment report, starting on page 70. There were 5 studies that met the EAG inclusion criteria. Of these, 2 assessed the cost effectiveness of the Reveal XT compared with standard care monitoring (DeAngelis et al. 2016 and Diamantopoulos et al. 2016). Another study assessed the BioMonitor 2-AF (Maervoet et al. 2017; further details provided as unpublished report and model by the device manufacturer), and 2 studies did not indicate which implantable cardiac monitor was being assessed (Quiroz et al. 2017 and Thijs

et al. 2018). Only 1 study (Diamantopoulos et al. 2016) was based on an NHS payer perspective and was discussed in the diagnostics assessment report. [redacted]

Diamantopoulos et al. (2016)

This study was a cost-utility analysis. It compared use of the Reveal XT in people who have had a cryptogenic stroke or TIA with conventional follow up, as assessed in the CRYSTAL-AF study. A Markov model structure was used with 3 main health states for atrial fibrillation status: free, detected and undetected. Further details on the model are in the diagnostics assessment report, starting on page 74. The deterministic base case produced an incremental cost-effectiveness ratio (ICER) of £17,175 per quality-adjusted life year (QALY) gained for the Reveal XT compared with standard care (£2,587 higher costs, 0.151 additional QALYs). The probabilistic ICER was lower.

The EAG considered that results from this model were potentially unreliable because there was uncertainty about how parameters in the model had been estimated. The estimation of treatment effects by indirect comparison, atrial fibrillation incidence and detection rates used in the analysis were particularly unclear. The study authors used indirect comparisons to estimate hazard ratios for the benefit of anticoagulants on the occurrence of ischaemic stroke, bleeding events, intracranial haemorrhages, extracranial haemorrhages and mortality. The EAG tried to verify these figures but was unable to because there were insufficient details in the publication about how the indirect comparisons were done and how publications that informed the analysis were identified. The EAG also considered that estimation of some of the hazard ratios could be flawed. For example, the authors estimated a hazard ratio to adjust mortality in the model, but the source data used are based on standardised mortality ratios. Furthermore, people without atrial fibrillation detected were assumed to be offered aspirin, but the EAG's clinical experts stated that clopidogrel would be used as an antiplatelet treatment.

Economic analysis

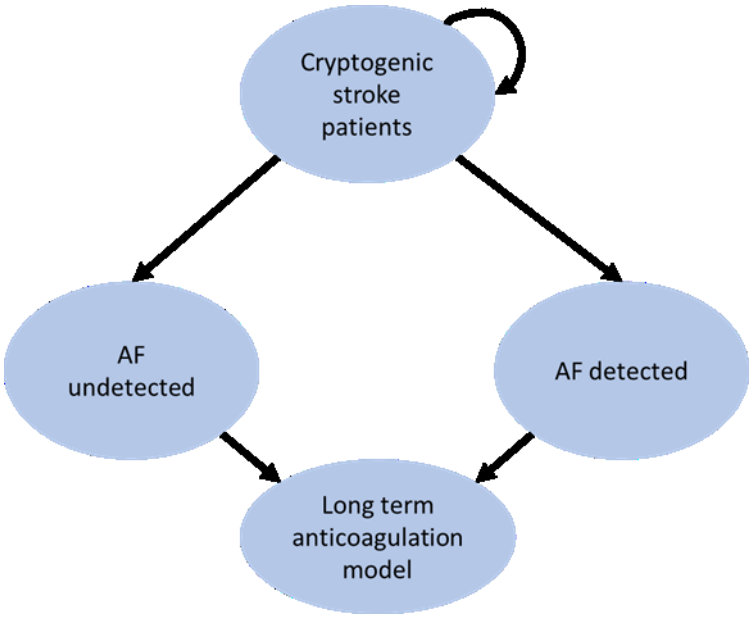
The EAG developed a de novo economic model to assess the cost effectiveness of using implantable cardiac monitors (BioMonitor 2-AF, Confirm Rx or Reveal LINQ) to assess for suspected paroxysmal atrial fibrillation in people who have had a cryptogenic stroke (including TIA).

Model structure

The EAG developed a 2-stage economic model:

(a) ***Short-term monitoring model.*** The first stage (an Excel model developed by the EAG) modelled people either having monitoring for suspected paroxysmal atrial fibrillation after a cryptogenic stroke (including TIA) with the implantable cardiac monitors or conventional follow up (see figure 1). Everyone starts the model having antiplatelet therapy (clopidogrel) for stroke prevention. At every 3-month cycle in the model a proportion of people have atrial fibrillation. For people with an implantable cardiac monitor, all cases of atrial fibrillation are detected, and treatment is switched to anticoagulants (AF detected). For people with conventional follow up, a proportion of people with atrial fibrillation are detected (and switch to anticoagulants) but most are not (AF undetected) and remain on antiplatelet therapy. The proportion of people with undetected atrial fibrillation in conventional follow up (compared with people with implantable cardiac monitors) was taken from CRYSTAL-AF. No one is assumed to be incorrectly diagnosed with atrial fibrillation in either arm of the model. This model stage lasts for up to 3 years.

Figure 1 Short-term monitoring model



Abbreviation: AF, atrial fibrillation

(b) ***Long-term anticoagulation model.*** The EAG adapted a published economic model to model the long-term effect of people with detected atrial fibrillation (anticoagulant treatment) or undetected atrial fibrillation (remain on antiplatelet therapy). This is the 'adapted direct oral anticoagulant (DOAC) model' (Sterne et al. 2017 and Welton et al. 2017). Further description of this model is in the diagnostics assessment report, starting on page 77. People enter the model after having atrial fibrillation in an 'AF well' state. After this, clinical events can occur. These are ischaemic stroke, intracranial haemorrhage, myocardial infarction or clinically relevant (extracranial) bleed. A person can have multiple events in the model, but only 1 of each type (for example, only 1 stroke). In addition, people can have a TIA or systemic embolism. These can occur in any health state and can happen multiple times. The risks of these events happening in the model were based on a population with a history of ischaemic stroke and paroxysmal atrial fibrillation. The model structure is the same for people with detected and undetected atrial fibrillation. However, the probability of the events happening depends on the

treatment used (anticoagulants or antiplatelet therapy). These treatment effects are discussed below. People can also die (from any cause), with the model run for people up to 100 years old.

After people on anticoagulants have ischaemic stroke or serious adverse events (such as intracranial haemorrhage) in the model, they can switch treatment (for example, from DOAC to warfarin or no treatment). For people on antiplatelet therapy, they can stop treatment after a bleed, TIA or systemic embolism. After a second stroke it is assumed that their atrial fibrillation remains undetected and they stay on antiplatelet therapy. Full details are in the diagnostics assessment report, starting on page 78.

Because this model is probabilistic, the EAG generated 10,000 estimates of costs and QALYs for people who had treatment with anticoagulants or antiplatelet therapy for each cycle in the model. A mean of these values per cycle was used in the deterministic model, the probabilistic model sampled from these values (discussed below).

Further description of the model structure is in the diagnostics assessment report, starting on page 83.

Model population

The population in the model was people who had had a cryptogenic stroke (including TIA), when there was suspected paroxysmal atrial fibrillation. These people had had at least 24 hours of outpatient external ambulatory ECG monitoring that had not detected atrial fibrillation. Characteristics were based on the CRYSTAL-AF population, with a mean age of 61 years and about 65% people assumed to be men. The EAG's clinical experts considered that the population in CRYSTAL-AF was generally reflective of UK patients, with any inconsistencies not considered significant.

Comparator

The scope for this assessment specified that the comparator was no further monitoring for atrial fibrillation (after at least 24 hours of outpatient external

ambulatory ECG monitoring that had not detected atrial fibrillation). The scope also noted that undetected atrial fibrillation could be found later if it causes symptoms (for example, palpitations). It could also be found incidentally when a person's pulse is checked (for example, when blood pressure is taken), or on investigation after a further stroke or TIA.

In the model, the EAG used data from the control arm of CRYSTAL-AF for the comparator. People in the study had assessment at scheduled visits (every 3 months) and unscheduled visits if they were having symptoms of atrial fibrillation. Tests included ECGs and Holter monitoring (for 24 hours, 48 hours or 7 days). Table 8 shows the proportion of tests done per year in the CRYSTAL-AF control arm.

Table 8 Tests done by year in control arm of CRYSTAL-AF

Period	Proportion of people having tests				
	No test	ECG[a]	24-hour Holter	48-hour Holter	7-day Holter
0 to 12 months	0.31	0.55	0.06	0.02	0.06
12 to 24 months	0.51	0.40	0.04	0.01	0.05
24 to 36 months	0.58	0.31	0.02	0.00	0.08
[a] No further details provided.					

Model inputs

Detection of atrial fibrillation

Diagnostic yield data from CRYSTAL-AF were used for the number of people with atrial fibrillation detected by an implantable cardiac monitor or by conventional follow up. No equivalent data were identified for the BioMonitor 2-AF or Confirm Rx (or current Reveal LINQ version). Therefore, the EAG assumed equal efficacy for all devices. The battery life of the BioMonitor 2-AF and Reveal LINQ was assumed to be 3 years (rather than 4 years for the BioMonitor 2-AF stated by the manufacturer because detection data are only available for 3 years) and 2 years for the Confirm Rx (as stated by the

manufacturer). No detection of atrial fibrillation was assumed after 3 years (or 2 years for the Confirm Rx because of shorter battery life).

The EAG assumed that the implantable cardiac monitors detected all cases of atrial fibrillation, and therefore that the device's detection rate is the true prevalence of atrial fibrillation. The number of people with undetected atrial fibrillation at each cycle in the conventional follow-up arm of the model was calculated from the difference between the detection rate for atrial fibrillation of the Reveal XT and conventional follow up.

Long-term clinical outcomes

A published model (Sterne et al. 2017 and Welton et al. 2017; the 'adapted DOAC' model) was used to model longer-term clinical outcomes for people with atrial fibrillation that is detected (treatment with an anticoagulant) or not detected (treatment with an antiplatelet drug). Outcomes included were ischaemic stroke, myocardial infarction, TIA, systemic embolism, clinically relevant extracranial bleed, intracranial haemorrhage and all-cause mortality. Up to 3 events could happen in the model. Systemic embolism and TIA have only short-term effects (1 model cycle; 3 months) on patients.

Risks of the events happening depended on the treatment patients had (oral anticoagulant or antiplatelet agent). Hazard ratios in the adapted DOAC model were determined using a competing risks network meta-analysis, based on a clinical effectiveness systematic literature review done for the study (Sterne et al. 2017). The hazard ratios used for DOACs compared with warfarin in the adapted DOAC model are shown in table 9. The EAG noted that the adapted DOAC model was run with risks of events adjusted to reflect a secondary stroke population with paroxysmal atrial fibrillation. Also, the effect of past health events and states on future event rates is also included in the model, which is described fully in Sterne et al. Further details on the long-term clinical outcomes are in the diagnostics assessment report, starting on page 88.

Table 9 Hazard ratios of direct oral anticoagulants compared with warfarin used in adapted DOAC model

	Hazard ratio (compared with warfarin)			
	Apixaban	Dabigatran	Edoxaban	Rivaroxaban
Ischaemic stroke	0.90	0.75	1.00	0.92
Intracranial haemorrhage	0.46	0.36	0.49	0.65
Major bleed	0.82	1.07	0.88	1.05
Myocardial infarction	0.86	1.27	0.95	0.79
Systemic embolism	0.65	0.65	0.58	0.95
TIA	0.74	2.68	2.76	2.68
All-cause mortality	0.89	0.88	0.92	0.83
Abbreviation; TIA, transient ischaemic attack				

The treatment effects for antiplatelet therapy in the adapted DOAC model are based on aspirin. The EAG's clinical experts advised that in current practice clopidogrel (75 mg once daily) is the long-term treatment for people after a stroke, if they are not diagnosed with atrial fibrillation. The EAG identified a systematic review and meta-analysis (Cameron et al. 2013; further details and results are in the diagnostics assessment report on page 89). Based on this review comparing aspirin and aspirin plus clopidogrel (dual antiplatelet therapy), the EAG assumed that clopidogrel is as effective as aspirin for patients with undetected atrial fibrillation. Therefore, the effectiveness estimates used for antiplatelet therapy in the adapted DOAC model remain unchanged. Table 10 shows the hazard ratios of antiplatelet therapy (aspirin less than 150 mg) compared with warfarin used in the model.

Table 10 Hazard ratios of aspirin (less than 150 mg) compared with warfarin used in adapted DOAC model

	Hazard ratio (aspirin [less than 150 mg] compared with warfarin)
Ischaemic stroke	2.26
Intracranial haemorrhage	0.57
Major bleed	0.73
Myocardial infarction	0.93
Systemic embolism	1.64
TIA	6.21
All-cause mortality	1.07
Abbreviation: TIA; transient ischaemic attack	

Anticoagulation treatment

In its base case, the EAG assumed that everyone with atrial fibrillation detected will start treatment with a DOAC. The relative proportions of DOAC used were taken from the openprescribing.net database (September 2017 to September 2018). These were: apixaban (48.0%), dabigatran etexilate (5.5%), rivaroxaban (43.6%) and edoxaban (2.9%). The EAG also did a scenario analysis including a proportion of people having warfarin.

In the adapted DOAC model people can switch treatment after an ischaemic stroke or serious adverse events (such as intracranial haemorrhage). Probabilities of this occurring were based on clinical opinion obtained by the authors of the DOAC model.

Costs

All costs in the model were valued in 2018, in UK pounds sterling.

Implantable cardiac monitor costs

Table 11 Cost of the implantable cardiac monitors

Device	Unit cost (£ excluding VAT)
BioMonitor 2-AF	1,030
Confirm Rx	1,600
Reveal LINQ	1,800

Medtronic also offer an optional triage service for use with the Reveal LINQ (FOCUSON) that was included in scenario analyses. There were 2 cost options included: £187 per patient per year or £374 per patient per device.

The EAG did not include the cost of reviewing alerts generated by the devices in the base case. This was because no data were available on the expected number of alerts generated that need review. The EAG's clinical experts advised that reviewing alerts is relatively quick and would form part of the clinician's normal workload. However, they noted that this would depend on volume.

Implantation and device removal costs

In the base case, the EAG estimated the cost of implanting the devices as £24.17. This was based on advice from clinical experts about the personnel involved (cardiologist and nurse) and time taken for the procedure (10 minutes). Further scenario analyses investigated the effect of alternative assumptions, which led to lower (£15.67) and higher (£50.90) costs of the procedure.

The cost of removing the devices was assumed to be £238, based on NHS reference costs schedule 2017/18 (EY13Z – removal of electrocardiography loop recorder, outpatient setting, treatment function code 320). In the base case, the EAG assumed that everyone has their implantable cardiac monitor removed. Sensitivity analyses assessed the effect of this assumption. Full details on implantation and removal costs are in the diagnostics assessment report, starting on page 93.

Costs associated with adverse events from implanting the devices were not included in the EAG's analysis. The EAG stated this was because there were no details on how severe the adverse events reported in CRYSTAL-AF were. The EAG did not expect this to have a substantial effect on the cost-effectiveness results, because of the small proportion of people having adverse events.

Comparator arm costs

The EAG based costs for the comparator on the conventional follow-up arm of CRYSTAL-AF (see above). The unit cost of monitoring was £141, based on the NHS reference costs schedule 2017/18 (HRG code EY51Z – electrocardiogram monitoring or stress testing [outpatient procedures, service code 320]). Costs per cycle in the model were calculated based on the proportion of people having testing every 3 months or no testing in CRYSTAL-AF (see table 8 above). The EAG also did a scenario analysis in which no follow-up monitoring was assumed in the conventional follow-up arm (that is, cost of monitoring is £0). Full details are in the diagnostics assessment report, starting on page 94.

Table 12 Cost of monitoring in the comparator arm (no implantable cardiac monitor use)

Time period (months)	Cost per patient per cycle (£)
0 to 12	24.37
12 to 24	17.29
24 to 36	14.70

Follow-up costs

The EAG assumed that people with an implantable cardiac monitor will have 1 face-to-face follow up a month after the procedure and then will be remotely monitored. For people in the conventional follow-up arm who do not have atrial fibrillation detected, follow-up appointments are assumed to happen after 1, 3, 6 and 12 months, based on clinical expert advice. If atrial fibrillation is detected, a follow-up appointment is assumed to discuss treatment. The cost of an initial follow up (£163.36) and subsequent follow up (£128.05) were taken from NHS reference costs.

Treatment costs

The costs of DOACs and clopidogrel were taken from the British national formulary September 2018 to March 2019 edition. The cost of warfarin (used in a scenario analysis) was from the original adapted DOAC model adjusted to 2018 prices. All treatments were assumed to be taken orally, and no

administration or monitoring costs were included. Full details on costs are in the diagnostics assessment report, starting on page 95.

Costs of atrial fibrillation and anticoagulant-related events

The acute costs for events used in the adapted DOAC model are shown in table 13. Full details of costs used are in the diagnostics assessment report, starting on page 96.

Table 13 Acute costs for events

Acute event	Mean cost (£)	Source and assumptions
Ischaemic stroke	14,522	Luengo-Fernandez et al. (2013). Based on data for all strokes, ischaemic stroke.
Intracranial haemorrhage	14,307	Luengo-Fernandez et al. (2013). Based on data for all strokes, haemorrhagic stroke.
Systemic embolism (non-fatal)	1,666	NHS reference costs. Weighted average of cost codes YQ50A-F.
TIA	988	NHS reference costs. Weighted average of cost codes AA29C-F.
Clinically relevant bleeding	1,397	NHS reference costs. Weighted average cost of FD03A-H and VB07Z.
Myocardial infarction	5,804	NHS reference costs. 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.
Abbreviation: TIA, transient ischaemic attack		

Chronic costs for ischaemic stroke and intracranial haemorrhage management in the adapted DOAC model were taken from Luengo-Fernandez et al. (2013). The costs of an intracranial haemorrhage were assumed to be the same as for stroke. The mean annual cost used (£4,514) was calculated by weighting the cost of stroke by severity (non-disabling, moderately or totally disabling) and relative frequency, and was adjusted to 2018 prices.

Health-related quality of life and QALY decrements

The EAG did a systematic review to identify relevant utility values to update the adapted DOAC model. Full details are in the diagnostics assessment report, starting on page 70. There were 2 papers (Berg et al. 2010 and Luengo-Fernandez et al. 2013) with relevant utility values for ischaemic stroke, intracranial haemorrhage, myocardial infarction and TIA events. These were included in the model and were used to update the adapted DOAC model. The papers estimate utilities using EQ-5D-3L data converted into UK population tariffs. For events with no further utility data identified, values from the adapted DOAC model were unchanged. The utility value used for people with atrial fibrillation in a 'well' health state (that is, when no clinical events such as stroke have occurred) was 0.78 (Berg et al. 2010). Utilities for acute events and other health states are shown in tables 14 and 15. The duration of disutility for an acute event was assumed to be 3 months (1 model cycle). Systemic embolism and TIA have only short-term effects on utility; whereas the other clinical events have a short-term acute effect for 3 months (table 14) and then a longer-term effect on utility as people move to different health states after a clinical event (chronic health conditions; table 15).

Table 14 Utility values for acute events

Acute event	Utility value	Duration of event	Reference or assumption
TIA (utility decrement)	-0.07	3 months	Luengo-Fernandez et al. 2013
Ischaemic stroke	0.64	3 months	Luengo-Fernandez et al. 2013
Intracranial haemorrhage	0.56	3 months	Luengo-Fernandez et al. 2013
Myocardial infarction	0.68	3 months	Adapted DOAC model
Clinically relevant bleed disutility	-0.03	3 months	Adapted DOAC model
Systemic embolism	-0.07	3 months	Assumed equal to TIA (as per adapted DOAC model)
Abbreviations: TIA, transient ischaemic attack; DOAC, direct-acting anticoagulants			

Table 15 Utility values for chronic health condition states

Health state	Utility	Reference
Ischaemic stroke	0.70	Luengo-Fernandez et al. 2013

Intracranial haemorrhage	0.67	Luengo-Fernandez et al. 2013
Myocardial infarction	0.72	Adapted DOAC model
Clinically relevant bleed	0.70	Assumed equal to stroke (as per adapted DOAC model)
Abbreviation: DOAC, direct-acting anticoagulants		

Utilities were adjusted for age and sex. People can have more than 1 chronic health condition in the model, in which case the utilities for the chronic health states were assumed to be multiplicative.

Base-case assumptions

The following assumptions (in addition to those described above) were applied in the base-case analysis:

- The prevalence of atrial fibrillation in this population was equal to the detection rate in CRYSTAL-AF; that is, the Reveal XT had 100% sensitivity.
- The Reveal LINQ was at least as good as the Reveal XT for detecting atrial fibrillation (the device used in CRYSTAL-AF).
- The BioMonitor 2-AF and Confirm RX were equivalent to the Reveal XT or Reveal LINQ for detecting atrial fibrillation.
- The detection of atrial fibrillation was capped at 3 years for the BioMonitor 2-AF even though the manufacturer stated the battery life is expected to be 4 years. This was because atrial fibrillation detection data were only available for 3 years follow up.
- Atrial fibrillation detection was capped at 2 years for the Confirm Rx because this is the expected battery life of the device, and clinical experts advised that devices are unlikely to be replaced once a battery expires.
- After 3 years, detection rates of atrial fibrillation are the same in both the implantable cardiac monitors and conventional follow-up arms.
- Once atrial fibrillation was detected, all patients accepted anticoagulation.
- DOACs were the only anticoagulation therapies offered (use of warfarin was investigated in a scenario analysis).

Base-case results

The ICERs per QALY gained or lost will be considered for decision making. In pairwise analyses, the 3 implantable cardiac monitors were compared independently with conventional follow up. Results are shown in table 16. The lower number of QALYs generated by Confirm Rx is because the battery is assumed to last 2 years, rather than 3 years. The EAG noted that if the BioMonitor 2-AF battery life was 4 years the device might detect more cases of atrial fibrillation than are captured in the analyses.

Table 16 Base-case deterministic pairwise cost-effectiveness analysis (compared with conventional follow up)

	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£)
Conventional follow up	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: QALY, quality-adjusted life year; ICER, incremental cost-effectiveness ratio					

The fully incremental analysis is shown in table 17. The EAG advised that the BioMonitor 2-AF and Confirm Rx results should be viewed with caution because they are based on a strong assumption of equivalence with the Reveal LINQ. The difference in costs between the BioMonitor 2-AF and Reveal LINQ is because of the difference in costs of the devices alone (see table 11).

Table 17 Base-case deterministic incremental cost-effectiveness analysis

	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£)
Conventional follow up	7,288	1.50	–	–	–
BioMonitor 2-AF	9,071	1.67	1,783	0.17	10,464
Confirm Rx	9,287	1.62	216	-0.05	Dominated
Reveal LINQ	9,841	1.67	770	0.00	Dominated
Abbreviations: QALY, quality-adjusted life year; ICER, incremental cost-effectiveness ratio					

Analysis of alternative scenarios

The EAG did some scenario analysis to assess the effect of some of the assumptions made in the model. A full description of the scenarios are in the diagnostic assessment report, starting on page 102. Selected results are shown in table 18 (full results are in table 41 of diagnostic assessment report).

Table 18 Selected scenario analyses

Scenario		ICER (£, compared with conventional follow up)		
		Reveal LINQ	BioMonitor 2-AF	Confirm Rx
Base case		***14,983***	***10,464***	***17,092***
Addition of FOCUSON triage service [a] Option 1: £187 per patient per year		18,166	NA	NA
Addition of FOCUSON triage service [a] Option 2: one-off fee of £374 per patient per device		17,179	NA	NA
Time horizon for device monitoring [b]	1 year	29,321	16,883	26,090
	2 years	18,803	12,217	NA
Long-term DOAC outcomes based on:	Apixaban	16,274	11,648	18,542
	Edoxaban	9,425	6,459	10,637
Inclusion of warfarin as a treatment option for patients diagnosed with atrial fibrillation		16,452	11,990	18,424
No removal of devices		13,721	9,202	15,189
No monitoring in conventional follow-up arm [c]		16,062	12,003	18,294

Abbreviations: ICER, incremental cost-effectiveness ratio; NA: not applicable

[a] Service provided by Medtronic for Reveal LINQ

[b] Assumption that the implantable cardiac monitors only detect atrial fibrillation for 1 or 2 years (any cases after this time in CRYSTAL-AF were assumed to be missed)

[c] Monitoring costs and cases of atrial fibrillation detected in the conventional follow-up arm removed.

Sensitivity analyses

One- and two-way sensitivity analysis

The EAG did several analyses varying 1 or 2 parameters at a time in the model between upper and lower values. Most changes had little effect on the ICERs of the 3 devices. To vary the outcomes from the adapted DOAC model, the EAG took the 2.5th and 97.5th percentiles from the 10,000 outputs for costs and QALYs from this model. These changes had the largest effect on ICERs, results are shown in table 19. Full results, including tornado plots, are in the diagnostics assessment report on page 107.

Table 19 Two-way sensitivity analysis

Parameter	Reveal LINQ		BioMonitor 2-AF		Confirm Rx	
	Lower value ICER[a]	Upper value ICER[b]	Lower value ICER[a]	Upper value ICER[b]	Lower value ICER[a]	Upper value ICER[b]
Adapted DOAC inputs	£22,006	£9,102	£12,953	£6,688	£24,517	£10,338

[a] From 2.5th percentile

[b] From 97.5th percentile

Abbreviations: ICER, incremental cost-effectiveness ratio, DOAC, direct-acting anticoagulants

Probabilistic sensitivity analysis

The EAG did a probabilistic sensitivity analysis with 10,000 simulations. For the adapted DOAC model, a value from the 10,000 outputs of costs and QALYs per cycle for people having each of the anticoagulants or antiplatelet therapy was selected at random to provide inputs for each probabilistic simulation. Full details of this, and the methods used to sample from

parameters in the Excel model, are in the diagnostics assessment report, starting on page 110.

Table 20 Probabilistic pairwise cost-effectiveness analysis (compared with conventional follow up)

	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£)
Conventional follow up	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: QALY, quality-adjusted life year; ICER, incremental cost-effectiveness ratio					

Total costs and QALYs for conventional follow up were similar to the deterministic analysis (see table 16). However, these were both much higher for the implantable cardiac devices in the probabilistic analysis.

Above a maximum acceptable ICER of about £12,500, all 3 devices had a more than 90% probability of being cost effective compared with conventional follow up (each was compared independently). Cost-effectiveness acceptability curves for the devices are in the diagnostics assessment report from page 115.

3 Summary

Clinical effectiveness

A single randomised controlled trial (CRYSTAL-AF) met the external assessment groups (EAG's) original inclusion criteria. The EAG widened the inclusion criteria to include non-comparative studies and found a further 26 studies, but advised that data from these studies should be interpreted with caution. Despite widening the criteria, no relevant data were found for the BioMonitor 2-AF or Confirm Rx in these studies. Evidence for these devices is limited to mixed population diagnostic accuracy and single-arm observational studies submitted by the companies.

The EAG commented that CRYSTAL-AF was the most robust evidence available to answer the decision problem. It considered that this study is generally applicable to patients who would be eligible for an implantable cardiac monitor in UK clinical practice. However, this study used an earlier version of the currently available Reveal LINQ device; the Reveal XT. Atrial fibrillation was detected in more people with Reveal XT than conventional follow up at all time points in CRYSTAL-AF. The EAG noted variable detection rates in the 26 observational studies and commented that it was impossible to make any meaningful comparison between the observational studies and CRYSTAL-AF.

The incidence of a recurrent stroke or TIA was higher in the conventional follow-up arm than in the Reveal XT arm in CRYSTAL-AF, but this was not statistically significant. Data from observational studies showed similar stroke recurrence levels to CRYSTAL-AF in people with Reveal devices implanted. It was not clear if recurrent stroke happened in people diagnosed with atrial fibrillation by the device or not. No studies reported data on other thromboembolisms or related morbidities. Health-related quality of life data collected in CRYSTAL-AF [redacted] The EAG noted that data on the acceptability of the devices to patients were anecdotal or limited to data in observational studies flagged by the companies.

There were 3 non-comparative observational studies (mostly using Reveal LINQ) reporting that non-atrial fibrillation arrhythmias were detected in about 10% patients monitored (mainly bigeminy, pause and bradycardia). Two studies reported that most episodes detected by the Reveal XT and Reveal LINQ were not atrial fibrillation, with more than 79% episodes not confirmed as such by clinician review. The extent of false positive alerts will depend on the settings of the device algorithms used and the version of the device or algorithms used.

Cost effectiveness

To model the cost effectiveness of all 3 devices, the EAG assumed that the effectiveness of the 3 implantable cardiac monitors were similar and used detection rates taken from CRYSTAL-AF for all the devices. The QALYs produced by BioMonitor 2-AF and Reveal LINQ were therefore equal; the Confirm Rx had lower QALYs because its battery life is 2 years, rather than 3 years.

In deterministic pairwise analysis, the ICERs of all 3 devices were less than £17,100 per QALY gained compared with conventional follow up. In probabilistic pairwise analysis, the ICERs of all 3 devices were less than £7,100 per QALY gained compared with conventional follow up. Above a maximum acceptable ICER of about £12,500 per QALY gained, all 3 devices had a more than 90% probability of being cost effective when compared independently with conventional follow up. In deterministic incremental cost-effectiveness analysis, the BioMonitor 2-AF dominated the other 2 devices. This was driven by the lower cost of the device because the effectiveness of the 3 devices was assumed to be equal.

In scenario analyses, including costs from a triage service offered by Medtronic for the Reveal LINQ device increased the ICER for this device by about £2,000 to £3,000 per QALY gained, depending on the cost option used. Limiting the length of monitoring with the devices to 1 year increased the ICERs up to almost £30,000 per QALY gained.

In one- and two-way sensitivity analyses, using the 2.5th percentile of results from the adapted DOAC model had the largest effect on the ICERs. This increased them to around £25,000 per QALY gained.

4 Issues for consideration

Clinical effectiveness

Clinical evidence for the Reveal LINQ is primarily from a single randomised controlled trial (CRYSTAL-AF). This study showed that a previous version of the Reveal LINQ detected more cases of atrial fibrillation than conventional follow up. Further data were identified from single-arm observational studies. However, because of heterogeneity in these studies, it was difficult to compare their results to CRYSTAL-AF.

Most people in CRYSTAL-AF had outpatient Holter monitoring before having either the Reveal XT fitted or starting conventional follow up (as per the NICE scope). However 29.7% did not, and only had inpatient telemetry monitoring of electrocardiogram (ECG). The effect of this deviation from the scope on the results was unclear.

Conventional follow up in CRYSTAL-AF included ECG monitoring every 3 months for some patients (see table 8). If this is more monitoring than would happen in the NHS, the increase in the number of cases of atrial fibrillation detected by implantable cardiac monitors might be higher than in CRYSTAL-AF.

The CRYSTAL-AF study used the Reveal XT; a previous version of the current Reveal LINQ. The EAG commented that evidence from the company suggests that the Reveal LINQ might have better sensitivity and specificity for detecting atrial fibrillation than the XT. Also, because of its smaller size it is likely to have fewer complications. However, there are no head-to-head studies to confirm these findings in a cryptogenic stroke population.

No evidence in a cryptogenic stroke population was identified for the BioMonitor 2-AF or Confirm Rx. Data for these devices were only available from mixed population diagnostic accuracy and single-arm observational studies submitted by the companies. Based on these studies, the Confirm

DM2102 (an older model of Confirm Rx) had a sensitivity of 100%. The BioMonitor 2-AF had a sensitivity of [redacted] The specificities were 85.7% and [redacted] respectively. The EAG commented that the data available for the Confirm Rx and BioMonitor 2-AF suggested they both have good sensitivity and specificity for detecting atrial fibrillation. However it is uncertain how they perform in people who have had a cryptogenic stroke or how any of the devices compare with each other.

Cost effectiveness

Data were not available to inform atrial fibrillation detection rates for the 3 implantable cardiac monitors included in the scope. For the Reveal LINQ, data from an earlier model were used in the economic model. The EAG commented that there is substantial uncertainty about the ICERs for the BioMonitor 2-AF and Confirm Rx because they were assumed to have the same effectiveness as Reveal XT or Reveal LINQ to detect atrial fibrillation.

The base-case model does not include costs of interpreting alerts produced by the implantable cardiac monitors. Identified observational studies reported that many episodes flagged by the Reveal XT or LINQ were false positive episodes (that is, they were not confirmed as atrial fibrillation by clinician review). However, the extent of this depends on device settings and the model of device and atrial fibrillation detecting algorithms used. The external assessment group (EAG) commented that no data were available to use in the model for the average number of alerts generated by the devices that needed review per day or month. When additional costs for reviewing alerts from the Reveal LINQ device were included in the model in scenario analyses (the FOCUSON triage service offered by Medtronic) the device's ICER increased by about £2,000 to £3,000 per QALY gained depending on the cost option used.

No effect of any adverse events caused by the implantable cardiac monitors was included in the model (either disutilities or costs). The EAG commented that no details were provided about how severe these events were in

CRYSTAL-AF. The EAG did not expect this to have a substantial effect on the cost effectiveness of the devices because relatively small proportions of people had adverse events.

If conventional follow up as included in the model (based on CRYSTAL-AF) includes more monitoring than would happen in the NHS, then the increase in the number of people with atrial fibrillation detected by the implantable cardiac monitors may be higher in clinical practice. However, the increase in costs of monitoring with the implantable devices would be higher. The EAG did scenario analyses that removed the monitoring costs and cases of atrial fibrillation detected in the conventional follow-up arm. This caused the ICERs for the 3 devices to increase by up to about £1,500 per QALY gained.

The economic model did not include detection of non-atrial fibrillation arrhythmias. The EAG identified few data on the number of these arrhythmias detected by the devices, and only in non-comparative observational studies. It was unclear if detecting these additional arrhythmias led to any change in treatment. Therefore the actual benefit to patients of detecting non-atrial fibrillation arrhythmias is unclear. The EAG commented that if the implantable cardiac monitors detect some arrhythmias that would otherwise go undetected, then the effect on the cost-effectiveness estimates is likely to be favourable towards the devices. However, the size of the effect is difficult to determine.

5 Equality considerations

NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others.

Men have a higher risk of developing atrial fibrillation than women. In addition, the incidence of atrial fibrillation increases with age. It has also been reported that women with atrial fibrillation have worse symptoms than men and have a higher risk of stroke and death (Ko et al. 2017). The incidence of atrial

fibrillation has been reported as lower for people of south Asian or Caribbean family origin (Amponsah, et al. 2013). These potential equalities issues are related to the incidence of the condition and are unlikely to be affected by using the technology.

People who have had a stroke may have a cognitive or physical disability and may need their carer to use a patient activation recorder and ensure data are transmitted.

People who live in rural areas may have less access to internet or cellular networks (such as 4G) and could have problems accessing, or have less reliable access to, the remote monitoring functions of the devices. If so, there may be a need for more hospital visits for monitoring. However, clinical experts commented that people living in remote areas may benefit from use of these devices because after implantation and check-up the remote monitoring feature means there is less need to visit hospital.

6 Implementation

Key considerations for adoption highlighted during the NICE adoption and impact team's discussions with expert contributors are:

Information governance and IT

Data sent remotely from the devices could be a risk to data protection and information governance if not done correctly. If clinicians and managers have a concern that using the devices could pose a risk to data protection and information governance, this could act as a barrier to adoption. Organisations seeking to adopt these technologies will need appropriate governance in place, with the flexibility to update as regulations and legislation change.

Implant card

Under the new EU Medical Devices Regulation (MDR), health providers using the implantable cardiac devices may need to ensure that implant cards are provided to patients with the devices.

Care pathways and cross-departmental working

An agreed care pathway would be needed to adopt this technology, which is not common in the NHS. Joint working between cardiology, stroke and care of the elderly services will be needed to develop these pathways. Experts commented that communication between teams was helped by using internal computerised referral forms and regular multidisciplinary team meetings to discuss patients who would be eligible. Arrangements also need to be put in place to check for alerts sent by the device, assess if the alert is a true or false positive and then decide on further monitoring or changes to treatment.

Clinician perceptions

Some experts highlighted that barriers to adoption relate to clinician perceptions of the incidence and clinical importance of atrial fibrillation in people with cryptogenic stroke. Other barriers include misconceptions about what is involved in implanting the device and a perceived lack of awareness of the technology among stroke physicians.

Device implantation

A lack of capacity in cardiology and stroke services to implant the devices was highlighted as a barrier to wide-scale adoption. Experts commented that the devices are being implanted by nurse specialists, cardiac physiologists and cardiologists. Experts also stated that the Reveal LINQ device is being implanted in outpatient settings, but the preferred location would be a clinical environment where cleanliness and a local sterile field could be guaranteed.

Adoption levers

Identified adoption levers that could help uptake of these devices are a recognition of the benefits of reducing recurrent strokes, the relative ease of

implanting the devices (compared with previous versions) and that data are automatically uploaded for review which would reduce hospital appointments. Also, the devices are already routinely used in the NHS, for example, for monitoring for arrhythmias in people with syncope.

7 Authors

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Appendix A: Sources of evidence considered in the preparation of the overview

A. The diagnostics assessment report for this assessment was prepared by BMJ Technology Assessment Group:

Edwards SJ et al. 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: a diagnostic assessment report. BMJ Technology Assessment Group, 2019.

B. The following organisations accepted the invitation to participate in this assessment as stakeholders. They were invited to attend the scoping workshop and to comment on the diagnostics assessment report.

Manufacturers of technologies included in the final scope:

- Abbott Medical UK
- Biotronik SE & Co KG
- Medtronic Limited

Other commercial organisations:

- None

Professional groups and patient/carer groups:

- AF Association
- Arrhythmia Alliance
- British Cardiovascular Society
- Cardiomyopathy UK
- Royal College of Physicians

Research groups:

- None

Associated guideline groups:

- None

Others:

- Department of Health
- Healthcare Improvement Scotland
- National Guideline Centre
- NHS England
- Northern England Clinical Networks (CVD)
- Welsh Government

Appendix B: Glossary of terms

Cardiac arrhythmia
An abnormality of the heart's rhythm when it beats too slowly, too quickly or irregularly.

Cryptogenic stroke
An ischaemic stroke with no identified probable cause after diagnostic assessment.

Electrocardiogram (ECG)
A test to monitor the heart's rhythm and electrical activity using sensors applied to the skin (see NHS Choices for more detail).

External ambulatory ECG monitor
An ECG monitor that allows people to move around relatively freely and which is attached without the need for surgical implantation, such as Holter monitors.

Implantable cardiac monitor
Devices that monitor heart rhythm over long periods of time and are implanted under the skin of a person's chest using a small incision under local anaesthetic.

Inpatient cardiac telemetry
Continuous monitoring of a person's heart, including ECG, with data transmitted from a monitor to a separate monitoring station.

Paroxysmal atrial fibrillation
Intermittent episodes of atrial fibrillation which usually last less than 2 days and stop without treatment.

Transient ischaemic attack (TIA)
A 'mini stroke' cause by a temporary disruption of blood flow to the brain (see the NHS website for more detail).