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

ERRATUM

This report was commissioned by the NIHR HTA Programme as project number 18/13/01

BMJ Technology Assessment Group

This document contains errata in respect of the EAG report in response to factual inaccuracies raised by the National Institute for Health and Care Excellence (NICE).

The table below lists the page to be replaced in the original document and the nature of the change:

Page No.	Change
xviii	Text on AF detection results in Crystal-AF amended.
7	Table 2 text on Reveal LINQ amended.
24	Incorrect reference to Table 1 removed
30	Text on Kaplan-Meier data added and reference to time to AF detection results deleted.
32-33	Text and table headings relating to time to AF detection results amended.
45	Text on false positive results amended.
50	Results for Ritter 2013 at 0.25 months amended.
66	Text on time to AF detection results amended.
91	Utility value for systemic embolism in Table 29 amended.
92	Changed 2017 to 2018 in the following sentence: 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 uplifted using the ONS Consumer Price Inflation Index for Medical Services (DKC3).
95 – 97	Replaced references to 2017 prices to 2018 prices.
101-116	Update of results for the base case.
101	In Table 40, column 'Intervention', Confirm RX and BioMonitor 2-AF swapped.
104	Table 41, removal of 'Addition of FOCUSON follow-up costs' from table.
106-107	Clarified that the DOAC outcomes sensitivity analysis is a two-way sensitivity analysis.
121-123	Updated discussion based on corrected base case results
119	Text on time to AF detection results amended.
161	Time to AF detection table row and column headings amended.

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. Median time to AF detection was longer with the ICM than conventional follow-up but the rate of AF detection was significantly higher with the Reveal XT compared with conventional follow-up (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, recurrent 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

Table 1. 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	£1,600	£1,800	N/A
ICM dimensions	88.4 x 15.2 x 6.2 (weight 10.1 g)	49.0 x 9.4 x 3.1 (weight 3.0 g)	44.8 x 7.2 x 4.0 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.	Atrial tachyarrhythmia (including Atrial Flutter/Atrial Fibrillation) (exclusive algorithm) P-wave morphology discriminator algorithm, bradyarrhythmia, ventricular tachyarrhythmia, 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 250 auto activated and patient-activated episodes (total 60 minutes)	14 months of daily time spend in AF (AF Burden), 27 minutes of automatic detected episodes, 2 minutes of the longest AF episode, 30 minutes of symptomatic patient-activated episodes.	27 minutes of automatic detections and 22.5 minutes 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

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 DAR 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 2). The EAG's clinical experts 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 2. 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.

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 **Error! Reference source not found.** 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.[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 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 **Error! Reference source not found.**, 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 (**Error! Reference source not found.**). At 6-months 8.6% of patients were diagnosed with AF in the ICM arm compared to only 1.4% of patients in the conventional follow-up arm. The number of patients with AF diagnosed had risen to 19.0% in the ICM arm at 36 months compared to only 2.3% in the conventional follow-up arm and this is despite incomplete and low numbers of patients followed-up at 36-months. The estimated AF detection rates are therefore higher in the 36-month Kaplan-Meier analysis due to the non-informative censoring of patients lost to follow-up (AF detection rate estimated as 30% with the ICM and 3% with conventional follow-up).

There was only 1 patient diagnosed with AF beyond 12 months follow-up in the conventional follow-up arm, whereas in the ICM arm a further 13 patients were diagnosed

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 (compared to 42 cases in the ICM study arm) and so it is difficult to draw any conclusions from the median time to AF detection data due to the low incidence of AF in the conventional follow-up study arm. Nevertheless, the data show that the number of patients detected with AF increased with longer follow-up, and therefore the median time to AF detection also increased. However, there was a greater increase in the median time to AF detection with the ICM compared to with conventional follow-up across all three timepoints (Table 3). The timing of study follow-up visits may 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. However, the low detection rate of AF in the conventional follow-up arm is likely to be the main reason for the discrepancy in median time to AF detection between the ICM and conventional follow-up groups.

Table 3. CRYSTAL-AF time to AF detection results

Outcome	Months	ICM		Conventional follow-up		HR for detection of AF: ICM versus conventional follow-up HR; 95% CI (p value)
		Median (IQR)	N	Median (IQR)	N	
First 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)
First AF detection, adjusted for PFO, hypertension and coronary artery disease	6	-	-	-	-	5.9; 1.7 to 19.8 (0.009)
First 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 (

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 a 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, **Error! Reference source not found.** 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.

Two 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 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.

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 recommended if confirmed.	0.25 (7 days)	5.0%
				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 some studies 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

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 **Error! Reference source not found.**). 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*: Median time to AF detection was longer for patients with the Reveal XT in CRYSTAL-AF compared with conventional follow-up at 6, 12 and 36 months which is partly due to the significantly higher AF detection rates with the ICM (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]: 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.

- *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,

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 **Error! Reference source not found.**, 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 4 presents the utility values applied for acute events and Table 5 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 4. 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 utility decrement	-0.07	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 5. 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 2018 UK pound sterling (£). Where unit costs have been obtained from the published literature before 2018, costs were uplifted using the ONS Consumer Price Inflation Index for Medical Services (DKC3).[88]

Device costs

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 6. 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

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 costs 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 7 presents the unit cost of follow-up appointments implemented in the short-term Excel model.

Table 7. Cost of follow-up appointments

Parameter	Unit cost	Source
Initial follow-up	£163.36	NHS reference costs 2017-2018) – WF01B (Treatment Function Code 320)
Subsequent follow-up	£128.05	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 8. 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 2018 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 8. 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 2018 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 9.

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 9. 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 2018 prices (Table 10) for the current analysis. As per the original model, it is assumed that the cost for ICH is the same as stroke.

Table 10. 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	66 (49%)	£2,135 (£3,675)
Moderately disabling	58 (43%)	£4,165 (£7,768)
Totally disabling	12 (9%)	£6,324 (£14,898)
Total weighted cost (uplifted to 2018 prices)		£4,514 (£8,585)
Abbreviations: SD, standard deviation.		

4.2.7 Summary of base case assumptions

Table 11 presents an overview of the parameter assumptions used in the base case model.

Table 11. 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.

5 COST-EFFECTIVENESS RESULTS

5.1.1 Base-case deterministic and probabilistic results

Table 12 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 1. Table 13 presents the fully incremental analysis of cost-effectiveness results and demonstrates that out of the ICMs under consideration, Reveal LINQ and Confirm RX are dominated by BioMonitor 2-AF.

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.

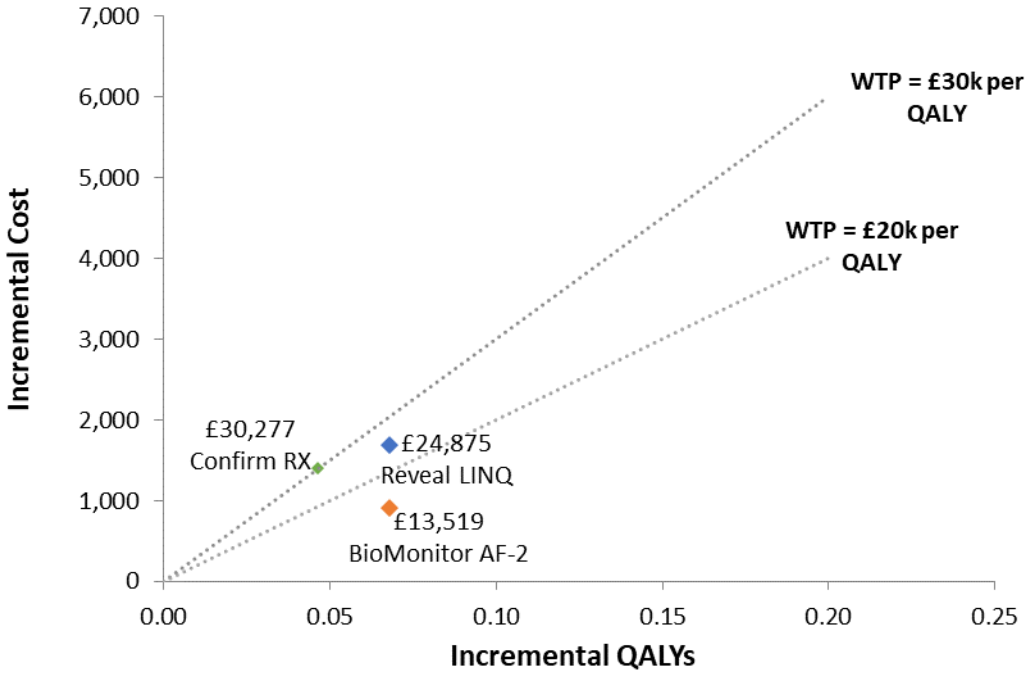
Table 12. Base case incremental pairwise cost effectiveness results (discounted)

Intervention	Total Costs	Total QALYs	Incremental costs	Incremental QALYs	ICER
Standard of Care	£7,672	1.66	-	-	-
Reveal LINQ	£9,359	1.73	£1,687	0.07	£24,875
BioMonitor 2-AF	£8,589	1.73	£917	0.07	£13,519
Confirm RX	£9,076	1.71	£1,404	0.05	£30,277
Abbreviations: ICER, incremental cost effectiveness ratio; QALY, quality adjusted life year.					

Table 13. Base case incremental cost effectiveness results (discounted)

Intervention	Total Costs	Total QALYs	Incremental costs	Incremental QALYs	ICER
Standard of Care	£7,672	1.66	-	-	-
BioMonitor 2-AF	£8,589	1.73	£917	0.07	£13,519
Confirm RX	£9,076	1.71	£487	-0.02	Dominated
Reveal LINQ	£9,359	1.73	£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 1. 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 DOAC 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 14. Scenario anlyses for each ICM versus SoC (Discounted ICERs)

Scenario	**ICERs versus SoC**		
	Reveal LINQ	**BioMonitor-2**	**Confirm RX**
Base case	*£24,875*	*£13,519*	*£30,277*
Addition of FOCUSON triage costs (Option 1)	£32,872	NA	NA
Addition of FOCUSON triage costs (Option 2)	£30,391	NA	NA
Addition BioMonitor 2-AF remote assistant device	NA	£16,911	NA
Addition BioMonitor 2-AF CardioMessenger	NA	£19,418	NA
Time horizon for ICM monitoring (1 year)	£55,935	£27,424	£48,530
Time horizon for ICM monitoring (2 year)	£34,591	£17,981	NA
Constant detection rates (exponential)	£24,731	£13,344	£29,978
Long-term DOAC outcomes based on apixaban	£33,677	£20,041	£40,753
Long-term DOAC outcomes based on dabigatran	£17,775	£6,716	£22,589
Long-term DOAC outcomes based on edoxaban	£19,070	£8,114	£23,870
Long-term DOAC outcomes based on rivaroxaban	£19,144	£9,508	£23,433
Inclusion of warfarin as a treatment option for patients diagnosed with AF	£86,218	£49,845	£104,956
No explantation of devices	£21,704	£10,348	£25,477
Implantation by Cardiac Physiologist (Band 7)	£24,749	£13,394	£30,094

Implantation assisted by Cardiac Physiologist (Band 5)	£24,872	£13,517	£30,273
Implantation assumptions based on Kanters *et al.* 2015[117]	£25,269	£13,913	£30,854
No SoC monitoring or AF detections	£27,592	£17,391	£33,304
Abbreviations: ICER, incremental cost effectiveness ratio; ICM, implantable cardiac monitor; QALY, quality adjusted life year; SoC, standard of care.			

Figure 2. Tornado plot for scenarios with greatest impact (Reveal LINQ versus SoC)

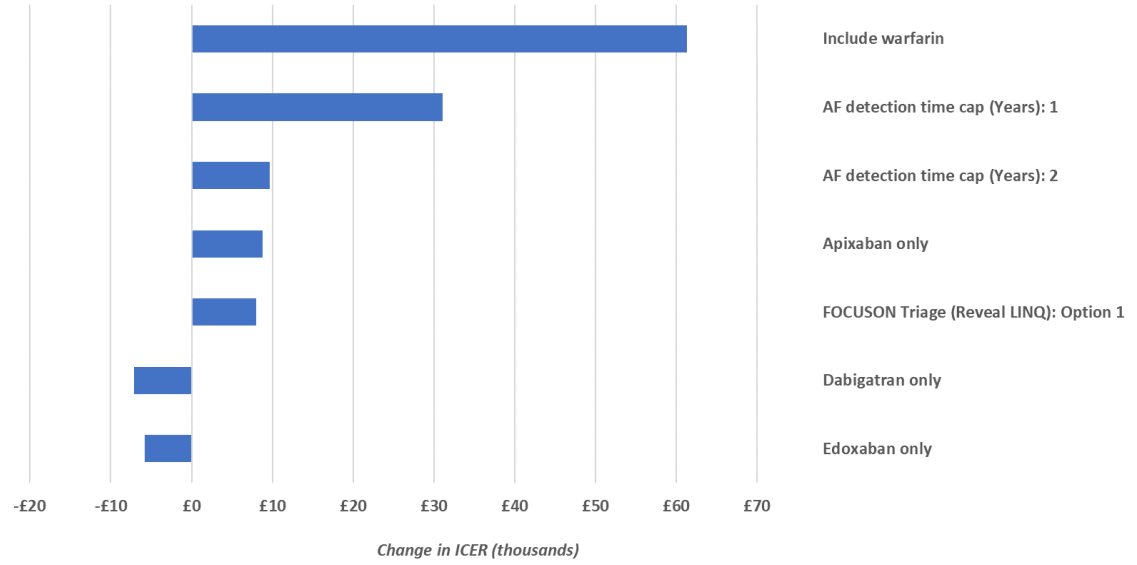


Figure 3. Tornado plot for scenarios with greatest impact (BioMonitor 2-AF versus SoC)

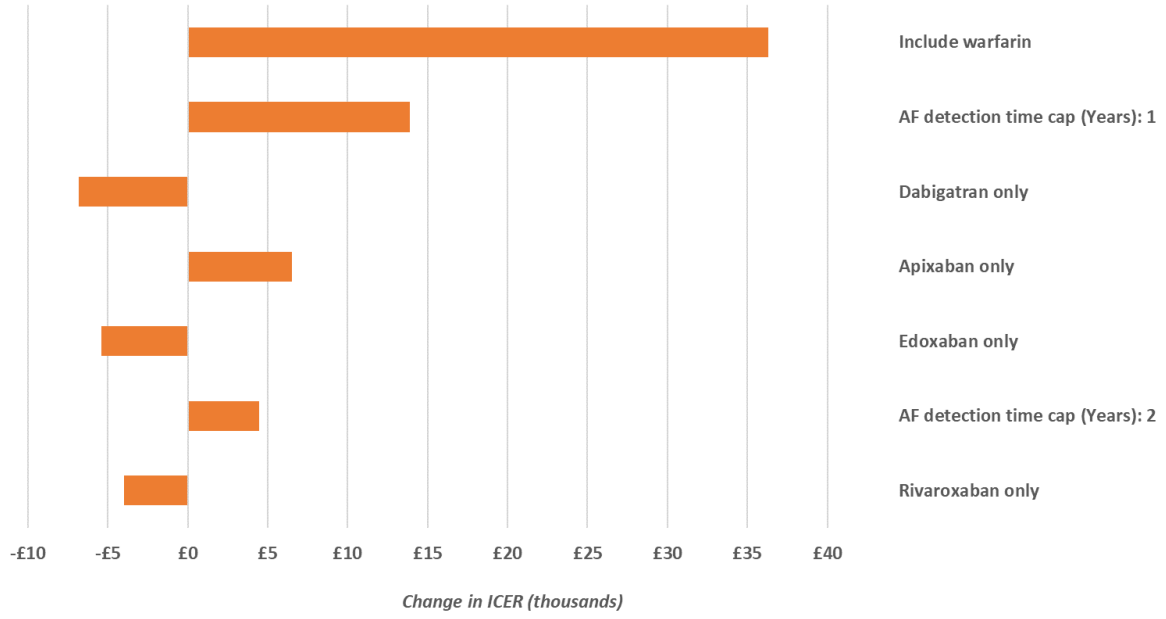
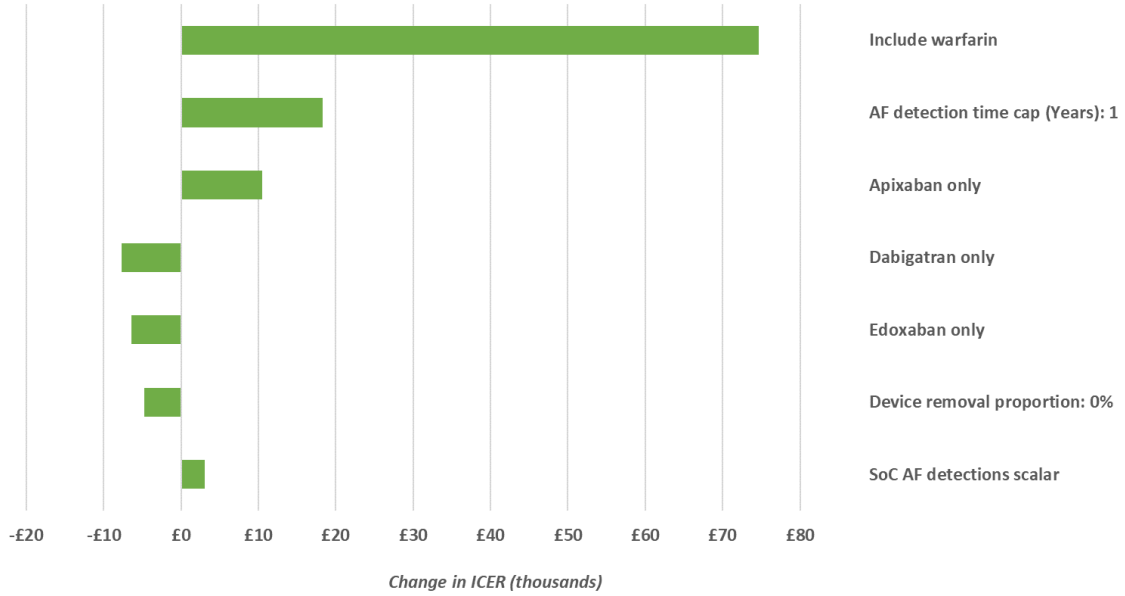


Figure 4. Tornado plot for scenarios with greatest impact (Confirm RX versus SoC)



5.1.3 Sensitivity analyses

5.1.3.1 One-way and two-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.

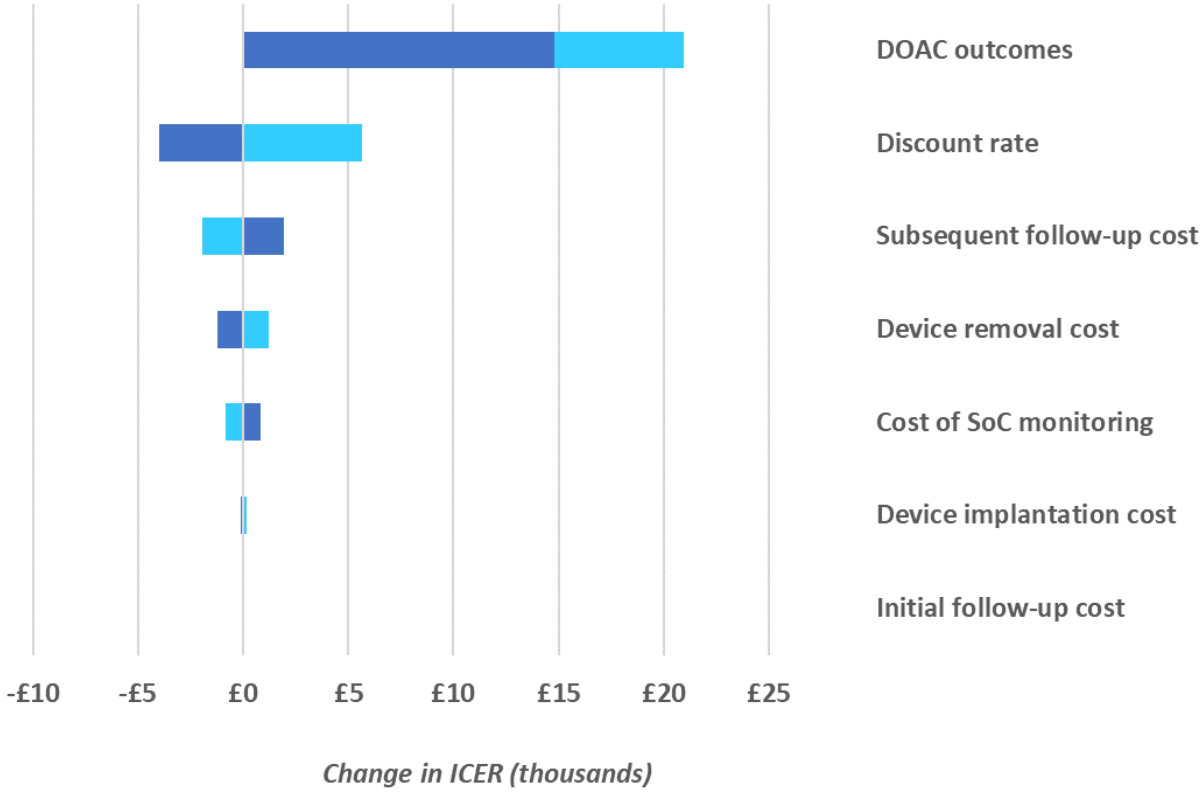
The most recent publication of NHS reference costs (2017-2018) no longer gives an inter-quartile range for the costs associated with each Healthcare Resource Group (HRG). Given the lack of data to inform the variation around the mean estimate, the EAG assumed a standard error of 20% of the mean value for each parameter. For DOAC outcomes (costs and QALYs), two-way sensitivity analysis around 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 **Error! Reference source not found.**.

Table 15. One-way and two-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	£24,875	£24,875	£13,519	£13,519	£30,277	£30,277
Device implantation cost	£24	£15	£34	£24,735	£25,015	£13,379	£13,659	£30,073	£30,481
Cost of SoC monitoring	£141	£85	£196	£25,688	£24,062	£14,332	£12,706	£31,466	£29,088
Device removal cost	£238	£145	£332	£23,632	£26,118	£12,276	£14,762	£28,395	£32,159
Subsequent follow-up cost	£128	£78	£178	£26,827	£22,923	£15,471	£11,567	£33,220	£27,334
Discount rate	3.5%	1.5%	6%	£20,863	£30,533	£11,533	£16,281	£25,322	£37,253
DOAC outcomes*	Mean	2.5th percentile	97.5th percentile	£39,688	£31,041	£21,927	£15,041	£45,374	£38,600

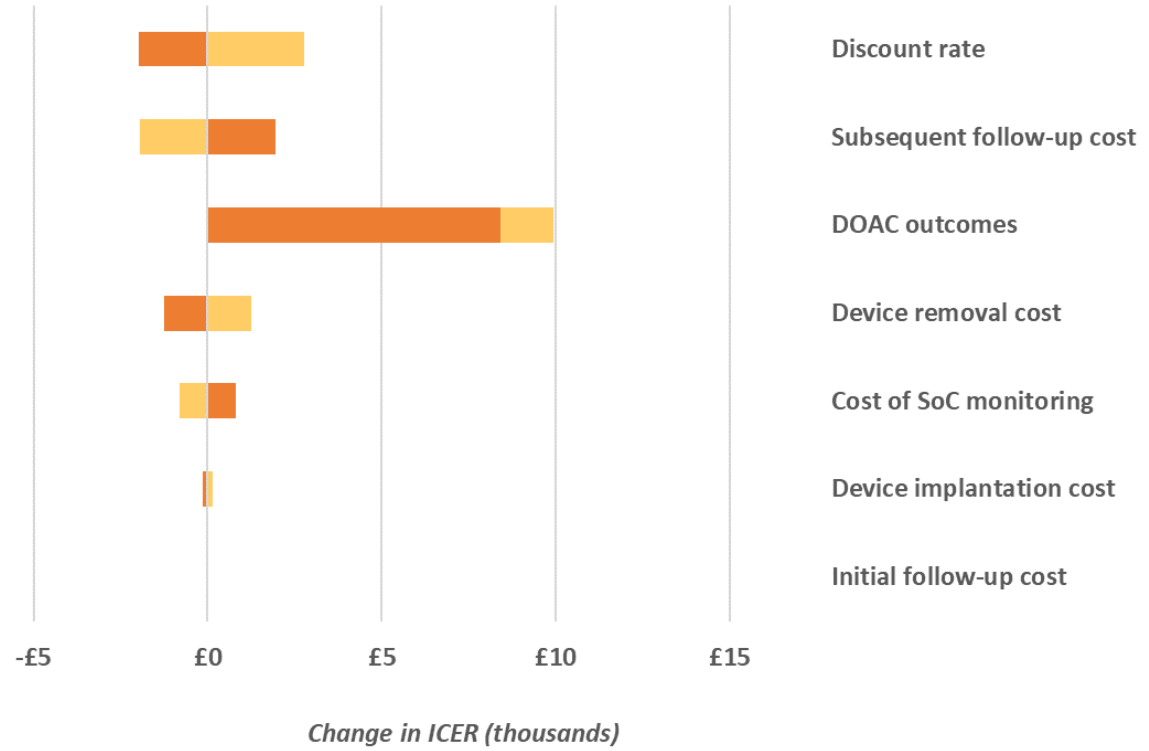
Abbreviations in table: DOAC, direct oral anticoagulant; ICER, incremental cost effectiveness ratio; SoC, standard of care.
*two-way sensitivity analysis
Note: The ICERs correspond to the lower and upper parameter inputs and in some cases the “lower ICER” is a larger number than the “upper ICER”.

Figure 5. Tornado plot showing OWSAs for Reveal LINQ versus SoC



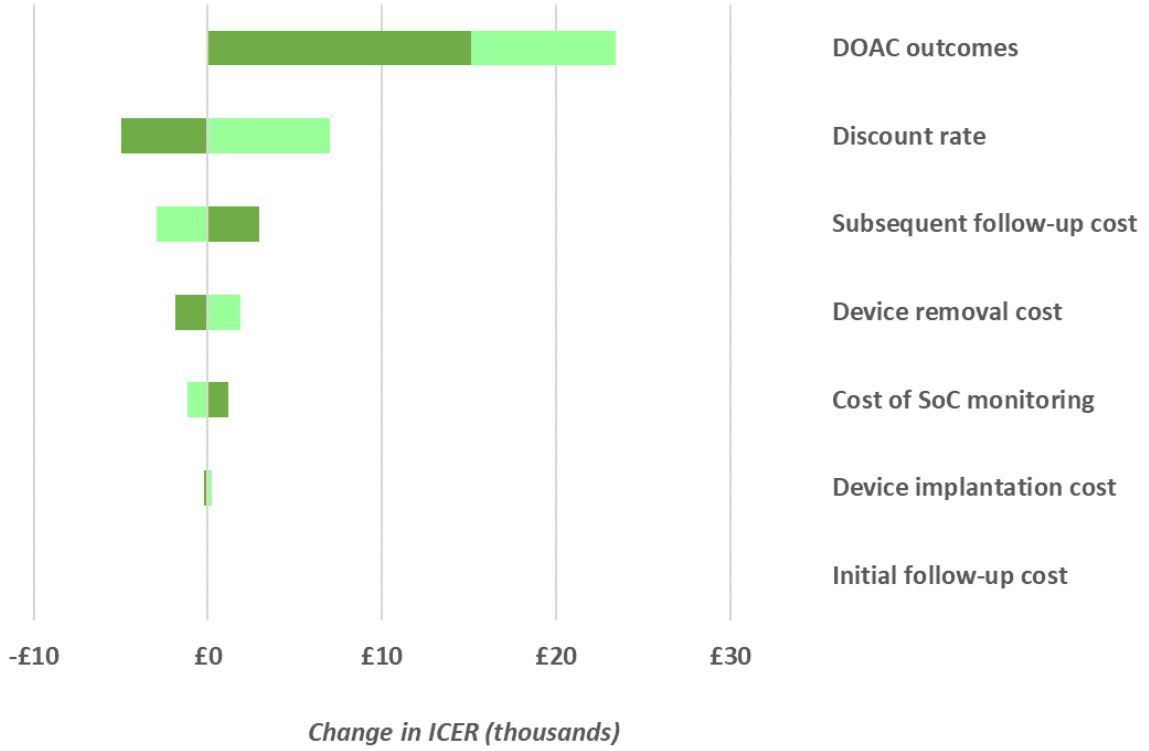
Abbreviations in figure: DOAC, direct oral anticoagulant; ICER, incremental cost effectiveness ratio; OWSA, one-way sensitivity analysis; SoC, standard of care.

Figure 6. 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 7. 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 EAG 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. The columns were sampled in the PSA one by one, from 1 to 10,000, to avoid sampling from the same column more than once. 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 16.

Table 16. 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	£163	£33	Gamma	25.00	6.53
Subsequent follow-up	£128	£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 $SE^2/Mean$

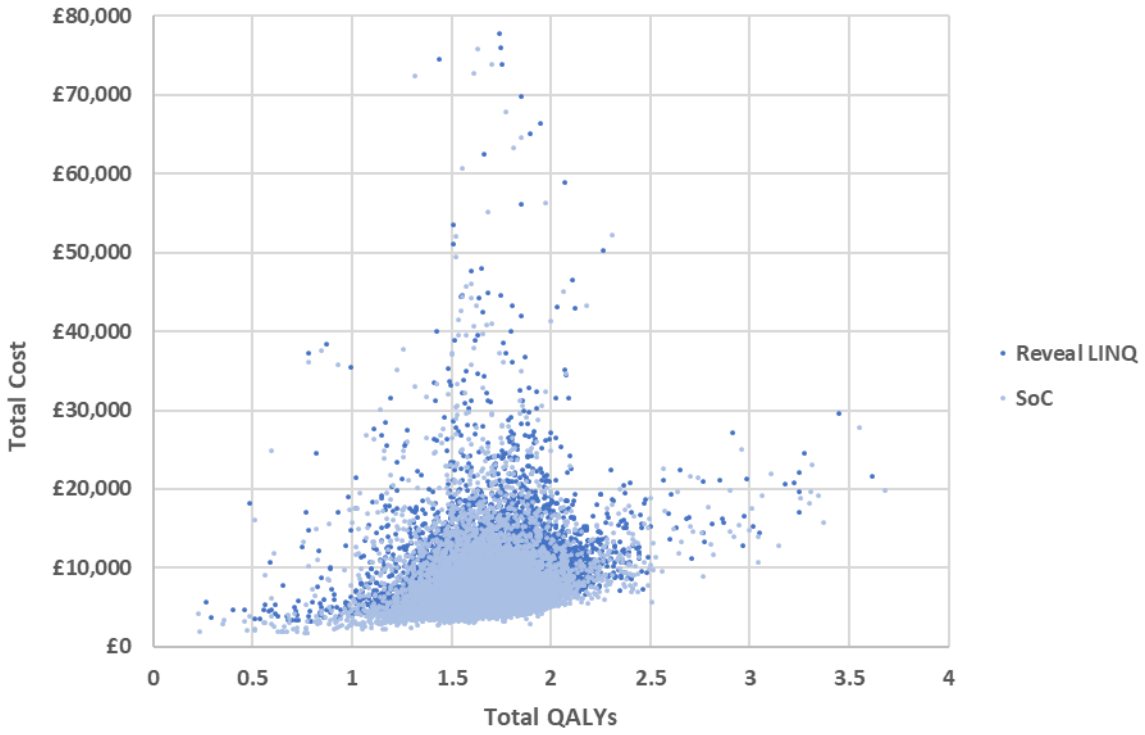
The results of the PSA for each ICM and SoC are given in Table 17, and a scatterplot showing the spread of results from the individual samples is given in Figure 8, Figure 9 and Figure 10, for Reveal LINQ, BioMonitor 2-AF and Confirm RX, respectively; each versus SoC. The incremental costs and QALYs relative to SoC are shown in the cost effectiveness planes in Figure 11, Figure 12, and Figure 13, 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 14, Figure 15, and Figure 16 for Reveal LINQ, BioMonitor 2-AF and Confirm RX, respectively.

Table 17. PSA results for each ICM compared with SoC (Discounted)

Intervention	Total Costs	Total QALYs	Incremental costs	Incremental QALYs	ICER
Standard of Care	£7,672	1.66			
Reveal LINQ	£9,359	1.73	£1,687	0.07	£24,866
BioMonitor 2-AF	£8,589	1.73	£917	0.07	£13,516
Confirm RX	£9,076	1.71	£1,404	0.05	£30,269

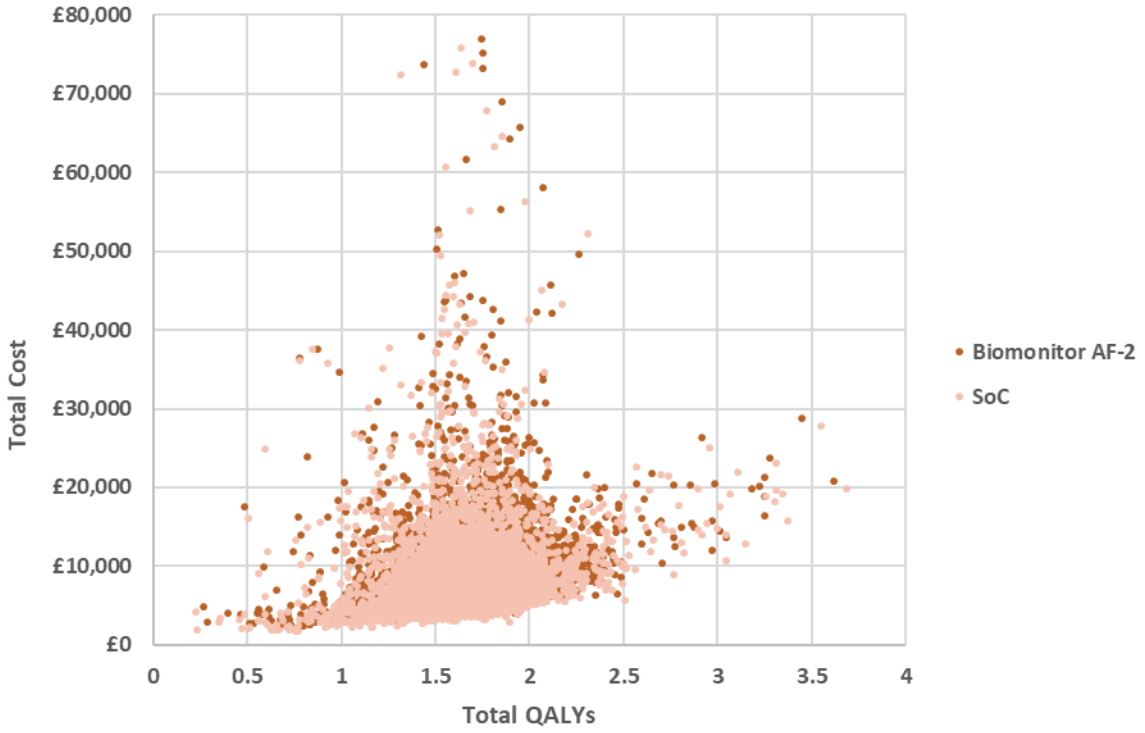
Abbreviations in table: ICER, incremental cost effectiveness ratio; QALY, quality adjusted life year.

Figure 8. PSA scatterplot for Reveal LINQ versus SoC



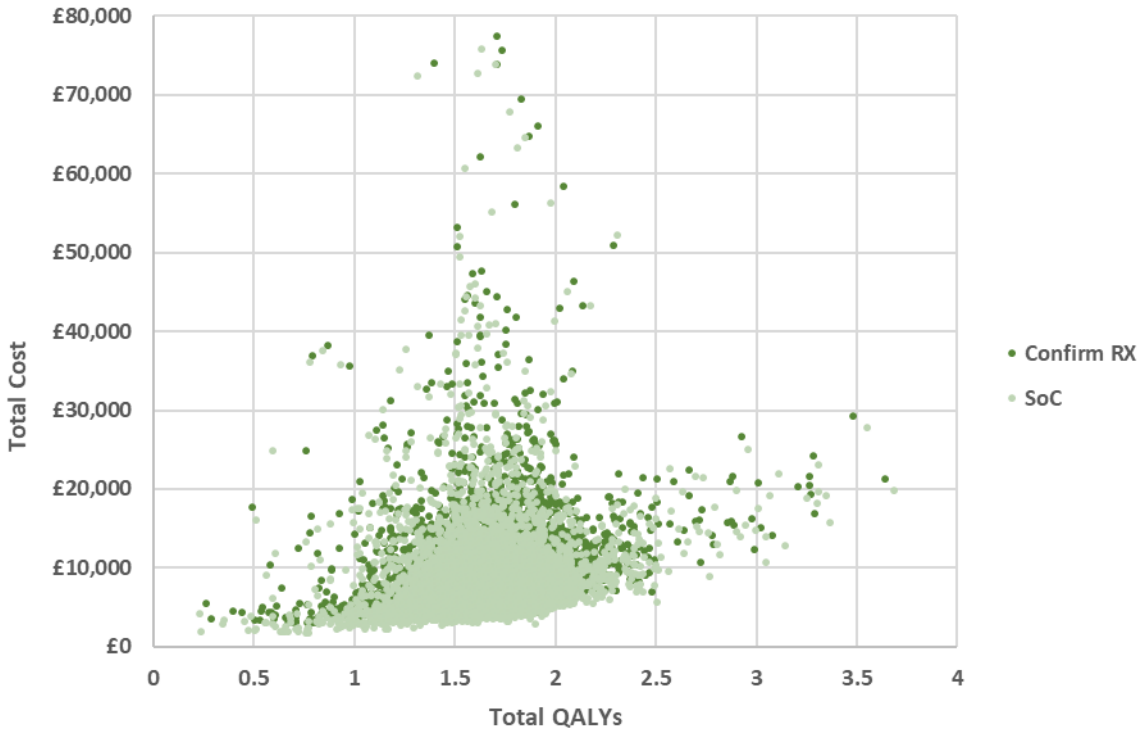
Abbreviations in figure: QALY, quality-adjusted life-year; SoC, standard of care.

Figure 9. PSA scatterplot for BioMonitor 2-AF versus SoC



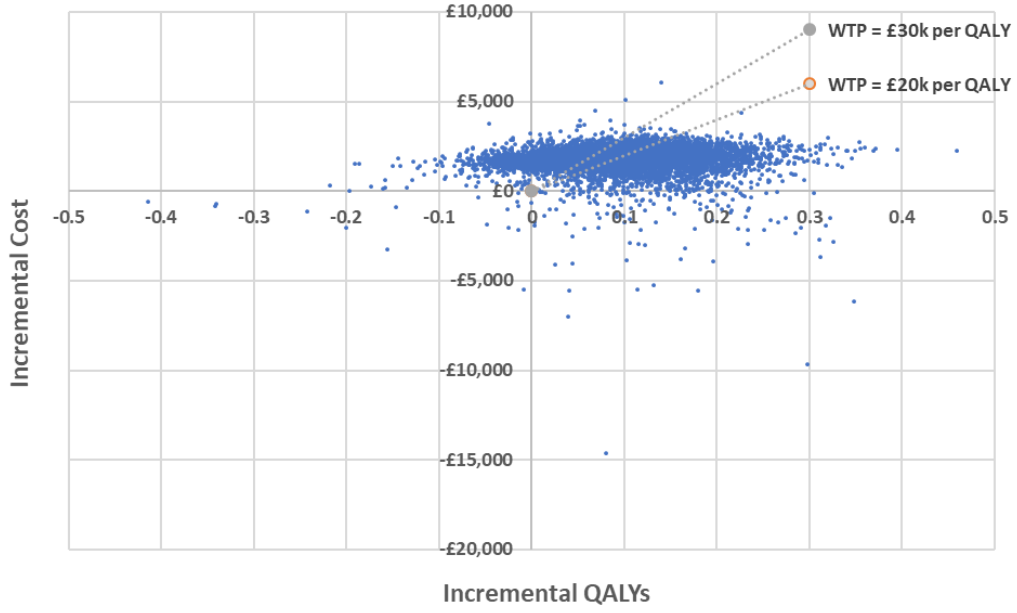
Abbreviations in figure: QALY, quality-adjusted life-year; SoC, standard of care.

Figure 10. PSA scatterplot for Confirm RX versus SoC



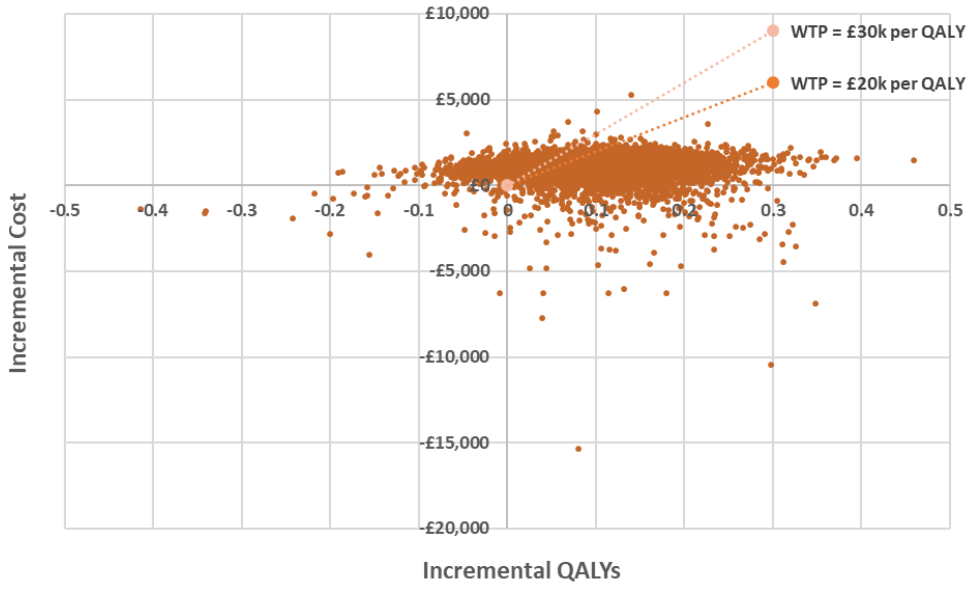
Abbreviations in figure: QALY, quality-adjusted life-year; SoC, standard of care.

Figure 11. Cost effectiveness plane for Reveal LINQ versus SoC



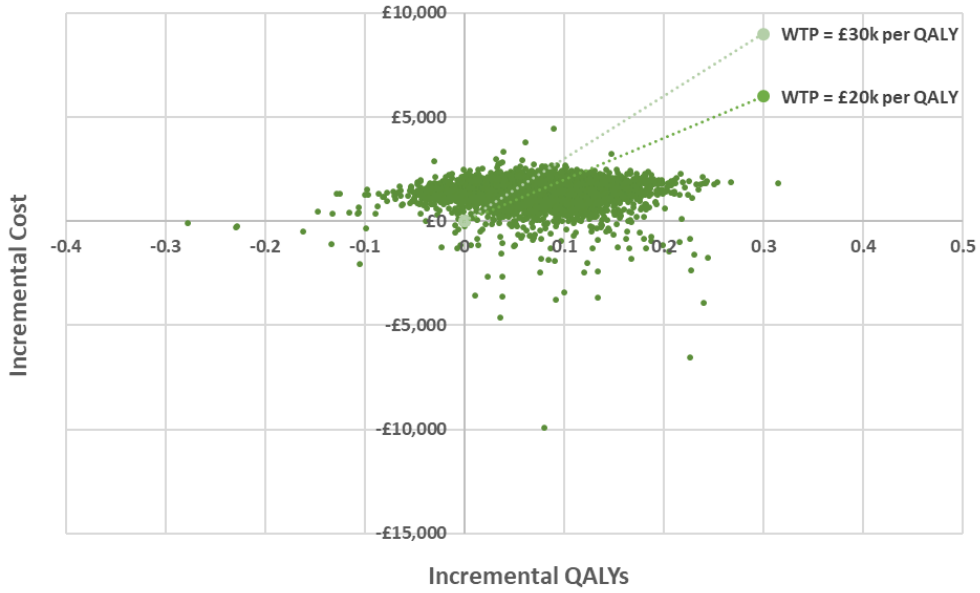
Abbreviations in figure: SoC, standard of care; WTP, willingness to pay.

Figure 12. Cost effectiveness plane for BioMonitor 2-AF versus SoC



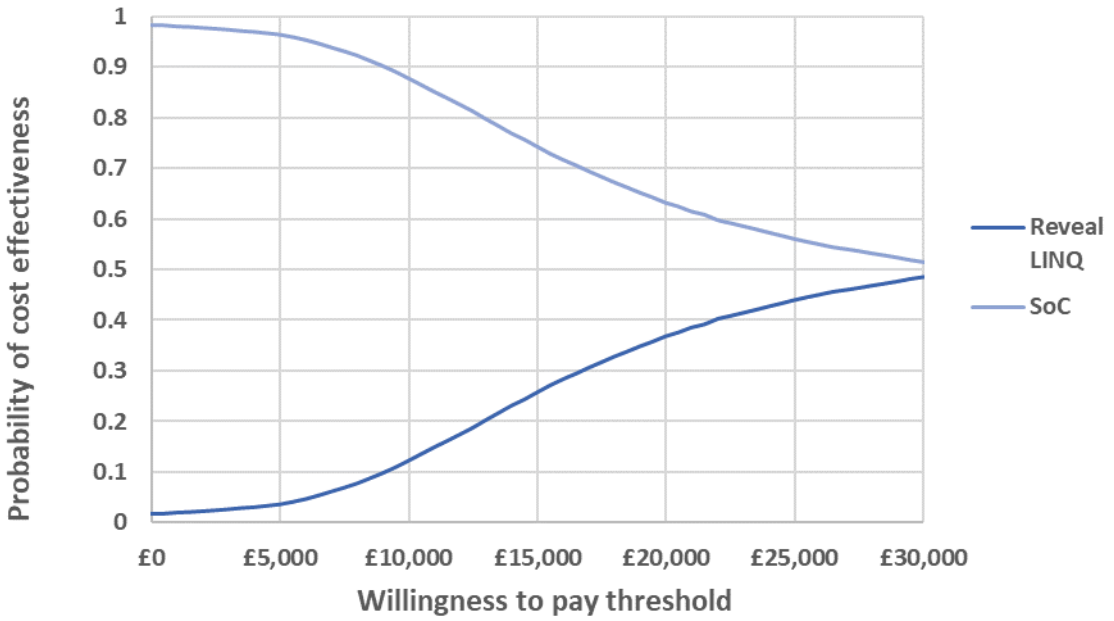
Abbreviations in figure: SoC, standard of care; WTP, willingness to pay.

Figure 13. Cost effectiveness plane for Confirm RX versus SoC



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

Figure 14. Cost effectiveness accepatibility curve for Reveal LINQ versus SoC



Abbreviations in table: SoC, standard of care.

Figure 15. Cost effectiveness accepatibility curve for BioMonitor 2-AF versus SoC

Figure 16. Cost effectiveness accepatibility curve for Confirm RX versus SoC

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 firmware, 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.

Median time to AF detection was longer for patients with the Reveal XT in CRYSTAL-AF compared with conventional follow-up at 6, 12 and 36 months (p value not reported). Nevertheless, 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 (36 months: HR 8.8, 95% CI: 3.5 to 22.2, $p<0.001$). 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

[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 the scenario which caused the most substantial change in the ICER for all three devices was the inclusion of warfarin. 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, which for Reveal LINQ and Confirm RX exceeded the £30,000 cost-effectiveness threshold.

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 0.151 QALYs, resulting in an ICER of £17,175 per QALY gained. This ICER is lower than the EAG's ICER for the Reveal LINQ (£24,875). 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 18 presents a comparison of the results produced by each model.

It can be seen that the EAG's model produces incremental costs which are lower, and this can be attributed to a lower baseline hazard of ischaemic stroke used in the long-term model and as such lower health state costs. Furthermore, there were differences between the two models 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 lower. The EAG considers that the difference in QALYs can also be attributed to a lower baseline hazard of ischaemic stroke used 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 18. 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	£1,687	0.07	£24,875
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

6.1.1 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

AF detection		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	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 m	23(11.6%) 4 (20.0%)	200 21	4 (2.2%) 0	201 19	
	Stroke TIA	36 m	(31.2%) NR	200 21	(3.3%) 0.0%	201 19	
AF detection with median time to first detection							
Outcome			**Median (IQR)**	**N**	**Median (IQR)**	**N**	**HR for detection of AF; 95% CI (p value)**
First AF detection, unadjusted		6 m	41 days (4 to 84)	19 detected	32 days (2 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)
First AF detection, adjusted for PFO, hypertension and coronary artery disease		6 m	-	-	-	-	5.9; 1.7 to 19.8 (0.009)
First 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)