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

EAG response to NICE request for further analysis

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BMJ Technology Assessment Group

This document presents the Evidence Assessment Group's response to a request from the National Institute of Health and Care Excellence (NICE) on behalf of the Diagnostic Assessment Committee (DAC) for further analysis to address outstanding uncertainties in the cost-effectiveness analyses.

The DAC have requested more information for the following areas:

1. Review of the probabilistic sensitivity analysis;
2. Scenario analysis for the cost of reviewing alerts generated by the implantable cardiac monitors (ICMs);
3. Further explanation of the total quality adjusted life years (QALYs) generated by the model;
4. Number of clinical events in each arm of the model.
5. Comparison with Medtronic cost-effectiveness analysis

In addition to the analyses request by NICE, the EAG discovered two errors in the R model code which required correction. Details of the model changes and the EAG's response to each of the requests from NICE are explored in turn in the remainder of this report.

Model corrections

The long-term directly acting oral anticoagulant (DOAC) model for this diagnostic assessment report (DAR) was based on R statistical software code that was used for two previously published models.[1, 2] After submission of the DAR, the EAG identified an issue with inconsistent treatment effect hazard ratios for some clinical events used in the DOAC model. The EAG contacted the original DOAC model developer for clarification on the issue and was informed that the code had gone through several iterations and what was provided to the EAG was an old version of the code which caused the mismatch in the hazard ratios and clinical events for each treatment.

In May, corrected code was provided to the EAG, which was implemented in the long-term DOAC model. However, when updating the code, the EAG spotted an error with event costs. Mean event costs in the model were input erroneously as the lower bound of uniform distributions, resulting in sampled costs which were too high. The EAG corrected the issue so that the lower and upper bounds of the uniform distribution were 50% either side of the mean cost.

As a result of the two amendments, the base-case cost-effectiveness results changed, and the updated results, scenarios and sensitivity analyses have been provided in an erratum to the EAG report. Table 1 presents the corrected base-case pairwise results for each of the implantable cardiac monitors (ICMs) compared with Standard of Care (SoC). Table 2 presents the base case incremental cost-effectiveness results.

Table 1. 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 2. 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.					

Probabilistic sensitivity analysis (PSA)

During the committee meeting, the Diagnostic Assessment Committee (DAC) were concerned that the PSA results were substantially different to the deterministic base case results and considered that there was an error in the PSA. The EAG investigated the issue and found that when performing random sampling for a single DOAC, there was a problem with the weighting of the DOAC costs and outcomes due to an error in the specification of the formula used for the PSA. The EAG corrected this and re-ran the PSA. Table 3 presents the corrected results, which are in line with the deterministic base case incremental cost-effectiveness ratios (ICERs). Updated cost-effectiveness planes and cost-effectiveness acceptability curves can be found in the updated erratum to the EAG report.

Table 3. 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.

Cost of reviewing alerts scenario analysis

The DAC considered that it was important to understand how the cost of reviewing alerts could potentially affect the ICER and suggested performing a threshold analysis. The EAG sought to estimate the number of alerts that would need to be reviewed for the ICER to exceed the £20,000 to £30,000 cost-effectiveness threshold. Based on the updated cost-effectiveness results, Confirm RX has an ICER above the £30,000 threshold and is therefore excluded from the analysis. Furthermore, BioMonitor 2-AF is the only device assessed at the £20,000 threshold, as the base case ICER is below £20,000.

The EAG contacted clinical experts to determine how long it would take to review an alert produced by an ICM and who would review the alert. For reference, an ICM would produce an alert if an unusual heart rhythm (e.g. atrial fibrillation [AF]) is detected by the device algorithm. In CRYSTAL-AF, an episode of AF was detected by the ICM if it lasted greater than 30 seconds, within a two-minute analysis window. There was consensus amongst the clinical experts that a cardiac physiologist would review the alerts (Band 4 to 8) and that these would be reviewed daily, with some of the clinical experts suggesting five days a week coverage and one expert stating that it would be seven days a week coverage. With regards to the time taken to review an alert, one clinical expert suggested it could take 30 seconds to review and another suggested it could be up to two minutes.

Based on the feedback from the EAG's clinical experts, the EAG performed two threshold analyses, with one analysis using the lower limits of the clinical expert's parameter estimates (Band 4 cardiac physiologist, 30 seconds review time) and another analysis looking at the upper limits (Band 8 cardiac physiologist, two minutes review). The EAG used the assumption that alerts are reviewed for 1 hour, daily. Table 4 presents the cost estimates used to inform the analyses. Table 5 presents the results of the two scenarios for BioMonitor 2-AF using the £20,000 threshold and Table 6 presents the results for Reveal LINQ and BioMonitor 2-AF using the £30,000 threshold. It should be noted that results presented are per patient for the duration of the device's battery life.

Table 4. Cost and resource use assumptions for scenarios

Parameter assumptions	Cost per hour (PSSRU, 2018)	Cost per minute	Cost per alert
Band 4 cardiac physiologist, 30 seconds alert review	£31	£0.52	£0.26
Band 8 cardiac physiologist, 2 minutes alert review	£67	£1.12	£2.23

Table 5. BioMonitor 2-AF - Number of alerts required for the EAG base case ICER to exceed £20,000

Device	Battery life (years)	Number of alerts	Review time (days)

Scenario 1: Lower limits - (Band 4 cardiac physiologist, 30 seconds alert review, 1 hour per day review)			
BioMonitor 2-AF	4*	1701	14.2
Scenario 2: Upper limits - (Band 8 cardiac physiologist, 2 minutes alert review, 1 hour per day review)			
BioMonitor 2-AF	4*	197	6.6
*Capped in the economic model to 3 years as atrial fibrillation detection rate data are only available for this time period.			

Table 6. Number of alerts required, by device, for the EAG base case ICER to exceed £30,000

Device	Battery life (years)	Number of alerts	Review time (days)
Scenario 1: Lower limits - (Band 4 cardiac physiologist, 30 seconds alert review, 1 hour per day review)			
Reveal LINQ	3	1,345	11.2
BioMonitor 2-AF	4*	4,326	36.0
Scenario 2: Upper limits - (Band 8 cardiac physiologist, 2 minutes alert review, 1 hour per day review)			
Reveal LINQ	3	156	5.2
BioMonitor 2-AF	4*	500	16.7
*Capped in the economic model to 3 years as atrial fibrillation detection rate data are only available for this time period.			

Number of QALYs generated by the model

When reviewing the total QALYs produced by the economic model, the DAC were concerned that the number was low and as such lacked face validity. For instance, total QALYs for the standard of care (SoC) arm were 1.66 and total QALYs for the ICM devices ranged from 1.71 to 1.73.

The key to understanding the total QALYs produced by the model is to consider how the population that enter the model (i.e. cryptogenic stroke patients where AF has not been diagnosed after at least 24 hours of external ambulatory ECG monitoring) is being treated. All patients at the beginning of the model are placed on antiplatelet treatment for stroke prevention as AF has not been diagnosed and as such this is the recommended treatment.

Based on data from CRYSTAL-AF, it is known that by the end of the three-year follow-up period of the trial, 30% of patients are diagnosed with AF. Some of the AF cohort would have developed AF over the time period and others may have had their AF missed by the initial monitoring due to the episodic nature of their AF. Thus, 70% of the starting cohort are being appropriately treated with antiplatelets and regardless of whether a patient is in the ICM arm or the SoC arm, long-term costs and benefits of being on antiplatelet treatment are the same and the incremental costs and benefits between the two arms would be zero.

Thus, the EAG took the pragmatic decision not to model the long-term impacts of the 70% of patients who do not develop AF as it makes no difference to the final ICERs, but consider that if it was modelled, the total QALYs for each comparator would be higher (as the DAC expected), but the incremental QALYs would remain the same as presented in the base case analysis. However, the 70% of patients who do not develop AF are still assigned the relevant costs of the intervention they are receiving (e.g. the costs associated with having an ICM or follow up costs for SoC). Therefore, total costs are reflective of the entire cohort.

With regards to the 30% of the cohort that develop AF over the three-year time horizon of the short-term model, it should be noted that the risk of secondary stroke and other events is relatively low. Table 7 presents the baseline mean hazards used in the DOAC (directly acting anticoagulant) model. As a reminder, warfarin was used as the baseline treatment in the model and hazard ratios for DOACs and antiplatelet treatment were applied to the baseline hazards. Furthermore, patients can experience multiple events (up to four), with past events impacting the risk of future events. For reference, in CRYSTAL-AF, 5.3% of patients in the ICM went on to have secondary stroke, compared with 8.6% of patients in the SoC. However, in CRYSTAL-AF, the number of secondary strokes for patients with confirmed AF in each arm of the trial was not presented. As such, some of the secondary stroke events

may have occurred in people who did not have AF, e.g. the 70% of the population who had an ICM implanted and were not diagnosed with AF.

Therefore, not only are utilities weighted by the low risk of events occurring but are also further weighted by the fact that only 30% of the initial cohort are affected, explaining the low total QALY estimates generated by the analysis.

Table 7. Baseline mean hazard of events used in the DOAC model (Sterne *et al.* 2017)

Event	Mean hazard (95% CI)
Ischaemic stroke	0.012 (0.01 to 0.013)
Transient ischaemic attack	0.025 (0.006 to 0.089)
Myocardial infarction	0.0079 (0.0064 to 0.01)
Systemic embolism	0.017 (0.0059 to 0.041)
Intracranial haemorrhage	0.0094 (0.0057 to 0.017)
Major bleed	0.066 (0.031 to 0.13)
Death (all causes)	0.038 (0.028 to 0.052)

Number of clinical events in each arm of the model

In order to understand the potential benefits of ICMs, the DAC requested the EAG to present the number of clinical events estimated for each arm of the model. In the model, based on a sensitivity of 100%, it is assumed that ICMs will detect all patients who have an AF event. As such, the detection rate for the ICM is used for the prevalence of AF in the CS population. In CRYSTAL-AF after 3 years 30% of patients fitted with an ICM were detected with AF, compared with 3% on SoC. All ICM patients **with AF** were assumed to switch to anticoagulation treatment (100%), as all AF events are detected. For patients **with AF** in the SoC arm, 10% switched to anticoagulation treatment due to detection (0.03/0.3) and 90% remained on antiplatelet treatment (0.27/0.30) as their AF remained undetected.

Table 8 presents the number of stroke events per 1000 patients with AF who have an ICM or on SoC. It is estimated that appropriate treatment of AF detected by ICMs prevents an additional 16 strokes per 1000 patients compared with SoC.

Table 8. Number of stroke events per 1000 patients with AF by treatment arm

Population	Strokes per 1000 AF patients
SoC	214
ICM	198
Difference	**16**

Abbreviations: AF, atrial fibrillation; ICM, implantable cardiac monitor; SoC, standard of care.

Comparison with Medtronic cost-effectiveness analyses

Based on the CRYSTAL-AF study, the manufacturer of the Reveal ICM device series, Medtronic funded a cost-effectiveness analysis of the Reveal XT device (Diamantopoulos *et al*. 2016)[3]. This analysis is discussed in depth in the main EAG report. Table 9 presents a comparison of the cost-effectiveness results from the Diamantopoulos *et al.* study and the current report. There is £900 difference in costs and 0.08 difference in QALYs between the two models.

Table 9. Comparison of results for the Reveal devices

Intervention	Incremental costs	Incremental QALYs	ICER
Reveal XT vs SoC (Diamantopoulos *et al.* 2016[3])	£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.			

The EAG considers that the differences between the two models are related to differences in modelling approach to anticoagulation treatment for AF and the associated outcomes. As mentioned in the EAG report, the Diamantopoulos *et al.* study used risk of subsequent ischaemic stroke determined by AF status, virtual CHADS2 score, age and treatment received.[3] Annual baseline stroke risk stratified by virtual CHADS2 score (AF-undetected health state) was obtained from a paper by Gage *et al*.[4] and a network meta-analysis (NMA) was conducted to estimate treatment effects. For AF-free patients on aspirin, a hazard ratio (HR) was obtained from a UK registry of patients with recent stroke.[5] For AF-detected patients on warfarin and apixaban, HRs were based on data from AVERROES[6] and ARISTOTLE[7] randomised controlled trials (RCTs). Treatment effects of any DOAC (apixaban, dabigatran or rivaroxaban) versus warfarin were obtained from a published meta-analysis[8]. However, there is limited detail on how the NMA was conducted, including whether a systematic literature review (SLR) was performed. However, for the apixaban analysis, the EAG considers all relevant studies were included and are aligned with Sterne *et al*[1] but that the comparisons of warfarin versus aspirin may have missed out some trials (such as AFASAK[9] and BAFTA[10]) which were included in the SLR used for the DOAC model.

In the DOAC model, risk of ischaemic stroke was not stratified by virtual CHADS2 score but was adjusted for by type of AF (paroxysmal), previous history of stroke, age and treatment received. Treatment effects used in the model were estimated using a competing risks NMA based on a clinical effectiveness SLR conducted by Sterne *et al*[1]. The clinical effectiveness SLR for the DOAC model identified twenty-three completed RCTs for inclusion in the review. Seventeen types of events were included in the NMA to account for correlation and competing risks. Three types of outcome data were incorporated into the model to estimate the HRs and included: number of first events; number of individuals experiencing at least one event of a given type; and total number of events. Baseline treatment in the DOAC model is warfarin (INR 2-3) and as such the authors developed a competing

risks model for warfarin separately to estimate the baseline hazard for the outcomes of interest in the model.

Due to the different structures of the two models, outcomes included and the mechanisms to estimate outcomes for anticoagulation and antiplatelet treatment, a like for like comparison of risk of stroke used in each model is difficult and as such, it is more insightful to compare the outcome of number of strokes avoided (that is the difference in stroke events between the ICM and SoC arms) estimated by each model. The number of stroke events avoided in the Diamantopoulos *et al.* study is approximately double the number estimated by the DOAC model (40 per 1000 patients), contributing to almost double the QALY benefit compared with the current analysis.

Furthermore, severity of stroke is included in the Diamantopoulos *et al.* study to assign specific costs and utilities by means of estimating the proportions of stroke events which would be mild, moderate, severe and fatal based on the overall risk of ischaemic stroke.[3] Table 10 presents the proportions used for each category of stroke severity and the associated costs and utilities for acute stroke and post stroke health states.

Severity of stroke was not included by the authors of the DOAC model citing that there was limited evidence from randomised controlled trials to estimate the relative rates of strokes events stratified by severity. Instead, average costs and utilities for ischaemic stroke (both acute and chronic) were used in the model, aligned to the overall risk of ischaemic stroke (

Table 11). It should be noted that the cost of chronic/post-stroke stroke management was calculated as a weighted average based on data from a study by Luengo-Fernandez *et al*.[11], which estimated the mean annual cost of stroke management by severity of disability (non-disabling, moderately disabling and totally disabling).

As such, the EAG consider that implementation of stroke severity in the Diamantopoulos *et al.* study is also contributing to the differences in costs and in particular QALYs compared with the DOAC model.

Table 10. Stroke severity assumptions used in Diamantopoulos *et al*.[3]

Stroke severity	Proportion	Unit costs - Acute	Unit costs – post-stroke	Utility - acute	Utility – post-stroke
Mild	42%	£3,682.51	£577.93	0.73	0.727
Moderate	26%	£19,211.62	£1,127.44	0.5	0.582
Severe	10%	£26,239.89	£1,711.86	0.13	0.397
Fatal	22%	£3,312.20	-	0	-

Table 11. Stroke costs and utilities used in the long-term DOAC model.

Parameter	Acute stroke	Chronic/ post-stroke management
Health state cost	£14,522	£4,514
Health state utility	0.64	0.7

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