

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 consultation comments addendum

August 2019

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

BMJ Technology
Assessment
Group

1 SUMMARY

In response to the National Institute of Health and Care Excellence (NICE) stakeholder comments on the diagnostics consultation document (DCD) for the assessment of implantable cardiac monitors (ICM) to detect atrial fibrillation after cryptogenic stroke, Medtronic identified an error with the R code used to estimate long-term treatment outcomes.

The coding error identified by Medtronic concerns how treatment switching is estimated for transient events (transient ischaemic attack [TIA] and systemic embolism [SE]). Transient events experienced by a patient in the model do not necessitate a change in health state. For instance, if a patient is in the AF well health state, on a direct oral anticoagulant (DOAC) and experiences a TIA, they will still remain in the AF well health state but could switch treatments to warfarin or no treatment. Medtronic found the way the R code was specified meant the probabilities of switching treatment after a TIA or SE were summed and multiplied by the sum of the probabilities of experiencing a TIA or SE. The correction proposed by Medtronic was that probabilities of switching treatment after a TIA or SE should be multiplied by the respective probabilities of experiencing a TIA or SE and then summed. Medtronic provided adapted R code in their stakeholder comments with this change applied.

The impact of the error is that it causes patients to end up on no treatment relatively quickly. The Evidence Assessment Group (EAG) verified Medtronic's suggested amendments to the R code and agreed that the error was correctly identified, and the suggested code fixes the issues.

To assure NICE and the committee of the integrity of the long-term DOAC model, the EAG performed further extensive quality assurance of R code and identified one further inaccuracy in the coding. The initial cohort vector was not specified to have exactly 100% of patients starting in the "AF well" state, but instead had a small proportion of patients who had already been allocated to the stroke state (note that prior stroke adjustments are applied so that no patients should be in the stroke state initially as this represents secondary stroke).

The change to the model code was made in "Main DOAC model code.R". Between current lines 61 and 63 there was previously some additional code that was altering some values in the variable "cohort.vector". These were removed so that this variable remains as defined in lines 58 and 61 of the current code file, without the subsequent alterations.

Although this was only a minor change to the starting cohort and had only a small impact on the costs and quality adjusted life years (QALYs) produced by the DOAC model, given that the incremental QALY gain in the cost-effectiveness results is relatively small, the incremental cost-effectiveness ratio (ICER), therefore, is fairly unstable. This small impact caused the ICER to reduce from £14,058 per

QALY to £10,340 per QALY for the Reveal LINQ device. Section 2 presents the updated EAG base case results including updated number of strokes prevented per 1000 due to use of ICMs.

2 UPDATED EAG BASE CASE RESULTS

Table 1 presents the corrected 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).¹ The corrected results are also plotted on the cost-effectiveness plane in Figure 1. Table 2 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.

Table 1. Base case incremental pairwise cost effectiveness results (discounted)

Intervention	Total Costs	Total QALYs	Incremental costs	Incremental QALYs	ICER
Standard of Care	£7,600	1.74	-	-	-
Reveal LINQ	£9,092	1.89	£1,492	0.14	£10,340
BioMonitor 2-AF	£8,322	1.89	£722	0.14	£5,005
Confirm RX	£8,866	1.84	£1,267	0.10	£12,875

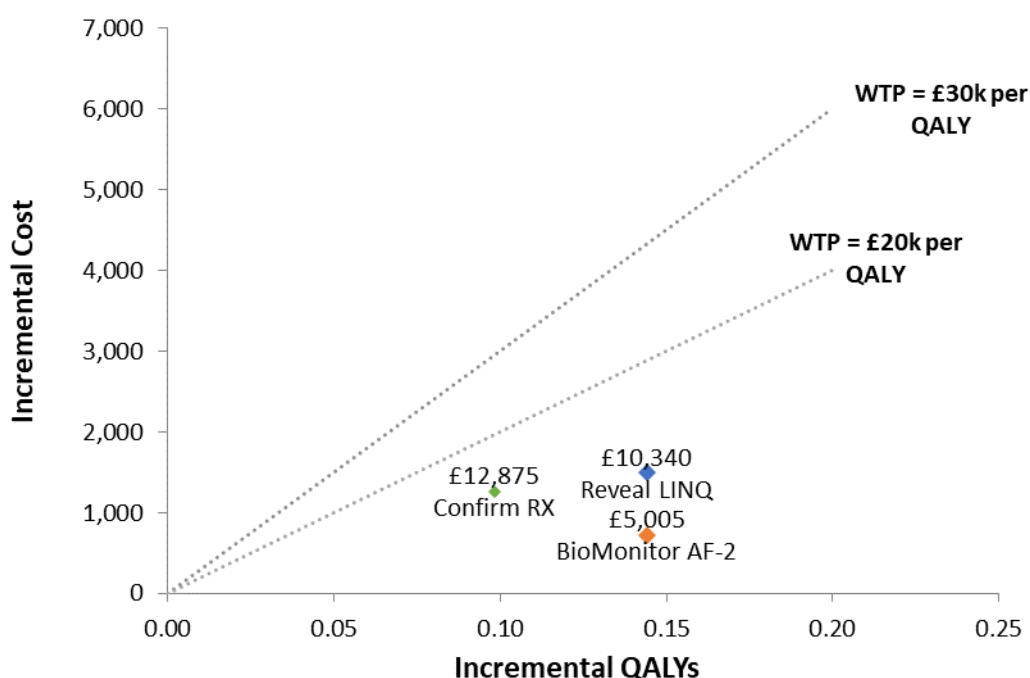
Abbreviations: ICER, incremental cost effectiveness ratio; QALY, quality adjusted life year.

Table 2. Base case incremental cost effectiveness results (discounted)

Intervention	Total Costs	Total QALYs	Incremental costs	Incremental QALYs	ICER
Standard of Care	£7,600	1.74	-	-	-
BioMonitor 2-AF	£8,322	1.89	£722	0.14	£5,005
Confirm RX	£8,866	1.84	£544	-0.05	Dominated
Reveal LINQ	£9,092	1.89	£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.

2.1 Scenario analyses

Table 3 presents corrected scenario analyses for each ICM versus SoC and Figure 2 - Figure 4 present updated tornado plots. Details of the scenarios can be found in the main EAG report, Section 5.1.2.

Table 3. Scenario analyses for each ICM versus SoC (Discounted ICERs)

Scenario	ICERs versus SoC		
	Reveal LINQ	BioMonitor-2	Confirm RX
Base case	£10,340	£5,005	£12,875
Addition of FOCUSON triage costs (Option 1)	£14,097	£5,005	£12,875
Addition of FOCUSON triage costs (Option 2)	£12,931	£5,005	£12,875
Addition BioMonitor 2-AF remote assistant device	£10,340	£6,598	£12,875
Addition BioMonitor 2-AF CardioMessenger	£10,340	£7,776	£12,875
Time horizon for ICM monitoring (1 year)	£24,955	£11,497	£21,460
Time horizon for ICM monitoring (2 year)	£14,908	£7,081	£12,875
Constant detection rates (exponential)	£10,283	£4,935	£12,752
Long-term DOAC outcomes based on apixaban	£8,386	£3,358	£10,753
Long-term DOAC outcomes based on dabigatran	£9,989	£3,578	£12,993
Long-term DOAC outcomes based on edoxaban	£11,664	£5,206	£14,722
Long-term DOAC outcomes based on rivaroxaban	£12,668	£7,143	£15,333
Inclusion of warfarin as a treatment option for patients diagnosed with AF	£18,227	£8,600	£22,612
No explantation of devices	£8,850	£3,515	£10,613

Implantation by Cardiac Physiologist (Band 7)	£10,281	£4,946	£12,789
Implantation assisted by Cardiac Physiologist (Band 5)	£10,339	£5,004	£12,874
Implantation assumptions based on Kanters <i>et al.</i> 2015 ³	£10,525	£5,190	£13,147
No SoC monitoring or AF detections	£11,615	£6,821	£14,301
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)

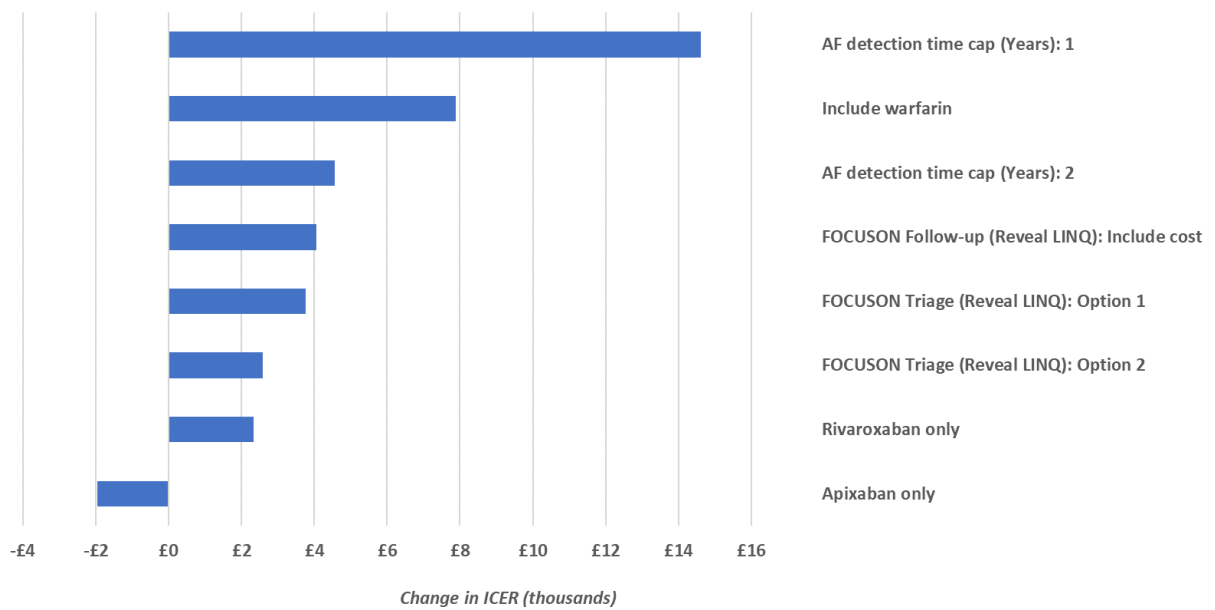


Figure 3. Tornado plot for scenarios with greatest impact (BioMonitor 2-AF versus SoC)

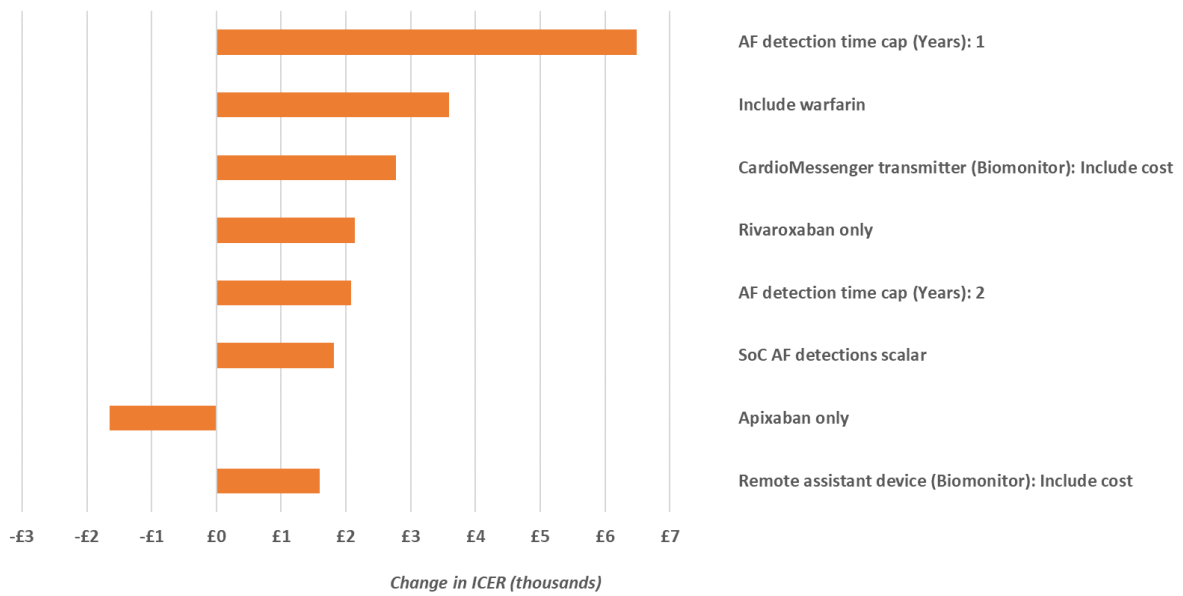
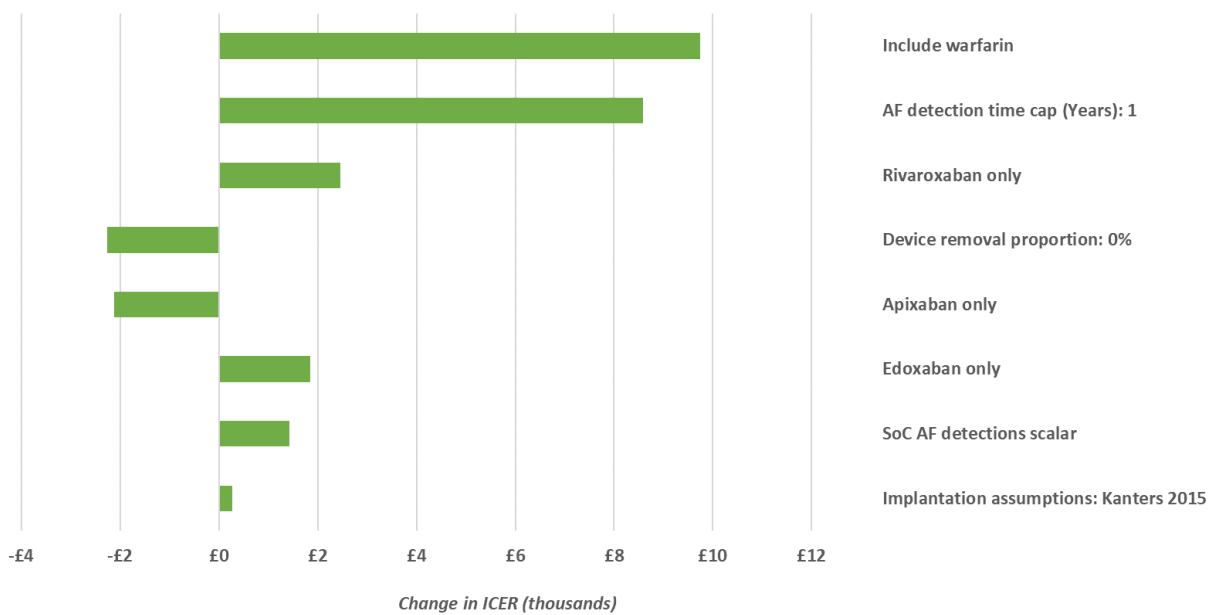


Figure 4. Tornado plot for scenarios with greatest impact (Confirm RX versus SoC)



2.2 Sensitivity analyses

Table 4 presents the corrected one and two-way sensitivity analyses and Figure 5 – Figure 7 presents the tornado plots. Details of the scenarios can be found in the main EAG report, Section 5.1.3.

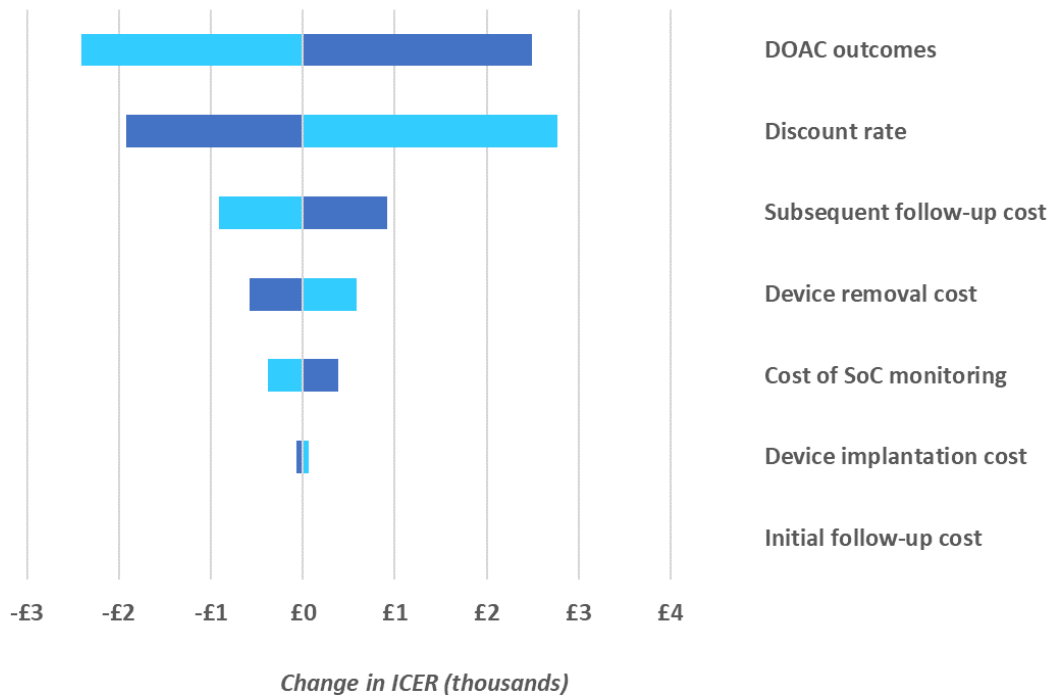
Table 4. One-way and two-way sensitivity analyses (Discounted ICERs)

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	£10,340	£10,340	£5,005	£5,005	£12,875	£12,875
Device implantation cost	£24	£15	£34	£10,274	£10,405	£4,939	£5,070	£12,779	£12,972
Cost of SoC monitoring	£141	£85	£196	£10,722	£9,958	£5,387	£4,623	£13,435	£12,315
Device removal cost	£238	£145	£332	£9,756	£10,924	£4,421	£5,589	£11,989	£13,762
Subsequent follow-up cost	£128	£78	£178	£11,257	£9,423	£5,922	£4,088	£14,262	£11,488
Discount rate	3.5%	1.5%	6%	£8,417	£13,112	£4,091	£6,313	£10,477	£16,322
DOAC outcomes	Mean	2.5 th percentile	97.5 th percentile	£12,835	£7,934	£7,785	£1,997	£15,064	£10,747

Abbreviations in table: DOAC, direct oral anticoagulant; ICER, incremental cost effectiveness ratio; SoC, standard of care.

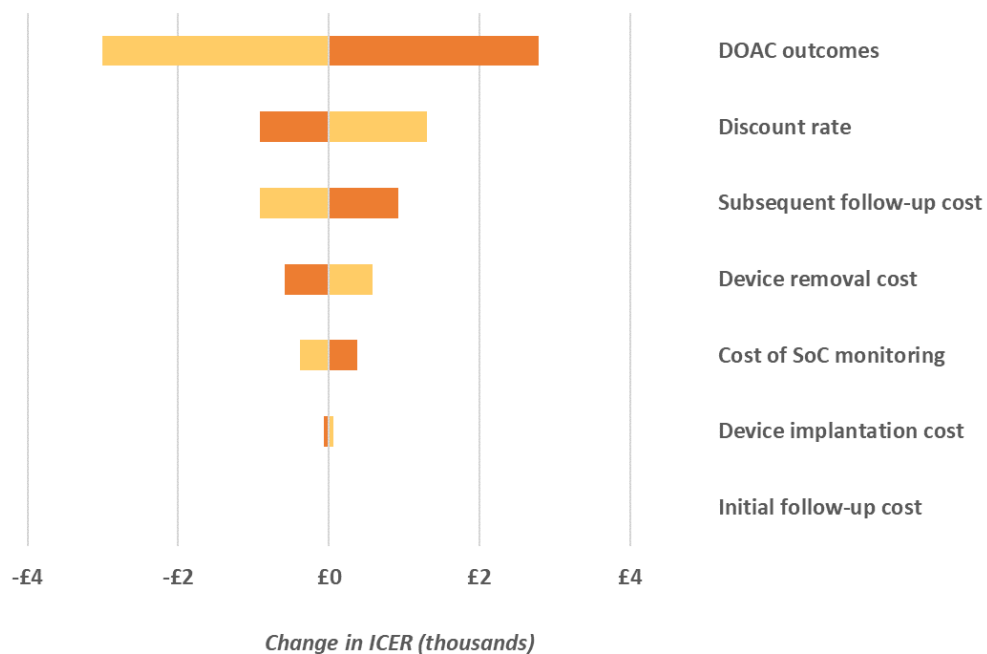
Note: The ICERs correspond to the lower and upper parameter inputs and in some cases the "lower ICER" is a larger number than the "upper ICER".

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



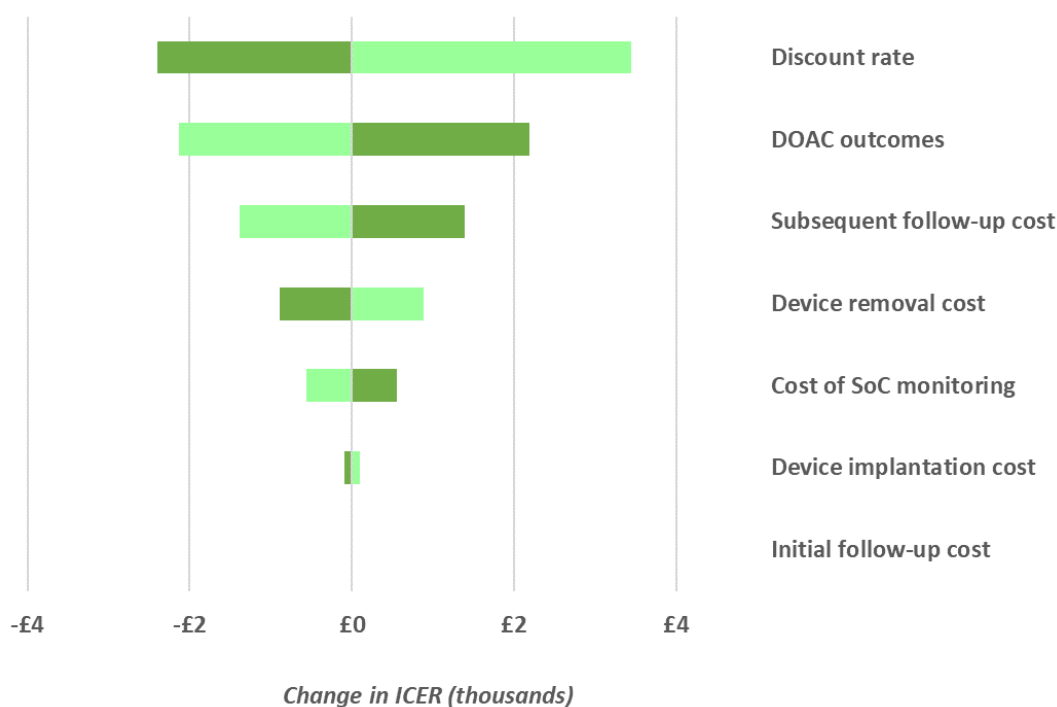
Abbreviations in figure: DOAC, direct oral anticoagulant; ICER, incremental cost effectiveness ratio; OWSA, one-way sensitivity analysis; SoC, standard of care.

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.

2.3 Probabilistic sensitivity analysis

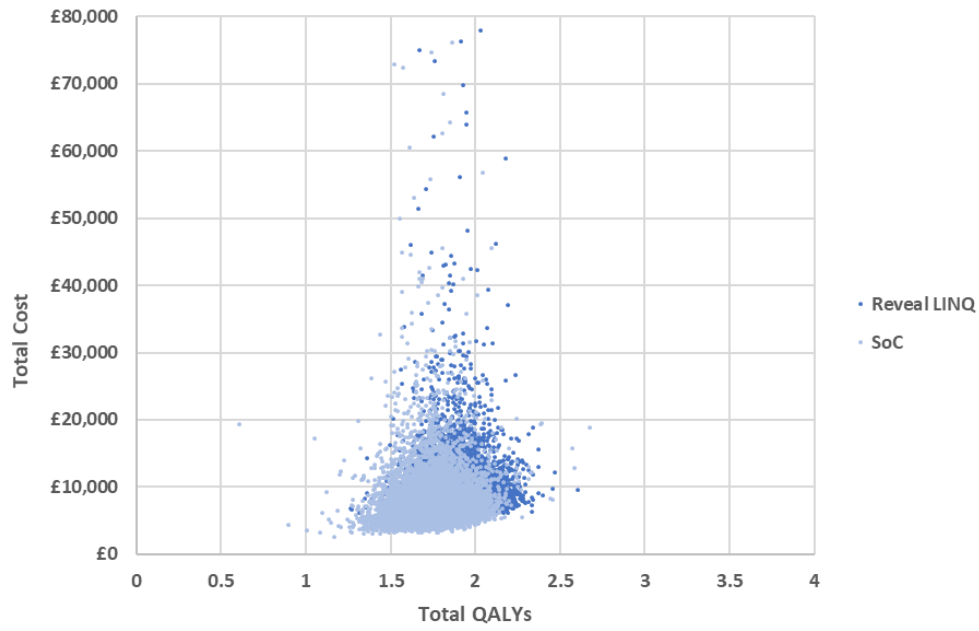
The results of the corrected PSA for each ICM and SoC are given in Table 5, and a scatterplots showing the spread of results from the individual samples is given in Figure 8, Figure 9 and Figure 10, for Reveal LINQ, BioMonitor 2-AF and Confirm RX, respectively; each versus SoC. The incremental costs 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 5. PSA results for each ICM compared with SoC (Discounted)

Intervention	Total Costs	Total QALYs	Incremental costs	Incremental QALYs	ICER
Standard of Care	£7,599	1.74	-	-	-
Reveal LINQ	£9,092	1.89	£1,493	0.14	£10,347
BioMonitor 2-AF	£8,322	1.89	£723	0.14	£5,011
Confirm RX	£8,867	1.84	£1,267	0.10	£12,883

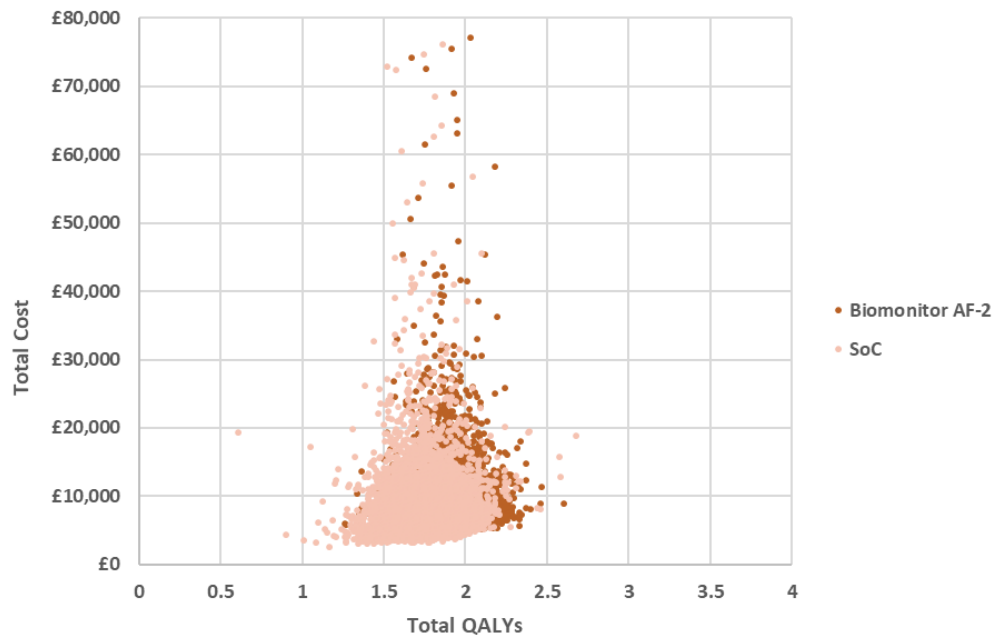
Abbreviations in table: ICER, incremental cost effectiveness ratio; QALY, quality adjusted life year.

Figure 8. PSA scatterplot for Reveal LINQ versus SoC



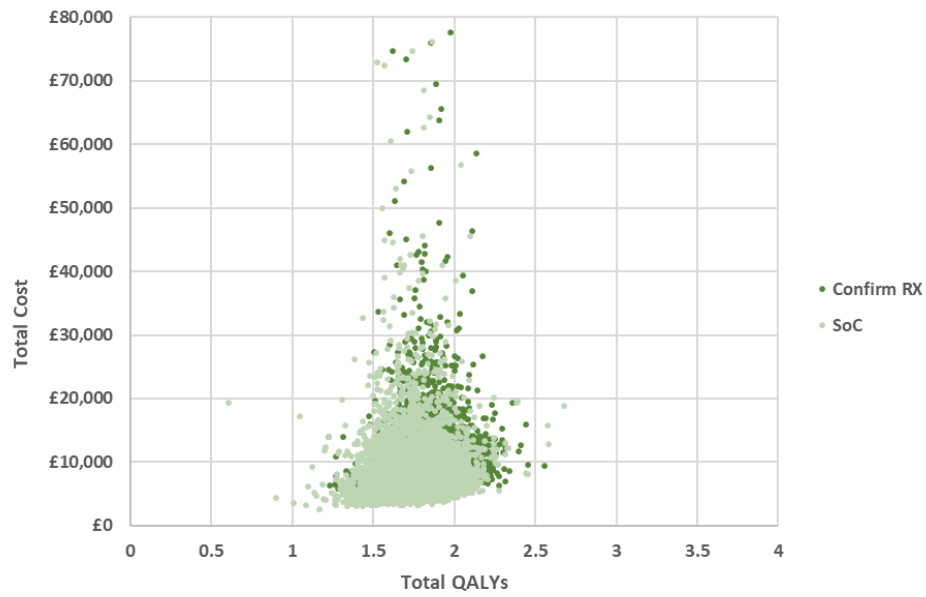
Abbreviations in figure: QALY, quality-adjusted life-year; SoC, standard of care.

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



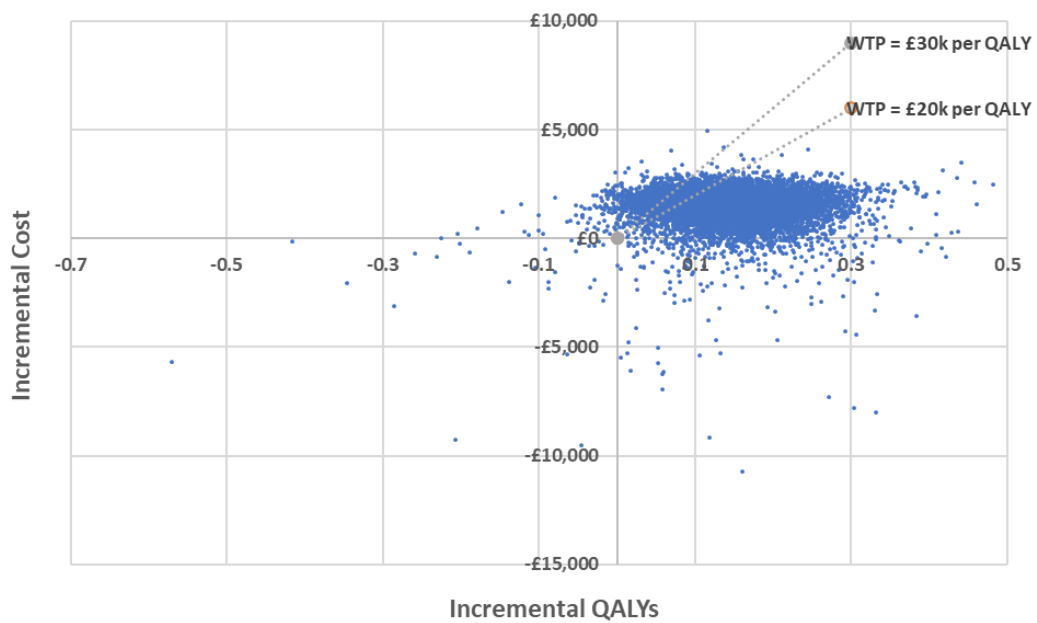
Abbreviations in figure: QALY, quality-adjusted life-year; SoC, standard of care.

Figure 10. PSA scatterplot for Confirm RX versus SoC



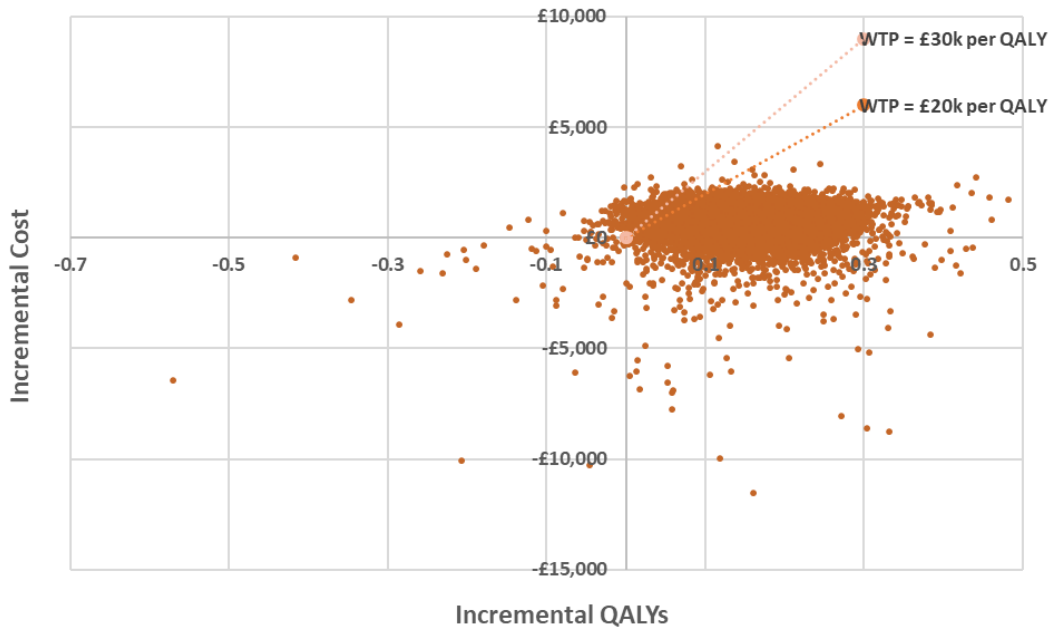
Abbreviations in figure: QALY, quality-adjusted life-year; SoC, standard of care.

Figure 11. Cost effectiveness plane for Reveal LINQ versus SoC



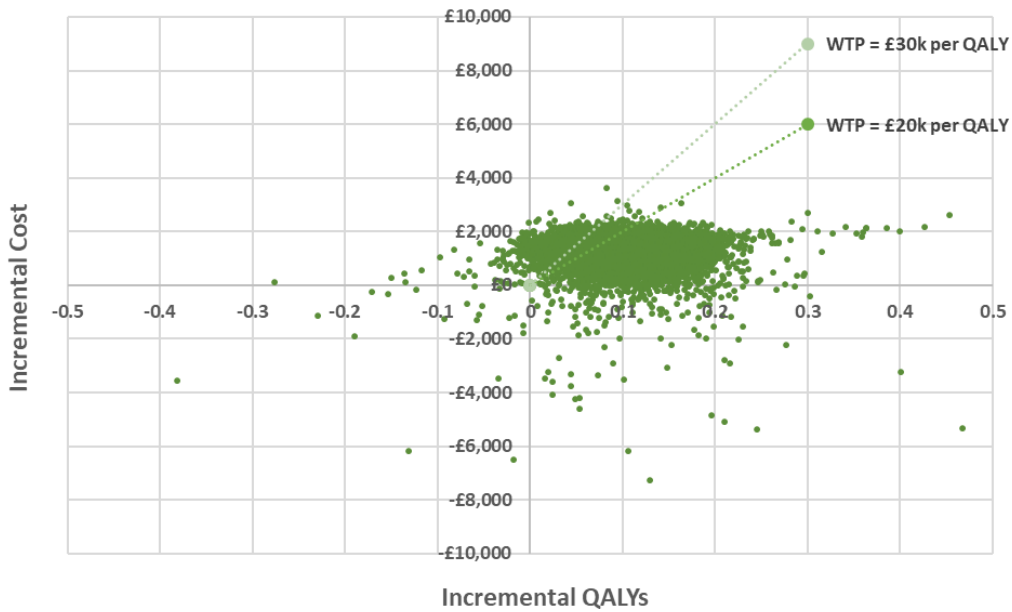
Abbreviations in figure: SoC, standard of care; WTP, willingness to pay.

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



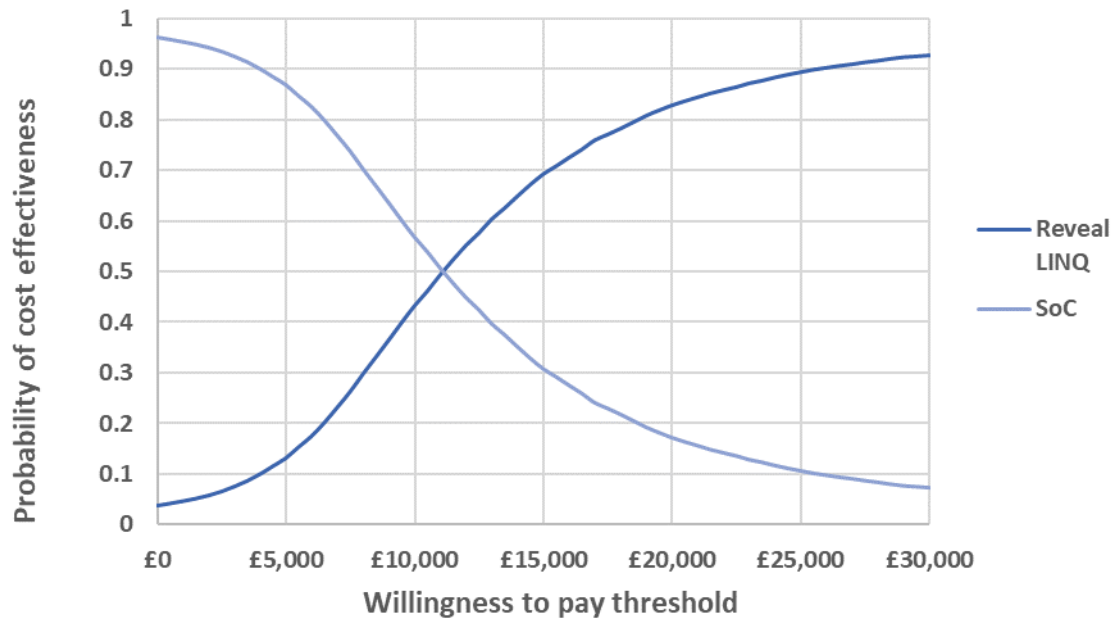
Abbreviations in figure: SoC, standard of care; WTP, willingness to pay.

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 acceptability curve for Reveal LINQ versus SoC



Abbreviations in table: SoC, standard of care.

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

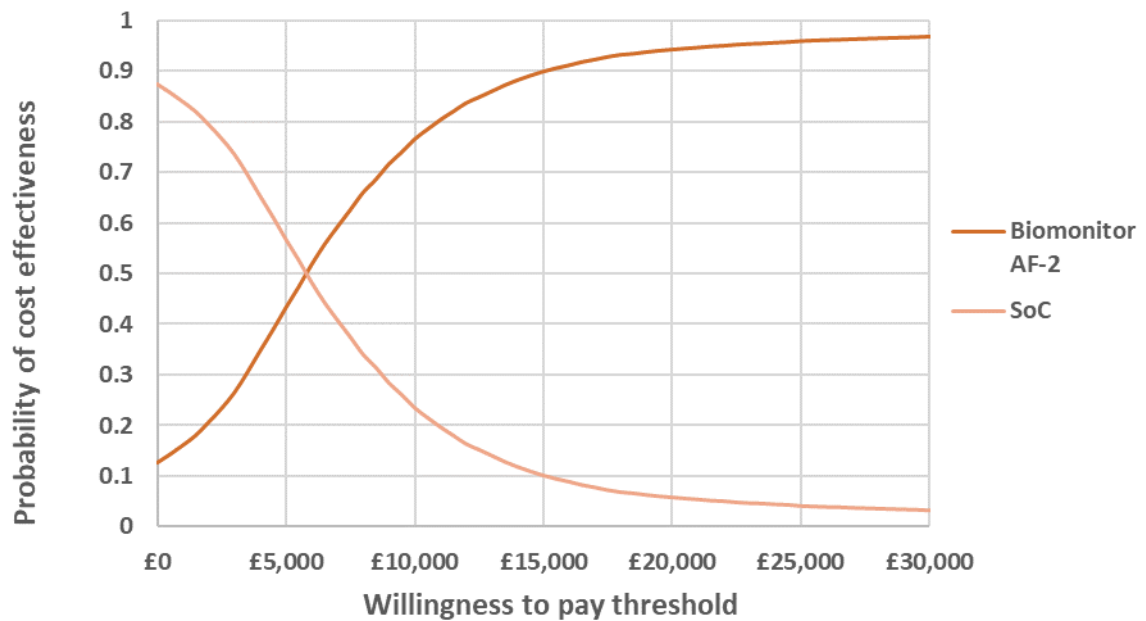
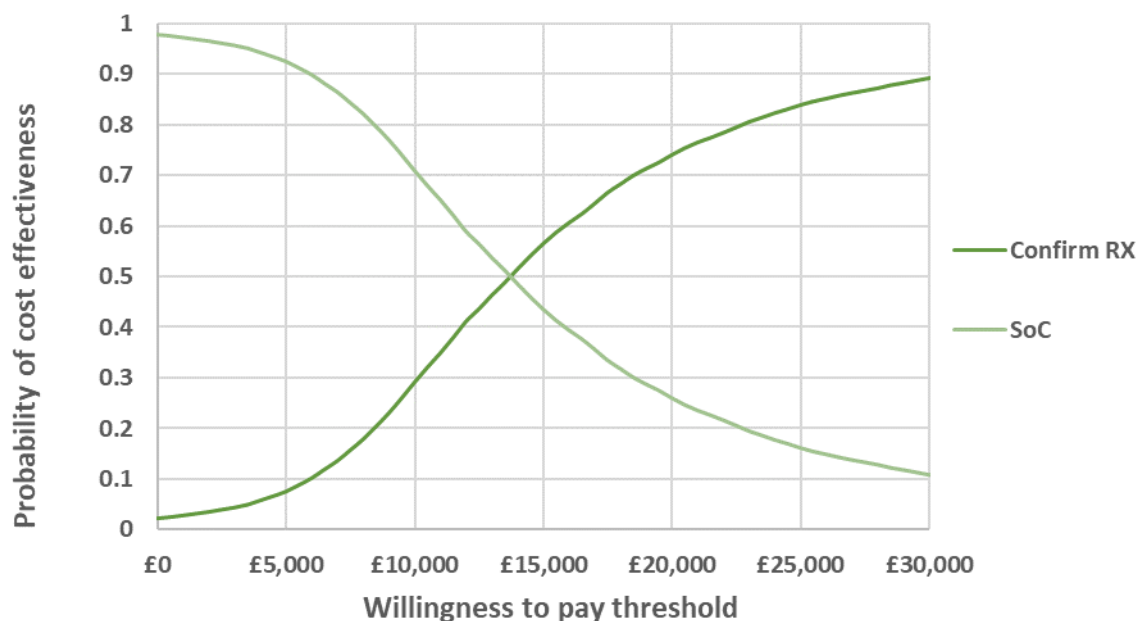


Figure 16. Cost effectiveness acceptability curve for Confirm RX versus SoC



2.4 Number of strokes prevented per 1000

In CRYSTAL-AF after 3 years 30% of patients fitted with an ICM were detected with AF, compared with 3% on SoC. Thus, 30% of ICM patients versus 3% of SoC patients go on to receive appropriate treatment for AF. Table 6 presents the number of stroke events per 1000 patients who have an ICM or on SoC. It is estimated that monitoring with an ICM prevents 25 strokes per 1000 patients compared with SoC.

Table 6. Number of stroke events per 1000 patients by treatment arm

Population	Strokes per 1000 AF patients
SoC	63
ICM	37
Difference*	25

Abbreviations: AF, atrial fibrillation; ICM, implantable cardiac monitor; SoC, standard of care.
 *Note: Due to rounding, the difference presented may not correspond with the difference of the separate figures

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 cryptogenic stroke (CS) population. It is assumed that all ICM patients *with AF* switched 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 7 presents the number of stroke events per 1000 patients for the sub-population *with AF* who have an ICM or on SoC. It is estimated that appropriate treatment of AF detected by ICMs prevents 85 strokes per 1000 patients compared with SoC.

Table 7. Number of stroke events per 1000 patients with AF by treatment arm

Population	Strokes per 1000 AF patients
SoC	209
ICM	124
Difference	85
Abbreviations: AF, atrial fibrillation; ICM, implantable cardiac monitor; SoC, standard of care.	

1. National Institute for Health and Care Excellence (NICE). Guide to the methods of technology appraisal 2013, 2013. Available from: <https://www.nice.org.uk/process/pmg9/chapter/foreword>. Date accessed: 18 December 2018.