National Institute for Health and Care Excellence

Medical technologies evaluation programme

KardiaMobile for detecting atrial fibrillation
Consultation comments table

There were 18 comments including 1 duplicate from 4 groups:

- Medicines and prescribing team, NICE Centre for Guidelines: 7 comments
- Healthcare professional: 1 comment
- Sponsor: 5 comments
- Independent health technology consultant: 5 comments

The comments are reproduced in full, arranged in the following groups:

- Recommendations (comments 1 to 7)
- Clinical evidence (comments 8 to 9)
- The technology (comments 10 to 12)
- Cost model (comments 13 to 15)
- Care pathway (comment 16)
- Digital technology assessment (comment 17)

Comment no.	Consultee ID	Group	Section	Comments	Notes for chair/committee leads
Recommendation (n=7)					
1	1	Medicines and prescribing team	1.1	The recommendation wording needs to be explicit about the context of the assessment; that is, people with palpitations or other symptoms of arrhythmia, not general screening for AF in asymptomatic people.	Thank you for your comment. The committee considered your comment. It decided to amend the recommendations to state that the case for adoption is supported for

					detecting atrial fibrillation in the NHS for people with suspected paroxysmal atrial fibrillation who present with symptoms such as palpitations and who are referred for ambulatory ECG monitoring by a clinician.
2	1	Medicines and prescribing team	1.2 Clinical evidence shows that more people had their AF detected using the KardiaMobile single-lead device compared with standard care, which usually involves wearing a continuous ECG monitor such as a 24-hour Holter monitor	This paragraph needs to specify the population being discussed, e.g. 'Clinical evidence shows that more people who have arrhythmia symptoms had their AF detected using...'	Thank you for your comment. Please see the response to comment 1.
3	1	Medicines and prescribing team	1.2 Evidence suggests that using KardiaMobile is likely to be cost saving or cost neutral for detecting atrial fibrillation and atrial fibrillation recurrence.	Please specify the population. I suggest 'Evidence suggests that using KardiaMobile is likely to be cost saving or cost neutral for detecting atrial fibrillation and atrial fibrillation recurrence in people who experience arrhythmia symptoms.'	Thank you for your comment. Please see the response to comment 1.
4	3	Independent health technology consultant	Section 1	I agree with the recommendations but make some suggestions to improve their clarity and usability.	Thank you for your comment.
5	3	Independent health	1.1	Recommendation 1.1 should in some way specify that it applies to people, in line with the decision problem, with	Thank you for your comment.

		technology consultant		signs and symptoms of AF, a history of AF and/or who have been referred for AF monitoring. This is needed to clarify the population supported by the evidence and for differentiation from the recommendations in DG35, which could helpfully be cross-referenced.	Please see the response to comment 1.
6	3	Independent health technology consultant	1.2	Given the number of devices procured by the NHS for the AHSN Network National AF Programme, some of which will still be in use, it would be helpful to include a recommendation to guide people who are already using KardiaMobile, such as on audit or prospective data collection.	Thank you for your comment. The committee considered your comment carefully and were advised that the population in the AHSN Network National AF Programme was explicitly asymptomatic. KardaMobile was used for single-time point testing in pharmacies, GP surgeries, and in community (football matches, supermarkets). This is out of the scope of this guidance. The committee decided not to amend the guidance.
7	4	Sponsor	1.2	The updated cost model has been modified and simplified to address the EAC's comments. Furthermore, various scenario analyses and probabilistic sensitivity analyses were performed to explore cost impact uncertainties. Therefore, the modified cost model should be used for making any decision. [see modified cost model and the supplementary information submitted by AliveCor] Main changes and additional analyses are explained in different sections of modified cost model and the supplementary information in response to the comments by the committee. Please see sections 3.10, 4.7, and 4.11.	Thank you for your comment. The committee considered your comment and the EAC's commentary of the updated costs model (Appendix A and B) carefully. It agreed that all 6 studies that informed the updated model were relevant to the decision problem. The model is simpler than the original model but still lacks transparency because of its complexity. Section 3.11 and 4.9 have been added and amended respectively to acknowledge the additional economic evidence by the company. The committee concluded that the company's modified model was relevant to the decision problem, but still featured limitations, and considered the EAC's additional cost modelling a more appropriate basis for its decision making.
Clinical evidence (n=2)					

8	1	Medicines and prescribing team	3.4 Evidence suggests that the KardiaMobile algorithm has a high diagnostic accuracy per electrocardiogram (ECG) recording	Not withstanding the caveat about the data being per ECG not per person, note that with a pre-test probability of 5%, a Sp of 92% gives a PPV of only about 38% or 39% (i.e. a little over 60 in 100 people who test positive are false positives). Even at 50% pre-test probability, the PPV with 92% Sp is about 92%, so about 8 in 100 false positives . At this higher pre-test probability and a Sn of 92% the NPV is also around 92%, so about 8 in 100 false negatives. The clinical implications of all this don't seem to have been discussed. See also my comment on section 4.1.	Thank you for your comment. The committee considered your comment carefully and acknowledged that all outputs from KardiaMobile should be reviewed by a healthcare professional, and false positives and negatives would be captured at clinical review. The committee amended section 3.4 to include consideration of the impact of clinical reviews on false positives and negatives. Section 3.4 currently states ''The EAC also noted that KardiaMobile is not intended to be used to confirm the presence of AF as a standalone test but to help detect AF. All interpretations should be reviewed by healthcare professionals for clinical decision-making. It is expected that false positives and negatives are likely to be captured by the clinical reviews.''
9	3	Independent health technology consultant	Section 3	As noted in the Supporting Documentation, a large number of KardiaMobile devices were procured and distributed during the AHNS Network National AF Programme in 2018-20. An evaluation report (https://www.ahsnnetwork.com/app/uploads/2020/03/Mobile-ECG-Evaluation-Report-Full-Report.pdf) of this programme is available which suggests that the target population overlapped with that for this guidance. It would be helpful to include in the guidance a brief statement on whether any relevant and usable real-world evidence was generated by the National AF Programme to inform the guidance development.	Thank you for your comment. Please see the response to comment 6.
The technology (n=3)					
10	1	Medicines and prescribing team	4 Clinical effectiveness	I don't think the distinction has been drawn here between using the device to record ECGs and using the app to diagnose AF. I can see that the device could bring benefits because of its ease of use whenever symptoms occur. But if all the ECGs have to be reviewed by a clinician, what benefit does the app bring? It could give hints, and at low pre-test probabilities it probably has a high NPV. But might it unconsciously bias a clinician's review, and either	Thank you for your comment. Please see the response to comment 8.

				encourage a false negative (with increased risk to the patient of stroke, etc.) or false positive (with increased burden of treatment, risk of major bleeds from anticoagulation, etc.)?	
11	1	Medicines and prescribing team	4.7	If all the ECGs have to be reviewed by a clinician, what benefit does the app bring? It could give hints, and at low pre-test probabilities it probably has a high NPV. But might it unconsciously bias a clinician's review, and either encourage a false negative (with increased risk to the patient of stroke, etc.) or false positive (with increased burden of treatment, risk of major bleeds from anticoagulation, etc.)?	Thank you for your comment. Please see the response to comment 8.
12	2	Healthcare professional	4.2	4.2The committee noted that all the evidence on the clinical effectiveness of KardiaMobile was on the single-lead device. It was advised that the single-lead device is commonly used in clinical practice to detect AF, and the use of the 6-lead device is limited in the NHS. The clinical experts agreed that the 6-lead device had no additional benefit for detecting AF but it could be helpful to detect other arrhythmia. The committee concluded there was no additional benefit from using the 6-lead device compared with the single lead KardiaMobile for AF detection. I was on the expert advisory meeting. I commented that the 6 lead is better than the single for AF detection. A single lead gives a view of the heart rhythm from 1 angle. Sometimes that is not a good angle to identify the rhythm. The 6 leads provides more angles for more accurate interpretation. That is why a 12 lead is still the gold standard for AF diagnosis	Thank you for your comment. The committee considered your comment carefully and was advised that the 6-lead device provides heart rhythm from multiple angles, and it could have incremental benefits in some people to detect other arrhythmias when a good quality ECG trace is available. It agreed that the single-lead device is adequate in most people for AF detection. Section 4.2 has been amended.
Cost model (n=3)					
13	4	Sponsor	3.10	Within the newly submitted modified cost model and the supplementary information the validation of the model has been supported. Please see how below 1. The following changes were made to the de novo model to reduce modeling complexity concerning the EAC comments 1.1. The decision-tree section of the model was simplified, and all time-dependent variables were removed. The new model structure captures disease progression for	Thank you for your comment. Please see the response to comment 7.

				those with AF detected and non-detected in the first round of AF monitoring. Only one round of subsequent monitoring is considered, and ultimately, all AF cases were detected by the end of the first year [see Model structure section in the supplementary information of the modified cost model - page 5 of 68] 1.2. KardiaMobile's direct comparator was assumed to be Holter in primary AF detection for both subpopulations, according to expert opinion. [see Technology and comparator(s) section in the supplementary information of the modified cost model - page 5 of 68] 1.3. The subsequent AF monitoring types considered in the analysis for AF missed cases were: o Holter, o Continuous event recorder (CER), o Patch, o Implantable loop recorder (ILR), for both subpopulations with different distribution of use, according to expert opinion. [see Table 1 in the supplementary information of the modified cost model - pages 8-9 of 68] 1.4. The annual risk of AF complications is estimated based on the proportion of time off or on anticoagulation, based on the mean delay to available monitoring results. [see Table 2 in the supplementary information of the modified cost model - page 12 of 68] 1.5. Costs parameters were changed to the recommended values by the EAC. [see NHS and unit costs section in the supplementary information of the modified cost model - page 12 of 68] 2. The following actions were taken to address EAC's comments regarding uncertainty on parameters: 2.1. Six clinical experts confirmed the main assumptions which were used in the modified cost model [see Table 1 in the supplementary information of the modified cost model] 2.2. Knowledge gaps regarding the preventive care and proportion of monitoring procedures were confirmed with these six clinical experts. [see Table 3 in the supplementary information of the modified cost model]	

				2.3. Efficacy of KardiaMobile and comparators are based on the results of six clinical studies as follows (similar to the EAC approach in the development of simple cost calculator) [see Table 3 in the supplementary information of the modified cost model] Narasimha et al. 2018 Reed et al. 2019 Goldenthal et al. 2019 Hermans et al. 2021 Hickey et al. 2017 Koh et al. 2021 2.4. Various scenario analyses considering different time intervals were performed to capture uncertainties around the base-case results. [see Scenario analysis section in the supplementary information of the modified cost model - page 45 of 68] 2.5. In another scenario, the impact of time for reviewing the KardiaMobile's ECGs was explored. In the cost calculator development, the EAC assumed that ECG review time was considered broadly equal in both arms and therefore excluded from the analysis. This assumption was explored in this scenario analysis over the different monitoring time intervals. [see Scenario analysis section in the supplementary information of the modified cost model - page 45 of 68] 2.6. The total cost of KardiaMobile per monitor session was estimated considering: Cost of device Device lifespan Preparation and training time Time for reviewing of ECGs The time interval between two monitoring periods [see Technology cost in the supplementary information of the modified cost model - page 27 of 68]	
14	4	Sponsor	4.7	We respect the committee's conclusion, and the modified cost model has been developed accordingly. However, an interview with five clinical experts showed that they did not review all negative results by KardiaMobile only those related to symptoms. Therefore, most ECGs (80% in	Thank you for your comment. The committee considered your comment and the EAC's commentary of the updated cost model (Appendix A and B) carefully. It agreed

				Hermans et al. 2021) may not be reviewed by experienced healthcare professionals. This approach implies less time for reviewing the KardiaMobile's ECGs, which leads to additional cost savings than the modified cost model estimated. Please see the below question to the interview clinical experts and their reply. "If you have previously issued KardiaMobile to patients for palpitations or AF recurrence, do you inform patients to email all ECG recordings or use a scenario or other below?" 1 only "Possible AF"? 2 only "Possible AF" and "Unclassified" results? 3 All symptomatic recordings, 4 Ask the patient to send in 4 per day for example 5 Other, please state EXPERT #1: Send 10 a fortnight correlating to symptoms or most pertinent most important to their patient EXPERT #2: 3 All symptomatic recordings and possible AF EXPERT #3: Palpitations all symptomatic ECG recordings, AF Recurrence only "Possible AF" and "Unclassified" results EXPERT #4: Possible AF and Unclassified EXPERT #5: NO ANSWER EXPERT #6: "Possible AF" and "Unclassified" results, All symptomatic recordings,	that all interpretations should be reviewed by a medical professional for clinical decision making as the instruction in use states. No changes were made to the guidance.
15	4	Sponsor	4.11	The following actions were taken to address this comment to support the robust modelling i- Two subpopulations were defined and implemented into the modified cost model. The results of six included clinical studies were used individually to capture the efficacy of KardiaMobile and comparators (similar to the EAC approach in the development of the simple cost calculator) [see Table 3 in the supplementary information of the modified cost model] 1. Patients with palpitation: Narasimha et al. 2018 Reed et al. 2019 2. Patients with a chance of AF recurrence: Goldenthal et al. 2019 Hermans et al. 2021	Thank you for your comment. Please see the response to comment 7.

				Hickey et al. 2017 Koh et al. 2021 ii- According to published literature results, age at diagnosis start, the proportion of subsequent tests, the proportion of preventive care, and AF complication risks were differentiated for subpopulations. [see Table 3 in the supplementary information of the modified cost model - pages 17-18 of 68] iii- Please see our comments on section 3.10 as well for other changes made in the cost model.	
Care pathway (n=1)					
16	1	Medicines and prescribing team	2.5 relevant pathway	Please amend the link to the updated NICE guidance on AF (NG196, April 2021), and make sure the text here reflects recs 1.1.2 and 1.1.3 in the guideline.	Thank you for your comment. Section 2.5 has been amended to link to and represent the updated NICE guidance (NG196).
Digital technology assessment (n=1)					
17	3	Independent health technology consultant	Section 2	It would be helpful for guidance users to confirm whether KardiaMobile has been evaluated against the NHS X Digital Technology Assessment Criteria and, if so, what was the outcome. This is referred to, but not confirmed, in the Supporting Documentation.	Thank you for your comment. The committee considered your comment carefully and was advised that the company has submitted its DTAC application and is still working through the process.

Appendix A – Updated company model

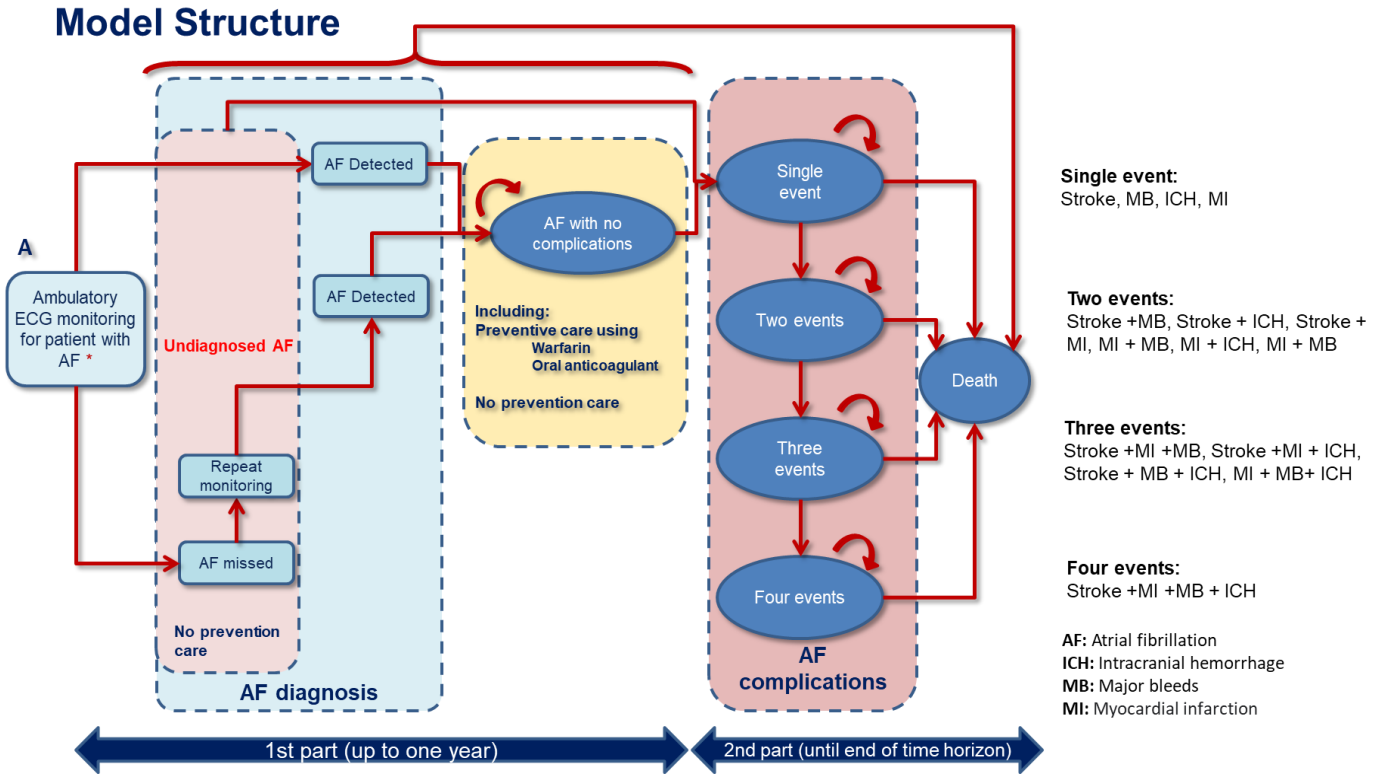
Additional work undertaken by the External Assessment Centre (EAC)

During consultation the company submitted a new economic model, and economic submission report. For the purposes of this report the original company model refers to "CEA_KardiaMobile_V3.1_19052021.xlsm" (received by the EAC on 19/05/2021). The updated company model refers to "Copy of CEA_KardiaMobile_V4_FINAL_09082021.xlsm" (received by the EAC on 04/10/2021).

Structure

The updated economic model submitted by the company has changed to include a one-year decision tree leading into a Markov model. The model was developed in an executable Excel spreadsheet, including approximately 90 parameters across 20 worksheets. However the outputs of the decision tree have changed; from true positive, false positive, true negative, false negative, inconclusive and no further follow-up, to AF detected and AF undetected, Figure 1, using data from 6 comparative studies. The perspective (NHS in England and Personal Social Services) and time horizon (5-years) are unchanged.

Figure 1: The updated economic model structure [From the updated economic submission]



Population

The company stated that they have modelled two sub-populations including patients with undiagnosed palpitations and patients with chance of AF recurrence following ablation treatment, with age at the start of the model being 40 and 64 respectively. However following a set of queries from the EAC, the company have since confirmed that they have only considered patients with AF (i.e.true positives and false negatives only, see Appendix B), and did not model the cost consequences of patients with palpitations who do not have AF. This is a deviation from the scope. The EAC states that the model lacks generalisability to the UK NHS.

Intervention

The intervention is the KardiaMobile single lead device (confirmed by device cost) which is in line with the feedback from clinical experts advising the EAC in the original assessment report (EAC Assessment Report, 2021). The duration of KardiaMobile monitoring is included as a model variable (which is editable on the "RESULTS" worksheet of the model.

Comparator

Whilst the comparator varies across the 6 comparative studies (external loop recorder in Narasimha et al. 2018; "standard care" in Reed et al. 2019, Goldenthal et al. 2019, Hickey et al. 2017; Holter in Hermans et al. 2021, 24-hour Holter in Koh et al. 2021 stated in the "RESULTS" worksheet of the company model), the comparator is fixed in the economic model as Holter monitoring, however the duration is not transparently reported in the updated Economic Submission (the EAC assumes a fixed duration of 24 hour from the costs applied in the comparator arm).

Outcomes

The outcome of the diagnosis phase is AF detected or undetected (i.e. true positive or false negative) as determined by the outcomes reported by 6 comparative studies which used KardiaMobile (2 in undiagnosed palpitations and 4 in AF recurrence). Repeated testing is only applied in the comparator arm, and is conducted with a range of devices (Holter, CER, ILR, patch).

Outcomes from the management phase are unchanged from previous version of the model (stroke, major bleed, intracranial haemorrhage, myocardial infarction and death). The updated model allows for multiple events, which is unchanged from the original model.

Time horizon

The company used a 5-year time horizon with an annual cycle duration to capture long-term outcomes, with a 3.5% discount rate. However the model does include functionality to increase the time-horizon between 1 year and a lifetime model (50 years). The EAC would question the clinical applicability of the lifetime model in palpitation and AF recurrence populations which begin the model at 40 and 64 years of age, where the populations are followed until 90 and 114 years of age respectively.

Model assumptions

The company has made changes to address some of the concerns raised in the EAC Assessment Report (2021):

- Time dependency of each monitoring device has been simplified. Time to diagnosis is included for all devices. However, as the diagnostic decision tree lasts 1 year, the EAC is unable to verify how the different time to diagnoses have been applied in the model.
- Diagnostic yield has been replaced with "proportion with AF detected" using data from 6 comparative studies; the EAC would consider this approach more robust than the original company economic model.
- The duration of monitoring can be changed (to 7, 14, 30, 45, 60 or 90 days) in the model, and varies for each of the 6 comparative studies. However Goldenthal *et al.* 2019 and Hickey *et al.* (2017) used KardiaMobile for 180 days; and these longer durations of monitoring cannot be applied in the updated company model (maximum 90 days can be applied in model).
- Time and costs for ECG review have been added to the KardiaMobile costs, which the EAC would consider is reflective of NHS practice.
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However, the updated model assumes retesting only applies to the comparator arm (not KardiaMobile); the EAC considers this an unrealistic assumption which would favour KardiaMobile. The model also assumes that all AF missed at first diagnostic monitoring are identified within 12 months which would favour the comparator arm.

Model parameters

The EAC has not conducted QA of all 90 model parameters (due to time-restrictions). However the EAC comments on the following parameters, Table 1.

Table 1: Updated economic model parameters queried by the EAC.

Variable	Value in updated company economic model: palpitations	Value in updated company economic model: AF recurrence	EAC comment
Risk of ischaemic stroke (undetected AF patients)	3.6%	7.85%	Assumed annual risk. These values represent a CHA_2DS_2-VASc score of between 3-4 and 5-6 in the palpitations and AF recurrence populations respectively. The EAC would consider these high estimates for both populations.
Risk of ischaemic stroke (detected AF patients)	1.14%	3.1%	Assumed annual risk. It is unclear to the EAC why the risk reduction treatment effect (1.14/3.6 = 0.32vs. 3.1/7.85 = 0.40) is

Variable	Value in updated company economic model: palpitations	Value in updated company economic model: AF recurrence	EAC comment
			different between palpitation and AF recurrence populations.
Risk of intracranial haemorrhage (warfarin)	0.90%	1.19%	Assumed annual risk. The EAC would recommend contacting clinical experts to comment on the validity of this (particularly on the relative rates when compared to risk of ischaemic stroke, and whether age dependent).
Risk of intracranial haemorrhage (NOAC)	0.41%	0.56%	Assumed annual risk. The EAC would recommend contacting clinical experts to comment on the validity of this (particularly on the relative rates when compared to risk of ischaemic stroke).
Risk of intracranial haemorrhage (undetected AF patients)	0.90%	1.47%	Assumed annual risk. It is unclear to the EAC why the risk of intracranial haemorrhage would be the same for warfarin and untreated patients in the palpitations population (both are 0.9%, however it is plausible that warfarin may lead to increased bleeding risk).
Risk of major bleeding (warfarin)	6.60%	1.11%	Assumed annual risk. It is unclear to the EAC why the risk of bleeding from warfarin and NOAC would differ between palpitations and AF recurrence populations.
Risk of major bleeding (NOAC)	5.41%	13.40%	Assumed annual risk. This parameter has not been updated in light of recommendation by EAC in original Assessment Report (2021): *"Three clinical experts considered these values incorrect and stated the rate for NOAC would be much lower. One expert provided a reference to the Stroke Prevention in Atrial Fibrillation Risk Tool (SPARC) tool, which suggest an annual risk of major bleed of 1% for aspirin, 4% for warfarin and 3% for NOAC."* Additionally it is unclear to the EAC why the risk of bleeding from warfarin and NOAC would differ between palpitations and AF recurrence populations.
Time to make a diagnosis (days)	KardiaMobile: 9.9 Comparator: 48 Holter: 70 CER: 88 Patch: 19 ILR: 88	*Same as palpitations*	It is unclear to the EAC why the duration of 'Comparator' (which is stated in the economic submission to be Holter monitoring) differs to 'Holter'. The mean time to symptomatic cardiac arrhythmia detection (not specific to AF) for KardiaMobile and Comparator are taken from Reed et al. (2019) study set in UK in patients presenting to emergency department with undiagnosed palpitations. Time to diagnosis for the remaining devices are taken from MTG52 (combining information from HES, FOI and assumptions). It is unclear if the underlying

Variable	Value in updated company economic model: palpitations	Value in updated company economic model: AF recurrence	EAC comment
			populations are the same for all estimates of time.

Base-case results

The EAC was able to use the updated economic model to recreate the base-case numbers reported in the updated Economic Submission report (Tables 9-15) using specific duration of monitoring as defined for each comparative study as summarised in Table 2 of this report. The EAC did not check the underlying mathematical calculations to verify how the base-case numbers have been derived. Comparison of results of the base-case scenarios between the original and updated company economic models are summarised in Table 2.

Table 2: Base-case results (per-person costs over 5 years) from original and updated economic models.

	Duration of monitoring	Subgroup	KardiaMobile	Comparator	Cost difference (KardiaMobile-Comparator)
Original company economic submission	14 days	N/A	£2941.19	£3262.69	-£321.50
Updated company economic submission: Narasimha et al. (2018)	30 days	Palpitations	£4001.81	£4115.88	-£114.07
Updated company economic submission: Reed et al. (2019)	90 days	Palpitations	£4229.61	£4513.39	-£213.78
Updated company economic submission: Goldenthal et al. (2019)	90 days (although duration of KardiaMobile was 6 months in that study)	AF recurrence	£5131.28	£5051.17	£80.10
Updated company economic submission: Hermans et al. (2021)	14 days (KardiaMobile duration in study was 4 weeks, however all AF was captured at 14 days)	AF recurrence	£4977.52	£5273.82	-£296.29
Updated company economic submission: Hickey et al. (2017)	90 days (although duration of KardiaMobile was 6 months in that study)	AF recurrence	£5131.28	£5309.31	-£178.03
Updated company economic submission: Koh et al. (2021)	30 days	AF recurrence	£5009.89	£5574.17	-£564.28

Data from 5/6 comparative studies demonstrate that use of KardiaMobile is cost saving when compared to the comparator arm (Holter); cost incurring when using data from 1/6 studies. However the EAC would not consider the company results as robust due to failure to pass face validity checks on outcomes.

In the palpitations population, KardiaMobile was cost saving by £114.07 (data from Narasimha et al. 2018), and cost saving by £213.78 (data from Reed et al. 2019). The EAC considered the absolute cost in the comparator arm (between £4000-£4500 per patient) to be unrealistic in an undiagnosed palpitation population. The company has confirmed that only patients with AF (TP and FN) are included within the new model (see company response received on 01/10/2021, Appendix B); which explains the high per-patient costs.

In the AF recurrence population, the range of cost difference was between KardiaMobile being cost incurring by £80.10 (data from Goldenthal et al. 2019) and KardiaMobile being cost saving by £564.28 (data from Koh et al. 2021).

Number Needed to Treat

In the undiagnosed palpitations population, the company have assumed an annual rate of stroke of 3.6% (untreated) and 1.14% (treated). The NNT to save one stroke per year is 41. The annual cost of treatment (67.23% NOAC, 21.21% warfarin) is £500, plus the annual cost of treating GI bleeds in the proportion affected (average of 6% between NOAC and warfarin in the model provided, costing £785 each; £47.10) a total of £547.10. The annual cost of treatment needed to save one stroke is £22,431. This exceeds the cost of ischaemic stroke (£9527) and haemorrhagic stroke (£15,690) included in the updated company model. Above a threshold of increased AF detection, the EAC would expect KardiaMobile to be in the upper right hand quadrant of the cost-effectiveness plane.

Sensitivity analysis

The company have conducted probabilistic sensitivity analysis (PSA) and have reported the distributions of 71 parameters which were included within it. The EAC notes that the PSA within the updated economic model does not address all areas of uncertainty (e.g. rate of retesting for KardiaMobile is kept at 0, and 100% for comparator arm, the number of device uses is not included, and the device cost for KardiaMobile should be fixed and not varied).

The results from PSA using the updated economic model, when the EAC conducts 1000 iterations applied for each comparative study, are summarised in Table 3. The EAC is unclear as to what "first stroke avoided" means. EAC then reviewed the distribution of cost savings (KardiaMobile-comparator) across the 1000 iterations from PSA, Table 4. The 95% confidence interval of cost difference between KardiaMobile and Holter spans £0 in 4/6 studies; demonstrating no cost difference (between KardiaMobile and Holter). Only 2/6 comparative studies demonstrated a cost saving (with 95% CI remaining cost saving); with Reed et al. 2019 and Koh et al. 2020 showing cost savings of £215 and £556 per patient, Table 4.

Duration of monitoring was not included in PSA, however it was included in separate scenario analysis where the duration of monitoring varied between 7 and 90 days. Given the feedback collated by the company from 6 clinical experts, the duration of monitoring between 30 days and 90 days is more representative of KardiaMobile use in the NHS. Cost savings decrease and the cost expenditure increases as the duration of KardiaMobile increases, as demonstrated by the scenario analysis in Table 17 of the company's updated Economic Submission. However this scenario analysis does not extend to 180 days which were used by Goldenthal et al. 2019 and Hickey et al. 2017.

Additional scenario analysis was conducted by the company which effectively removed nurse ECG review time from the KardiaMobile arm ("nurse time for reviewing a KardiaMobile 30 second ECG, min" = 0 in the economic model). The KardiaMobile instructions for use explicitly state: "Interpretations made by this device are potential findings, not a complete diagnosis of cardiac conditions. All interpretations should be reviewed by a medical professional for clinical decision-making". Therefore the EAC would consider this scenario modelling an off-licence use of the device, and should be disregarded.

Multiple one-way sensitivity analysis were also reported in the updated economic model (across 90 parameters). Each parameter was varied between its upper and lower 95% confidence interval where available, between plus and minus 20% otherwise and between plus and minus 30%, for cost parameters.

Table 3: Results from PSA when EAC ran 1000 iterations for all comparative studies

	Base-case		Probabilistic Sensitivity Analysis							
Study (year)	Cost per patient (KardiaMobile)	Cost per patient (comparator)	Average cost per patient (KardiaMobile)	Average cost per patient (comparator)	Incremental cost per patient	First stroke avoided % with KardiaMobile	First stroke avoided % (comparator)	Incremental stroke avoided	Incremental cost per first stroke avoided cases	Probability of KardiaMobile being cost saving
Narasimha et al. (2018)	£4001.81	£4115.88	£4027	£4114	-£87	3.52%	3.28%	0.24	Dominant	68.40%
Reed et al. (2019)	£4229.61	£4513.39	£4293	£4509	-£216	3.80	3.24	0.56	Dominant	99.90%
Goldenthal et al. (2019)	£5131.28	£5051.17	£5165	£5080	£84	6.53	6.12	0.42	£20,295	24.50%
Hermans et al. (2021)	£4977.52	£5273.82	£4969	£5249	-£281	6.77	6.12	0.65	Dominant	96.20%
Hickey et al. (2017)	£5131.28	£5309.31	£5133	£5304	-£171	6.83	6.08	0.75	Dominant	82.30%
Koh et al. (2021)	£5009.89	£5574.17	£4993	£5539	-£545	7.15	6.11	1.04	Dominant	99.8%

Table 4: Summary of PSA 1000 iterations

Study (year)	Cost difference per patient (KardiaMobile - Holter) [95%CI]
Narasimha et al. (2018)	-£119.26 [-£451.42 to +£368.53]
Reed et al. (2019)	-£215.35 [-£371.44 to -£71.16]
Goldenthal et al. (2019)	£83.73 [-£164.46 to +£326.54]
Hermans et al. (2021)	-£289.84 [-£557.31 to +£35.73]
Hickey et al. (2017)	-£174.75 [-£528.20 to +£182.81]
Koh et al. (2021)	-£556.18 [-£845.54 to -£201.06]

Conclusions

The company have altered their model to address some of the concerns raised by the EAC in the original assessment report, which addresses some of the uncertainties raised by committee. The 6 comparative studies included in the updated economic model are all relevant to the decision problem and demonstrate AF detection across undiagnosed palpitations and AF recurrence populations, which the committee felt were the most appropriate patient subgroups to include in further economic modelling. The updated model from the company only includes patients with AF (true positives and false negatives) which is a deviation from scope, and therefore the model results are not generalisable to the UK NHS setting when used in patients presenting with undiagnosed palpitations and for monitoring AF recurrence in patients post-treatment. Sensitivity analysis does not cover all areas of uncertainty, however 4/6 scenarios demonstrate no cost difference between KardiaMobile and comparator (24-hour Holter monitoring).

The updated model still lacks transparency, has not been replicated by the EAC and does not fully address the decision problem. The EAC is not confident that the revised model represents the robust economic evidence requested by committee.

Appendix B – EAC commentary on undiagnosed palpitations using data from Reed et al. 2019

The updated economic model uses data from 6 comparative studies. The EAC drafted a commentary on a single scenario using data from the only UK study (Reed et al. 2019), however as the same model structure and parameters have been used across all 6 comparative studies, the issues raised are applicable to all scenarios.

Responses in blue received by company on 01/10/2021. The EAC notes that the responses were to an EAC commentary on an earlier version of the model (03082021), but the EAC's comments stand, with the exception of the major bleed cost, which has been addressed.

Palpitations base case

The company's per-patient base case results are shown in Table 1. The total per-patient cost over a 5 year time horizon for Kardia Mobile was 4063.06 GBP and the total cost for Holter was 4183.71 GBP. The EAC reviews each row in the base case in the following sections.

Table 1: Table 1. Company base case for palpitations (GBP)

Cost.category	KardiaMobile	Holter
Costs of initial AF monitoring (device-related)	367.12	176.42
Costs of repeat monitoring (device-related)	0	258.3
Costs of secondary care visits (initial monitoring)	154.43	154.43
Costs of secondary care visits (repeat monitoring)	0	154.43
Costs of anticoagulants	1756.25	1554.15
Costs of stroke	243.69	321.84
Costs of MB	0	0
Costs of ICH	137.36	153.76
Costs of MI	136.73	125.11
Costs of fatal stroke	23.86	29.18
Costs of fatal MB	70.68	66.02
Costs of fatal ICH	14.63	15.05
Costs of fatal MI	11.35	10.53
Costs of two events	1013.18	1028.06
Costs of three events	131.21	133.74
Costs of four events	2.57	2.69

Clarification point from company: Before we answer the questions, we need to make some clarifications about the above table. The above table represents a breakdown of average costs per **patient** which means that the model captures costs for those with AF or missed AF. This has been shown in the model structure (Appendix A) and explained in the model structure section on page 5 of 68 in the supplementary document. This approach was used for the following reasons:

1- The prevalence of AF is unknown: patients can be asymptomatic and some patients may not be identified as having AF at the time of recording (paroxysmal AF); therefore, the true diagnostic accuracy of monitoring procedures is unknown *[refer to the point highlighted by the EAC in the*

Economic Evaluation of KardiaMobile for detecting AF document]. Therefore, it would be difficult to determine the real efficacy of monitoring procedures and other diagnostic tests such as a laboratory test with a defined gold standard.

2- Real costs of initial AF monitoring (device-related) for Holter were unknown, as we explained on page 57 of 68 in the supplementary document (i.e., this is a main source of uncertainty). Therefore, if a comprehensive cost analysis was performed, we expect that the "costs of initial AF monitoring (device-related)" for KardiaMobile will be cheaper compared to Holter monitoring due to a cheaper device price and less review time for ECGs. Therefore, focusing on patients with AF in the analysis can be considered to be a conservative scenario for KardiaMobile, where we have excluded cost-savings associated with negative cases (with no treatment costs) from the analysis.

Consequently, we decided to develop the updated model while considering that KardiaMobile can result in the commencement of disease management sooner than the comparator. After all the discussion over the past number of months, we think that the development of the model based on a standard approach of other diagnostic tests will imply considerable uncertainties in the analysis. the updated model captures costs and outcomes for AF detected plus AF missed in one arm, and then compares it with all AF detected cases in another arm. We tried to avoid making assumptions in the absence of clinical evidence, where possible, and we believe that our updated model reflect this.

Cost of monitoring

The device cost of Kardia Mobile was assumed to be 82.50 GBP and the maximum number of times used in its lifetime was assumed to be 8. After training, which takes a nurse 10 minutes, each patient was assumed to use the device for 90 days and to record 2.9 ECG traces per day. The nurse time to review an ECG trace was assumed to be 0.8 minutes, at a rate of 50 GBP/hour. Combining these, the cost of a test with Kardia Mobile is 192.65 GBP.

• As the cost of a secondary care visit for initial monitoring is included separately in the base case (154.43 GBP), it is not clear to the EAC why the per-person of Kardia Mobile in the model is 367.12. This is close to the per use cost (192.65 GBP) plus a cardiology appointment cost (154.43 GBP) and a GP visit cost (33 GBP), total 380.08 GBP.

ANSWER: As it has been highlighted in **Table 5** on **page 31 of 68** in the supplementary document, KardiaMobile was used as an adjuvant diagnostic in Reed et al. 2019. Therefore, "Costs of initial AF monitoring (device-related)" for this study were estimated as 190.70+176.42 = 376.12 (KardiaMobile + Holter). Cost of secondary visits is displayed in another row called "Costs of secondary care visits (initial monitoring)".

Cost of repeat monitoring

• It is not clear to the EAC why the 5 year per person cost of repeat monitoring for Holter is higher than the 5 year cost per person for the initial test, when only 50.44% of patients are assumed to have a repeat test and everyone has the initial test. The EAC surmises this is because a proportion of repeat tests are assumed to be with more costly interventions (e.g. loop recorders).

ANSWER: This is correct. In the study by Reed et al. 2019, there is no AF detected for Holter monitoring. Therefore, for each AF detected case in the KardiaMobile arm, one person in the Holter arm should undergo one additional monitoring as follow (RANGE A):

Holter	50.44%
CER	27.79%
Patch	16.99%
ILR	4.78%

If we consider the following costs for monitoring procedures (RANGE B):

Costs of Holter monitoring (£)	176.42

Costs of CER (£)	176.42
Cost of Patch (£)	265.00
Costs of implantable loop recorder (£)	1574.97

The additional cost for each AF missed in the Holter arm would be equal to SUMPRODUCT(RANGE A:RANGE B) = 258.30 GBP (for each missed AF). As the model focuses on patients with AF, and according to Reed et al. 2019, there is no AF detected in the comparator arm, therefore, 100% of patients in the comparator arm underwent one additional monitoring.

Cost of secondary care visits See EAC note on cost of monitoring.

ANSWER: Please see our response for the previous question (Cost of repeat monitoring).

Cost of anticoagulants

From the tab "Decision Tree", after repeat monitoring, the proportions of people with AF in both arms who received treatment were 21.22% (warfarin), 67.23% (NOAC) and 11.25% (no treatment). The annual cost of warfarin was assumed to be 0.056 GBP per day and NOAC 2.017 GBP per day. With these values, and assuming a prevalence of AF of 6.5%, the per-person costs of anticoagulants taken over the full 5 years are 1.41 GBP for warfarin and 160.86 GBP for NOAC; 162.27 GBP in total.

- Accepting that in the company's model, the costs of anticoagulants will be higher for Kardia Mobile than for Holter, it is not clear why the per person costs seem to be around 10 times higher than expected.

Answer: As mentioned in the previous question and in the clarification point, the model captures costs and outcomes among patients with AF. Therefore, there is no need to include the prevalence of AF in the estimation again.

Please see our responses in the next second question below regarding the estimated costs of anticoagulants (preventive care).

- It is not clear to the EAC that false positives have been considered in the model.

Answer: This is based on an assumption made by the EAC in the previous cost model (page 110 of 231 External Assessment Centre report: GID-MT554 KardiaMobile):

All KardiaMobile ECGs are reviewed by an authorized staff, therefore it is assumed that KardiaMobile has 100% sensitivity and 100% specificity (therefore no cost impact of false negative or false positive results).

Therefore, as an authorized staff should review the ECGs in both arms, we assumed that the probability of false positive should be identical in both arms and can be removed from the analysis.

- It is not clear to the EAC why the per-cycle costs of DOACs (spreadsheet tab "KM", column CK) reduce so quickly during the 10 year time horizon. Once diagnosed, most patients would continue to take a DOAC and the EAC would expect the cost per cycle to be quite stable, increasing slowly as more patients are found to have AF through repeat testing and reducing slowly as patients die.

Answer: What the model captures in the sheet tab "KM", column CK, is the costs of anticoagulants before any complications (preventive care) as highlighted in the model structure. When any complication occurs, the costs of anticoagulants are part of treatment costs. For example, anticoagulants are part of stroke treatment, or any modification may happen in patients with ICH. Therefore, including all alive patients in estimating the costs of anticoagulants, regardless of their health states, leads to overestimating the costs for anticoagulants in preventive care.

Cost of stroke

The cost of stroke was 9527 GBP and 2193 GBP per year in subsequent years. The rate of stroke (described as "hazard ratio") was 0.012 and the hazard ratio of stroke, given a prior stroke was 4.015.

As an approximate estimate, if everyone with AF is at unmodified risk of stroke, the cost of first stroke per patient over 5 years is equal to the prevalence of AF (6.5%) multiplied by the risk of stroke per year and the cost of stroke × 5 (years), 37.16 GBP. Assuming that that everyone who has a stroke needs annual care for 2.5 years, the cost of ongoing care per person, over 5 years is 4.28 GBP, a total of 41.43 GBP per person over 5 years.

For later strokes, it is assumed that all those who had had a stroke are at 4.015 times the baseline risk of stroke, i.e. a stroke rate of 4.818% per year. The cost per person of a second stroke over 5 years is therefore 1.79 GBP and the after care is 0.21 GBP. The combined cost per person over 5 years is thus 43.43 GBP. This is an upper limit because it does not apply the effect of taking a DOAC which will reduce stroke rates.

- It is not clear to the EAC why the cost of stroke per person over 5 years in the company's base case is around 6 times higher than this estimate.

Answer: Please see the clarification point and our responses for the previous questions. Moreover, 0.012 was labeled as a baseline probability of stroke in the model and not as a HR.

Cost of major bleed

- It is not clear to the EAC why this is zero, in the base case, given that people are receiving anticoagulants.

  Particularly as there are costs assigned to "fatal major bleeding".

Answer: We cannot replicate this error. Please see the below screen shot from the model results which is exactly the same as the reported results on page 37 of 68 in the supplementary document.

Patient population: Palpitation
Diagnostic data source: Reed et al. 2019 UK (n=240)
Comparator: Standard care
Time horizon: Five years
Inclusion of anticoagulants adverse events: Yes
Duration of monitoring (KardiaMobile): 90 days (3 months)

Costs (average cost per patient) (£)

The duration of KardiaMobile used in this study was 90 days.

	KardiaMobile	Standard care	Incremental Δ
Costs of initial AF monitoring (device-related)	367.12	176.42	190.70
Costs of repeat monitorings (device-related)	0.00	258.30	-258.30
Costs of secondary care visits (initial monitoring)	154.43	154.43	0.00
Costs of secondary care visits (repeat monitoring)	0.00	154.43	-154.43
Costs -Anticoagulants	1,756.25	1,554.15	202.09
Costs of stroke	352.35	513.10	-160.75
Costs of MB	45.04	36.66	8.37
Costs of ICH	209.53	246.92	-37.39
Costs of MI	147.40	133.69	13.71
Costs of fatal stroke	23.86	29.18	-5.32
Costs of fatal MB	70.68	66.02	4.66
Costs of fatal ICH	14.63	15.05	-0.42
Costs of fatal MI	11.35	10.53	0.82
Costs of two events	1,013.18	1,028.06	-14.88
Costs of three events	131.21	133.74	-2.52
Costs of four events	2.57	2.69	-0.12
Total costs per patient	4,299.61	4,513.39	-213.78

Cost of fatal major bleeding

- It is unclear why the costs associated with fatal major gastor-intestinal bleeding are higher than costs for fatal stroke, intracranial haemorrhage and myocardial infarction combined.

Answer: This is due to a higher baseline probability of major bleeding (0.066) compared to the baseline probability of stroke (0.012), ICH (0.009), and MI (0.008) according to Nathan R. Hill et al. 2020

Costs of two events

The EAC assumes that this represents the cost per person who have two events.

- It is not clear to the EAC why the cost per patient over the 5 years of having two events (1013.18 GBP) exceeds the per-patient costs over 5 years of any two single events combined.

Answer: it has been mentioned in Table 3, page 20 of 68 in the supplementary document that patients with two events were distributed in six sub-health states:

Stroke + MB

Stroke + ICH

Stroke + MI

MI + MB

MI + ICH

MB + ICH

The costs associated with two events was based on the likelihood of accruing the second event, which differs for various event. Therefore, we do not think this would be an appropriate method to validate costs associated with two events with simply the sum of two events. Moreover, we know that managing two events simultaneously does not equate to the sum of the costs of two single events, due to an overlap of management costs. Therefore, to estimate costs associated with two events, we assumed that the additional post-event management costs were the maximum management costs for the constituent events. This approach was used in Sterne et al. 2019, page 32.

Costs of three events

• It is not clear to the EAC why the cost per patient over the 5 years of having three events is comparable with the per-patient 5 year costs of having a single event. This suggests that the probability of having three events is around one third the probability of having a single event. That seems implausible when the rates of adverse events are small.

Answer: This is based on the likelihood of three events occurring over a five year time horizon as well as the approach that we used in the estimation of costs of two events. Please remember that these are average costs per patient and so, they consider the likelihood of three events occurring. Please see our response to the previous question (costs of two events)